Supporting Information

Strong and Confined Acids Enable a Catalytic Asymmetric Nazarov Cyclization of Simple Divinyl Ketones

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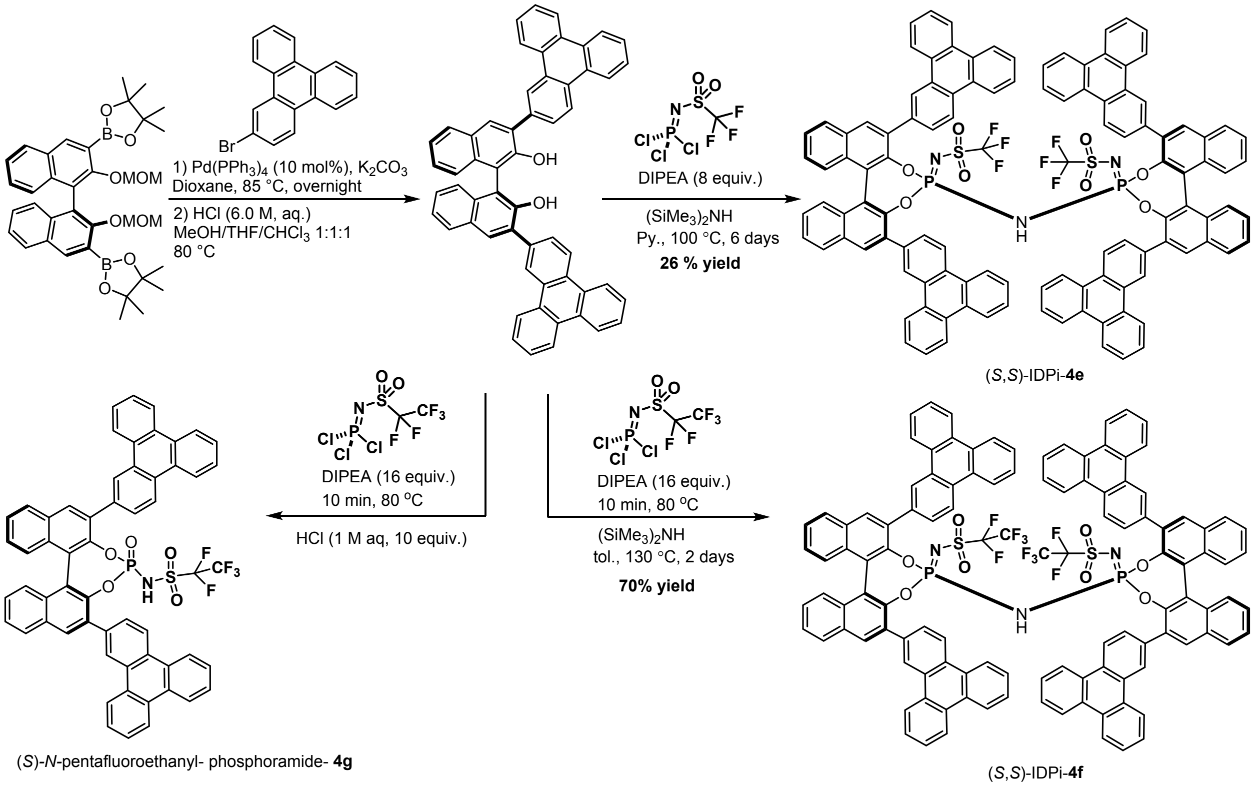
General information

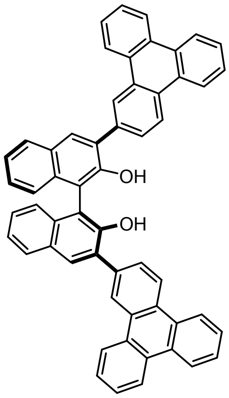
Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Aldehydes were distilled and stored under Ar prior to use. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography (TLC) on silica gel pre-coated plastic sheets (0.2 mm, Macherey-Nagel) or glass plates (SIL G-25 UV254, 0.25 mm, Macherey-Nagel). Visualization was accomplished by irradiation with UV light at 254 nm and/or *p*-anisaldehyde (PAA) stain. PAA stain: to absolute EtOH (135 mL) was added conc. sulfuric acid (5 mL), glacial acetic acid (1.5 mL) and *p*-anisaldehyde (3.7 mL). Column chromatography was performed on Merck silica gel (60, particle size 0.040–0.063 mm). NMR spectra were recorded on Bruker AV-500, Bruker AV-400 or Bruker AV-300 spectrometer in deuterated solvents. Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ δ 7.26 ppm; CD_2Cl_2 δ 5.32 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, h = heptet, m = multiplet, br = broad), coupling constants (Hz) and integration. ^{13}C chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ δ 77.16 ppm; CD_2Cl_2 δ 53.84 ppm). High resolution mass spectra were determined on a Bruker APEX III FTMS (7 T magnet). All reported yields, unless otherwise specified, refer to spectroscopically and chromatographically pure compounds. Optical rotations were determined with Autopol IV polarimeter (Rudolph Research Analytical) at 589 nm and 25 °C. Data are reported as follows: $[\alpha]_{\lambda}^{temp}$, concentration (*c*; g/100 mL), and solvents. Enantiomeric ratios (e.r.) were determined by GC or HPLC analysis employing a chiral stationary phase column specified in the individual experiment, by comparing the samples with the appropriate racemic mixtures. Diastereomeric ratios (d.r.) were determined by ^{1}H NMR spectra of the crude reaction mixtures.

Synthesis & Characterization of Catalysts



Scheme 1. Preparation of catalyst **4e, 4f, 4g**

(*S*)-3,3'-di(triphenylen-2-yl)-[1,1'-binaphthalene]-2,2'-diol



To a flame dried two-neck round-bottom flask with a condenser was added (*S*)-2,2'-(2,2'-bis(methoxymethoxy)-1,1'binaphthyl-3,3'-diyl)bis(4,4,-5,5-tetramethyl-1,3,2-dioxaborolane) (2.0 g, 3.2 mmol, 1.0 equiv), 2-bromotriphenylene (2.3 g, 7.3 mmol, 2.3 equiv) and tetrakis(triphenylphosphine)palladium (0.37 g, 0.32 mmol, 0.1 equiv). After degassing the reaction mixture with argon for 20 min, 1,4-dioxane (25 ml) and a degassed solution of K_2CO_3 (2.0 M, aq., 15 mL) were sequentially added. The mixture was then heated to 85 °C and stirred at that temperature overnight. After cooling the reaction to room temperature, the product precipitated and was filtered using a Büchner funnel, washing with hexane three times. The compound was further purified by column chromatography to afford (*S*)-2,2'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)ditriphenylene (2.2 g, 3.0 mmol, 93%) as a white solid. Subsequently, the solid was dissolved in chloroform (20 mL), MeOH (50 mL) and

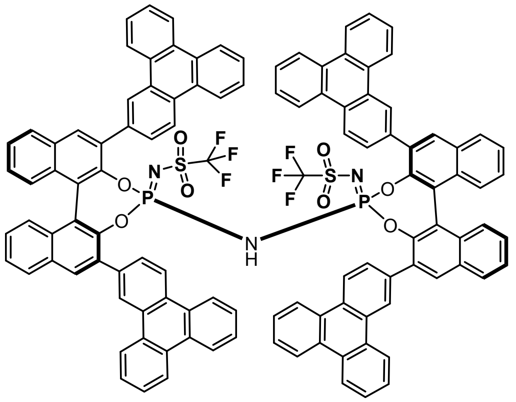
THF (50 mL) and a solution of HCl (6 M. aq., 20 mL) was added at room temperature. This mixture was heated to 80 °C and stirred overnight until the starting material was consumed (as monitored by TLC analysis). The reaction was then cooled to room temperature and quenched with water (100 mL). The resulting mixture was extracted with DCM (2 x 100 mL) and dried over anhydrous $MgSO_4$. Following filtration of the suspension through Celite, the volatiles were removed under reduced pressure. The resulting residue was purified by column chromatography (EtOAc: isohexane = 1:5) to afford (*S*)-3,3'-di(triphenylen-2-yl)-[1,1'-binaphthalene]-2,2'-diol (1.9 g, 2.57 mmol, 85%) as a light yellow solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.08 (d, *J* = 1.7 Hz, 2H), 8.81–8.76 (m, 4H), 8.72 (ddd, *J* = 9.5, 7.5, 3.2 Hz, 6H), 8.28 (s, 2H), 8.09 (dd, *J* = 8.5, 1.8 Hz, 2H), 8.05 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.70 (m, *J* = 8H), 7.47 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 2H), 7.41 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 2H), 7.34 (dd, *J* = 8.4, 1.1 Hz, 2H), 5.69 (s, 2H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 151.0, 136.9, 133.7, 132.2, 131.0, 130.4, 130.3, 130.2, 130.1, 129.9, 129.5, 129.2, 129.0, 127.9, 127.8, 127.8, 124.9, 124.8, 124.7, 123.8, 123.8, 123.8, 113.1. (The missing carbon singlets were due to overlap.)

HRMS (ESI$^-$) (*m/z*): calculated for $C_{56}H_{33}O_2$ [M–H]$^-$: 737.2486; found 737.2497.

Imidodiphosphorimidates (IDPi, **4e**)



In a flame dried Schlenk flask under Ar, *N*-Tf trichlorophosphazene (69.4 mg, 0.244 mmol, 2.03 equiv.) was dissolved in pyridine (2.5 mL), the corresponding diol (182.2 mg, 0.247 mmol, 2.05 equiv.) and then *N,N*-diisopropylethylamine (0.168 mL, 0.962 mmol, 8.0 equiv.) was added. The mixture was stirred at room temperature for 20 minutes and then hexamethyldisilazane (25.1 μL, 0.120 mmol, 1.0 equiv.) was added. After being stirred at room temperature for 15 minutes, the mixture was heated to 100 °C for 6 d. The reaction mixture was cooled to room temperature and all the volatiles were removed *in vacuo*. To the residue was added DCM and HCl (1M, aq). The two phases were separated and the aqueous layer was washed with DCM twice. The combined organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (eluant: 20% ethyl acetate in hexane then 7:3:1 hexane-MTBE-DCM) followed by acidification in DCM with HCl (6 M, aq) and dried in *vacuo* afforded the desired compound **4e** as a yellowish solid (58.0 mg, 26%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.95 (d, *J* = 1.7 Hz, 2H), 8.78 (dd, *J* = 8.4, 4.8 Hz,4H), 8.61 – 8.56 (m, 2H), 8.50 – 8.40 (m, 10H), 8.19 (dd, *J* = 8.4, 1.4 Hz, 2H), 8.11–8.06 (m, 4H), 8.06 – 8.00 (m, 6H), 8.00 – 7.91 (m, 4H), 7.82 (ddd, *J* = 8.4, 7.0, 1.1 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.72 – 7.66 (m, 6H), 7.63 (d, *J* = 8.6 Hz, 6H), 7.58 – 7.41 (m, 16H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.15 (dd, *J* = 8.5, 1.8 Hz, 2H), 5.69 (d, *J* = 8.5 Hz, 2H).

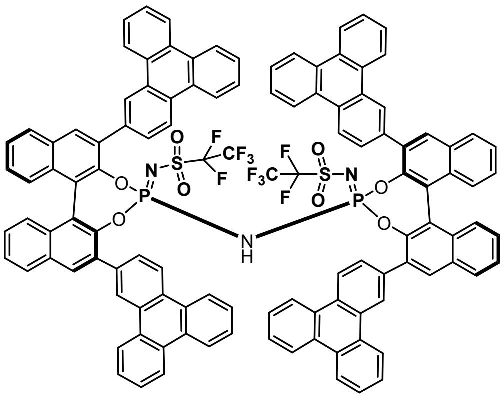
^{13}C NMR (125 MHz, CD_2Cl_2) δ 143.5, 143.1, 134.6, 132.3, 132.3, 132.1, 131.7, 131.6, 130.2, 129.9, 129.7, 129.4, 129.4, 129.3, 129.3, 129.3, 129.2, 129.1, 129.1, 128.8, 128.5, 128.0, 127.7, 127.6, 127.4, 127.3, 127.2, 127.2, 127.04, 126.8, 126.8, 126.8, 126.6, 126.4, 124.9, 124.4, 123.7, 123.6, 123.4, 123.4, 123.3, 123.2, 123.2, 122.9, 122.8, 122.80, 122.4, 122.0.

^{19}F NMR (470 MHz, CD_2Cl_2) δ -79.31.

^{31}P NMR (202 MHz, CD_2Cl_2) δ -14.50.

HRMS (ESI$^-$) (*m/z*): calculated for $C_{114}H_{64}F_6N_3O_8P_2S_2$ [M–H]$^-$: 1842.3520; found 1842.3538.

Imidodiphosphorimidates (IDPi, **4f**)



In a flame-dried J. Young Schlenk flask under Ar, dry diol (114 mg, 0.15 mmol, 2.1 equiv) was dissolved in toluene (3 mL). Subsequently, *N*,*N*-diisopropylethylamine (DIPEA, 151 mg, 1.16 mmol, 16.0 equiv) and ((perfluoroethyl)sulfonyl)phosphorimidoyl trichloride, $P(NSO_2C_2F_5)Cl_3$[1] (51 mg, 0.15 mmol, 2.1 equiv) were sequentially added at 80 °C. After stirring the solution for 15 min, 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 12 mg, 0.073 mmol, 1.0 equiv) was added under Ar. The mixture was stirred at 80 °C for 10 min, and then heated to 130 °C for 2 days. The reaction mixture was cooled to room temperature, diluted with DCM (15 mL), and stirred with HCl (1.0 M, aq., 3 mL) for 30 min. The organic phase was then separated, and the aqueous layer was extracted with DCM (2 x 10 mL). All combined organic layers were dried over anhydrous $MgSO_4$. The suspension was filtered and the organic solvent was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc: isohexane = 1:4) to give a colorless solid, which was then acidified in DCM (5 mL) with HCl (6.0 M, aq., 6 mL) by stirring at room temperature for 15 min. The mixture was diluted with DCM (10 mL), and the organic layer was separated, and washed with HCl (6.0 M, aq., 2 x 20 mL), followed by drying under reduced pressure to provide compound **4e** as a light yellow solid (98 mg, 0.051 mmol, 70%)

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.81 (d, *J* = 1.8 Hz, 2H), 8.63 (d, *J* = 8.3 Hz, 2H), 8.59 (d, *J* = 8.4 Hz, 2H), 8.41 (dd, *J* = 8.1, 1.6 Hz, 2H), 8.38–8.29 (m, 8H), 8.28–8.20 (m, 2H), 8.10 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.99 (dd, *J* = 8.6, 1.3 Hz, 2H), 7.96–7.85 (m, 6H), 7.81 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 7.79–7.71 (m, 6H), 7.62–7.54 (m, 6H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.42 (tdd, *J* = 8.3, 3.7, 1.3 Hz, 4H), 7.39–7.25 (m, 10H), 6.46 (d, *J* = 8.8 Hz, 2H), 6.06 (dd, *J* = 8.6, 1.8 Hz, 2H), 5.71 (dd, *J* = 8.5, 1.8 Hz, 2H).

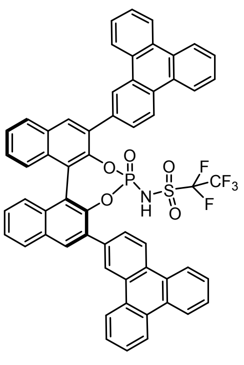
^{13}C NMR (125 MHz, CD_2Cl_2) δ 143.8, 143.8, 143.8, 143.7, 134.9, 134.2, 134.1, 134.0, 132.7, 132.7, 132.6, 132.4, 132.2, 132.2, 130.6, 130.4, 130.1, 129.9, 129.9, 129.8, 129.7, 129.7, 129.5, 129.3, 129.1, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3, 127.3, 127.3, 127.2, 127.1, 126.8, 125.2, 124.6, 124.2, 123.9, 123.8, 123.7, 123.6, 123.3, 123.3, 123.2, 122.7, 122.3.

^{19}F NMR (470 MHz, CD_2Cl_2): δ –79.15, –116.54, –116.61

^{31}P NMR (202 MHz, CD_2Cl_2): δ –15.60

HRMS (ESI^-) (*m*/*z*): calculated for $C_{116}H_{64}F_{10}N_3O_8P_2S_2$ $[M–H]^-$: 1942.3456; found 1942.3466.

(*S*)-*N*-pentafluoroethanyl- phosphoramide- **4g**



In a flame-dried J. Young Schlenk flask under Ar, dry diol (50 mg, 0.07 mmol, 1 equiv) was dissolved in toluene (3 mL). Subsequently, *N*,*N*-diisopropylethylamine (DIPEA, 67 mg, 0.52 mmol, 7 equiv) and ((perfluoroethyl)sulfonyl)phosphorimidoyl trichloride, $P(NSO_2C_2F_5)Cl_3$[1] (23 mg, 0.07 mmol, 1 equiv) were sequentially added at 80 °C. After stirring the solution for 30 min, HCl (1 M, aq, 10 equiv) was added under Ar. The mixture was stirred at 80 °C for 10 min, and then diluted with DCM (15 mL) and water (10 mL). The organic phase was separated, and the aqueous layer was extracted with DCM (2 x 10 mL). All combined organic layers were dried over anhydrous $MgSO_4$. The suspension was filtered, and the organic solvent was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc: isohexane = 1:4 to 1:1) to give a colorless solid, which was then acidified in DCM (5 mL) with HCl (6.0 M, aq., 6 mL) by stirring at room temperature for 15 min. The mixture was diluted with DCM (10 mL), and the organic layer was separated, and washed with HCl (6.0 M, aq., 2 x 20 mL), followed by drying under reduced pressure to provide compound **4g** as a light yellow solid (30 mg, 0.03 mmol, 46%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.92 (d, *J* = 1.9 Hz, 1H), 8.73 (t, *J* = 8.0 Hz, 3H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.52 (dq, *J* = 8.6, 1.7 Hz, 3H), 8.40 (dd, *J* = 15.5, 8.2 Hz, 2H), 8.32 (s, 1H), 8.26 (d, *J* = 7.3 Hz, 2H), 8.12 – 8.03 (m, 3H), 7.93 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.64 (ddd, *J* = 8.3, 6.2, 1.8 Hz, 1H), 7.58 – 7.39 (m, 10H), 7.34 – 7.26 (m, 3H), 7.22 (s, 2H).

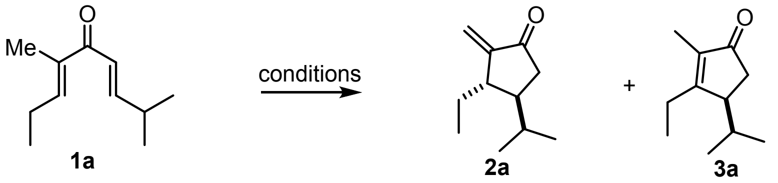
^{13}C NMR (125 MHz, CD_2Cl_2) δ 134.8, 134.6, 133.6, 132.4, 132.2, 132.0, 131.9, 130.1, 129.8, 129.7, 129.5, 129.39, 129.1, 128.9, 128.7, 128.7, 127.4, 127.2, 127.2, 127.1, 127.1, 127.0, 126.9, 126.7, 126.6, 125.5, 123.6, 123.5, 123.43, 123.4, 123.1, 122.9, 122.8, 66.8.

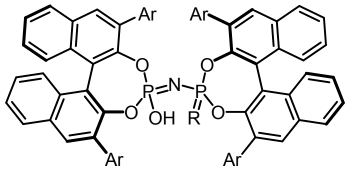
^{19}F NMR (470 MHz, CD_2Cl_2) δ -79.53, -115.85.

^{31}P NMR (202 MHz, CD_2Cl_2) δ -5.29.

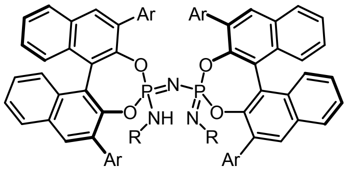
HRMS (ESI^-) (*m*/*z*): calculated for $C_{58}H_{32}N_1O_5P_1S_1F_5$ $[M–H]^-$: 980.1665; found 980.1656.

Table S1. Selected optimization experiments in the reaction of divinyl ketone 1a.

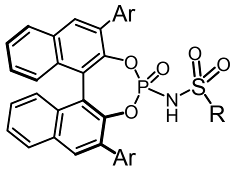




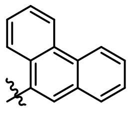
(*S,S*)-IDP-**4a**: Ar = Ph, R = O
(*S,S*)-*i*IDP-**4b**: Ar = Ph, R = NTf



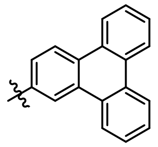
(*S,S*)-IDPi-**4c:** Ar= phenyl, R= SO_2CF_3
(*S,S*)-IDPi-**4e:** Ar= 2-triphenylenyl, R= SO_2CF_3
(*S,S*)-IDPi-**4f:** Ar= 2-triphenylenyl, R= $SO_2C_2F_5$



(S)-**4c:** Ar= 9-phenanthryl, R = CF_3
(*S*)-**4g:** Ar= 2-triphenylenyl, R=C_2F_5



9-phenanthryl



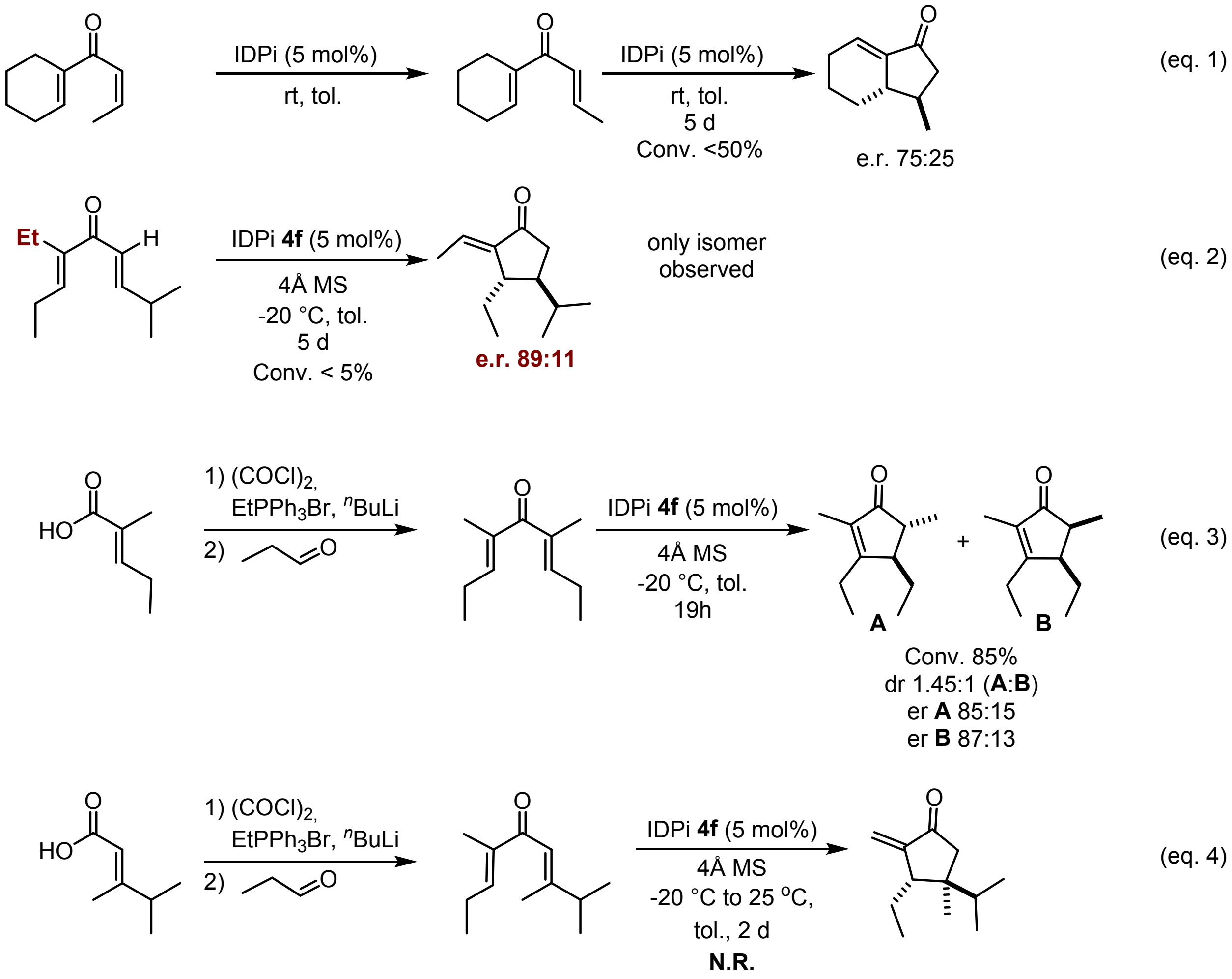
2-triphenylenyl

Entry	Catalysts	Loading	Sol.	T/°C	Time	Additive	Conc./M	Conv.[b]	r.r.[b]	e.r.$_{2a}$[c]	e.r.$_{3a}$[c]
1	(*S*)-**4a**	5 mol%	Tol.	25	16 h	4 Å MS	0.05	N.R.	N.D.	N.D.	N.D.
2	(*S*)-**4b**	5 mol%	Tol.	25	16 h	4 Å MS	0.05	N.R.	N.D.	N.D.	N.D.
3	(*S*)-**4c**	5 mol%	$CHCl_3$	25	16 h	/	0.2	75%	1:2	52:48	61:39
4	(*S*)-**4c**	5 mol%	Tol.	25	16 h	4 Å MS	0.05	13%	1.7:1	56:44	67:33
5	(*S*)-**4g**	5 mol%	Tol.	25	16 h	4 Å MS	0.05	51%	1.9:1	51:49	84:16
6	(*S,S*)-**4d**	5 mol%	Tol.	25	16 h	4 Å MS	0.05	N.R.	N.D.	N.D.	N.D.
7	(*S,S*)-**4e**	5 mol%	Tol.	25	16 h	4 Å MS	0.05	70%	>20:1	81:19	N.D.
8	(*S,S*)-**4f**	5 mol%	Tol.	25	16 h	4 Å MS	0.05	full	>20:1	86:14	N.D.
9	(*S,S*)-**4f**	2 mol%	Tol.	25	29 h	4 Å MS	0.05	85%	>20:1	86:14	N.D.
10	(*S,S*)-**4f**	10 mol%	Tol.	25	7 h	4 Å MS	0.05	full	>20:1	86:14	N.D.
11	(*S,S*)-**4f**	5 mol%	Tol.	25	16 h	/	0.2	full	11:1	84:16	90:10
12	(*S,S*)-**4f**	5 mol%	Et_2O	25	16 h	/	0.2	N.R.	N.D.	N.D.	N.D.
13	(*S,S*)-**4f**	5 mol%	$CHCl_3$	25	16 h	/	0.2	62%	14:1	74:26	86:14
14	(*S,S*)-**4f**	5 mol%	Tol.	0	4 d	/	0.2	full	14:1	91:9	97:3
15	(*S,S*)-**4f**	5 mol%	Tol.	–20	4 d	/	0.2	78%	20:1	96:4	98:2
16	(*S,S*)-**4f**	5 mol%	Tol.	–40	4 d	/	0.2	N.R.	N.D.	N.D.	N.D.
17	(*S,S*)-**4f**	5 mol%	Tol.	–20	3.5 d	4 Å MS	0.05	full	>20:1	97:3	N.D.
18	(*S,S*)-**4f**	10 mol%	Tol.	–20	29 h	4 Å MS	0.05	86%	>20:1	97:3	N.D.

a) Unless otherwise indicated, the reactions were performed with **1a** (0.02 mmol) all diastereomeric ratios (d.r.) of **2a** were >20:1; b) all conversions (Conv.) and regiomeric ratios (r.r. of **2a**:**3a**) were obtained by ^1H NMR with Ph_3CH as internal standard, N. R.: no reaction, N.D. : not determined; c) The enantiomeric ratios (e.r.) were detected by GC.

Limitations of the method

Below we provide examples that demonstrate limitations in the developed method with four different substrate classes. Namely, we found a *Z*-configured olefin did not react, but rather isomerized to the *E*-configured olefin under the reaction conditions. This was determined by monitoring the reaction by TLC, which showed a spot-to-spot conversion of the *Z*- to the *E*-isomer of 1-(cyclohex-1-en-1-yl)but-2-en-1-one. The *E*-isomer of this substrate has independently been shown to convert to the cyclized product (Scheme 2, eq. 1). Please note that both of these reactions were performed with an IDPi catalyst containing a 2-napthyl unit in the 3,3′ position.[2] Further, in the manuscript, all substrates contained a methyl group in the α-position of the divinyl ketone. When this methyl group is simply replaced with an ethyl group, we observe very poor conversion of the starting material. Only one isomer is apparently formed, which is suggested to be the exocyclic vinyl cyclopentenone (by empirical analogy to product **2a**). The enantiomeric ratio of this product was determined to be 89:11 (Scheme 2, eq. 2). The reaction of the α,α-dimethyl divinyl ketone actually proceeded much more rapidly than our model substrate (**1a**) to afford two endocyclic diasteroisomers (d.r. 1.45:1). This is in contrast to the exocyclic isomer that we typically observe with the α-methyl-substituted substrates. The enantioselectivities were determined to be 85:15 and 87:13 for each isomer (Scheme 2, eq. 3). We also attempted to cyclize a substrate with β,β-dialkyl substitution to form a quaternary center. However, this substrate was unreactive (Scheme 2, eq. 4).



Scheme 2. Limitations in reactivity or selectivity for four substrate classes

Kinetic study via ^1H NMR

In order to investigate the mechanism of this catalytic asymmetric Nazarov reaction, the kinetic profile was elucidated using ^1H NMR analysis(Fig. S1). The concentration of the substrate and the product was calculated based on an external standard and plotted over the reaction time. (Fig. S2A) Excel's Solver Add-in feature was used to fit the data to a simple exponential model based on first-order kinetics. In addition, the rate of the reaction was plotted over the concentration of the substrate and determined by using the LINEST function in Excel (Fig. S2B). The linearity of this function suggests that the free catalyst is the resting.

Procedure for kinetic study[3]:

In a 1.5 mL headspace vial, divinylketone **1a** (4.2 mg, 0.025 mmol, 1.0 equiv) was dissolved in 0.5 mL of tol-*d8*. Subsequently, catalyst **4f** (2.45 mg, 1.3 μmol, 0.05 equiv.) and 4 Å molecular sieves (10 mg) were added to the 5 mm NMR tube. The reaction solution was transferred to a NMR tube using a syringe. A 1-mm sealed glass tube filled with CH2Br2 (approx. 11.34 mg in 0.2 mL of tol-d8) was centered inside of the NMR tube to act as an in situ external standard, in order to prevent any possible change in mechanism as a result of an internal standards' possible participation in the reaction. Then the sample was quickly introduced into the NMR spectrometer (Bruker AV400 equipped with a BBFO probehead), which was pre-shimmed and precooled to – 20 ºC. As soon as the sample was equilibrated, a first short ^1H NMR spectrum was immediately recorded to determine the substrate concentration relative to the external standard. After that, the sample tuning and shimming was optimized, and ^1H measurements were taken every 30 minutes for 5 days (30°-pulse, 5.5s delay, 128 scans, 64k points), interleaved with automatic shimming and tuning (Fig. S1) Note that due to the presence of the molecular sieves and the insert with external standard, the sample was not rotated during the experiments.

The data was processed with Topsin 3.5, using zero-filling to 64k complex points, exponential line broadening to 0.3Hz, and fourier transform followed by phase- and baseline-correction (polynomial, n=3). The 228 spectra were imported into MestreNova 12, where the integrals for well-resolved substrate and product peaks (see figure S2A) as well as the external signal peak at 3.85ppm (CH_2Br_2) were measured using the data analysis tool. The concentrations of the substrate and of the product were calculated based on the external standard and plotted over the reaction time (Fig. S2A). We used the Solver Add-in feature of Excel to fit the data to a simple exponential function based on first-order kinetics.

$$[S] = [S]_0 e^{-k_s(t - t_0)} + \mathrm{C} \tag{1}$$

$$[P] = [S]_0\left(1 - e^{-k_p(t - t_0)}\right) + \mathrm{C} \tag{2}$$

By minimizing the sum of the squared differences, the curve fitting was optimized with rate constants k_s = 0.053 h^{-1} and k_p = 0.051 h^{-1} (for all parameters see Table S1), with excellent accuracy. In Fig. S2B we show the linearity of the differential representation of the decay functions:

$$k_s[S] = -\frac{d[S]}{dt} \tag{3}$$

with a goodness-of-fit R^2=0.997.

Note that the growth in the concentration of product only reaches 84% of the theoretical complete conversion (fitted $[S]_0$ = 42.5 mM). This is probably due to deterioration of the catalyst as well as further reaction of the product within the imperfect reaction conditions of the NMR tube.

Table. S2. Parameter-fitting to first order exponential functions (colors correspond to signals in Figure S2.

	🟪 1a	🟥 1a	🟩 2a	🟦 2a
***$[S]_0$** (mM)*	49.5	50.0	41.7	41.2
***k** (h-1)*	0.053		0.051	
***t_0** (h)*	0.00	0.00	0.00	0.00
***C** (mM)*	0.00	0.00	0.00	0.00
R^2	0.997		0.998	

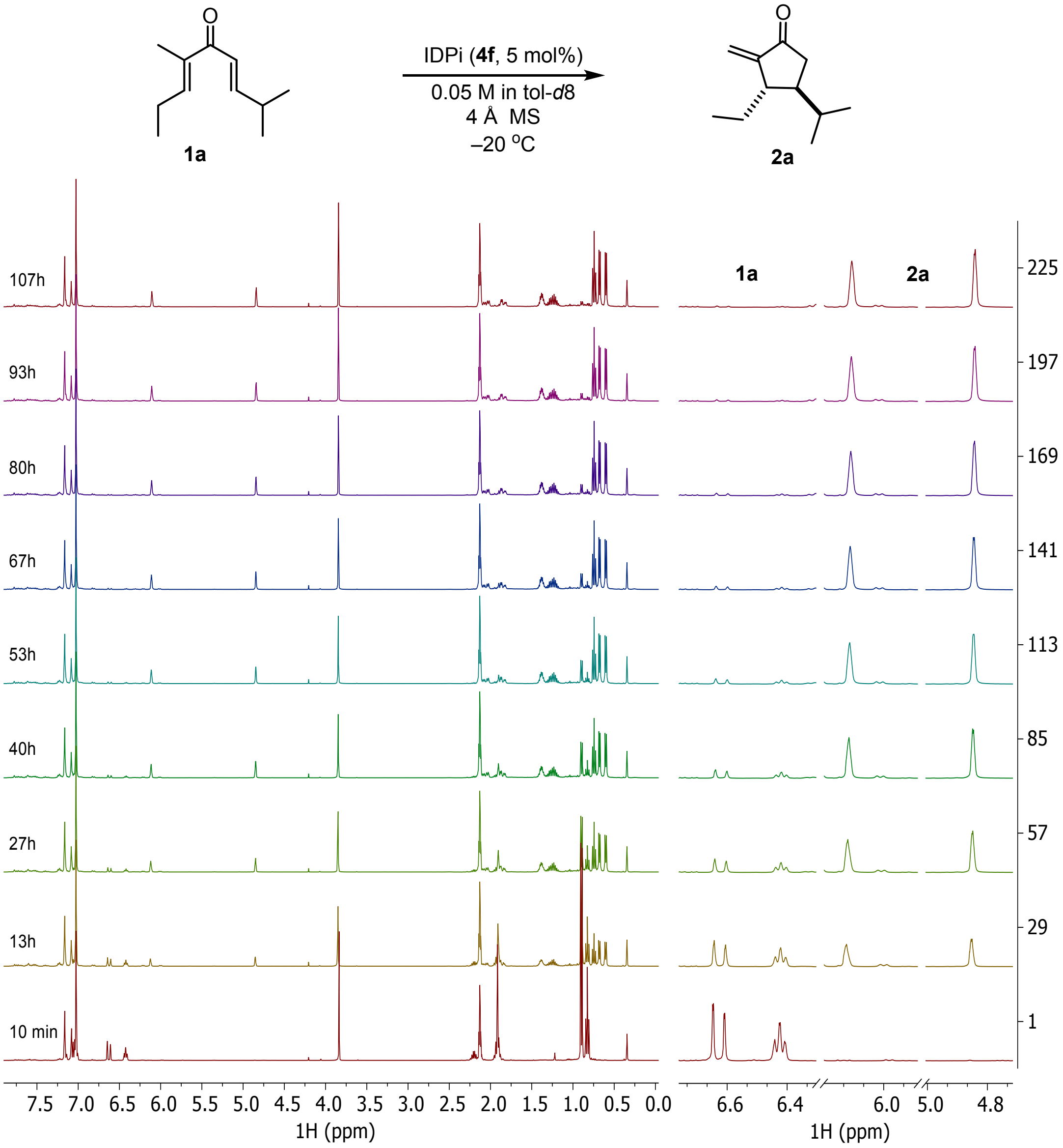


Fig. S1. Kinetic studies of catalytic asymmetric Nazarov reaction

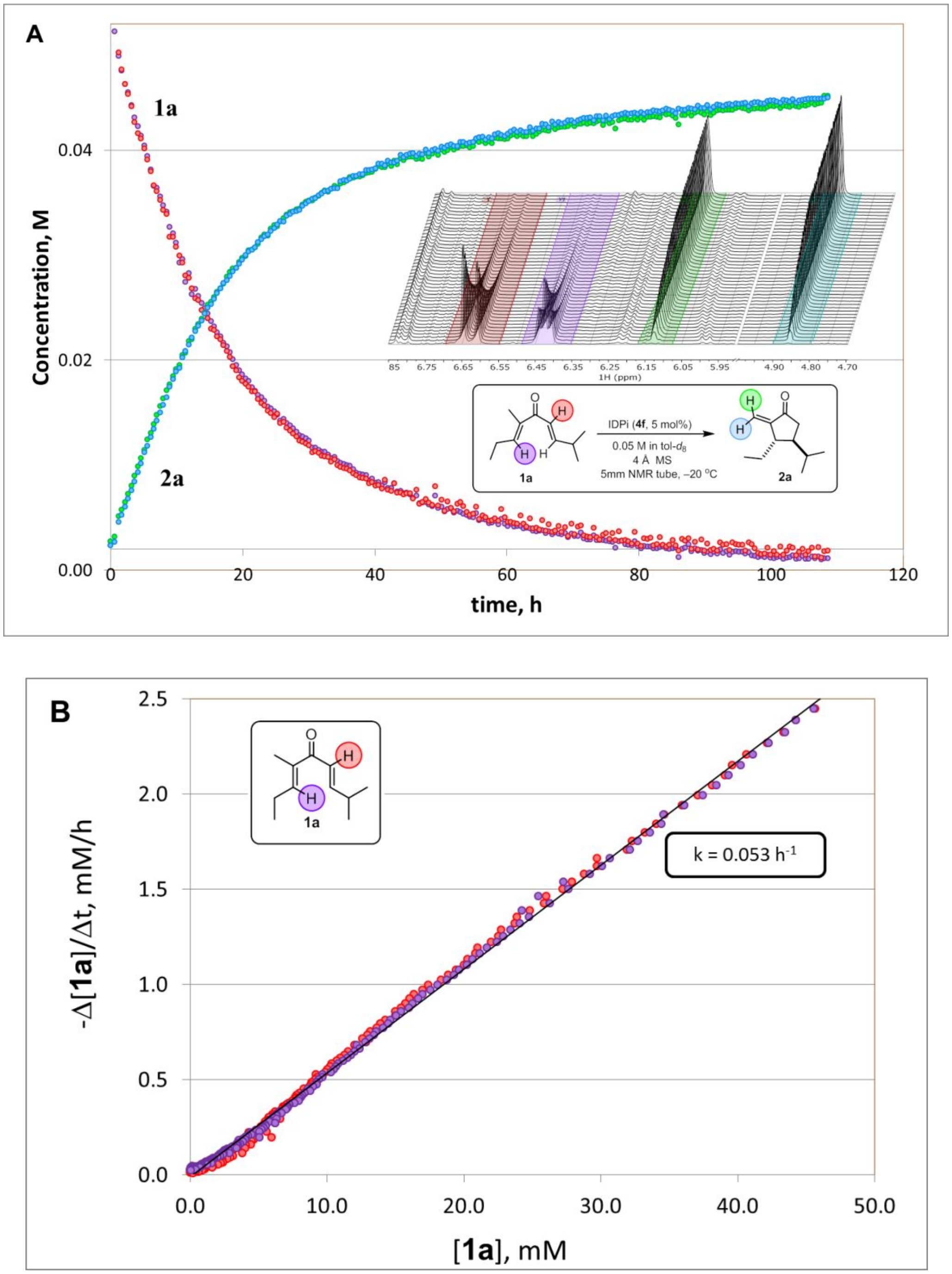


Fig. S2. Kinetic plot of the Nazarov cyclization. (A) concentration of the substrate and product over the course of the reaction. The red/purple (blue/green) dots represent the calculated concentration of the substrate (product) as evaluated by ^{1}H NMR based on the external standard. (B) Differential representation of the first-order reaction kinetics of the substrate (reaction rate vs. substrate concentration), showing an excellent fit with a rate constant k_s = 0.053 h^{-1} with a coefficient of determination R^2= 0.997.

Synthesis[4] & characterization of substrates

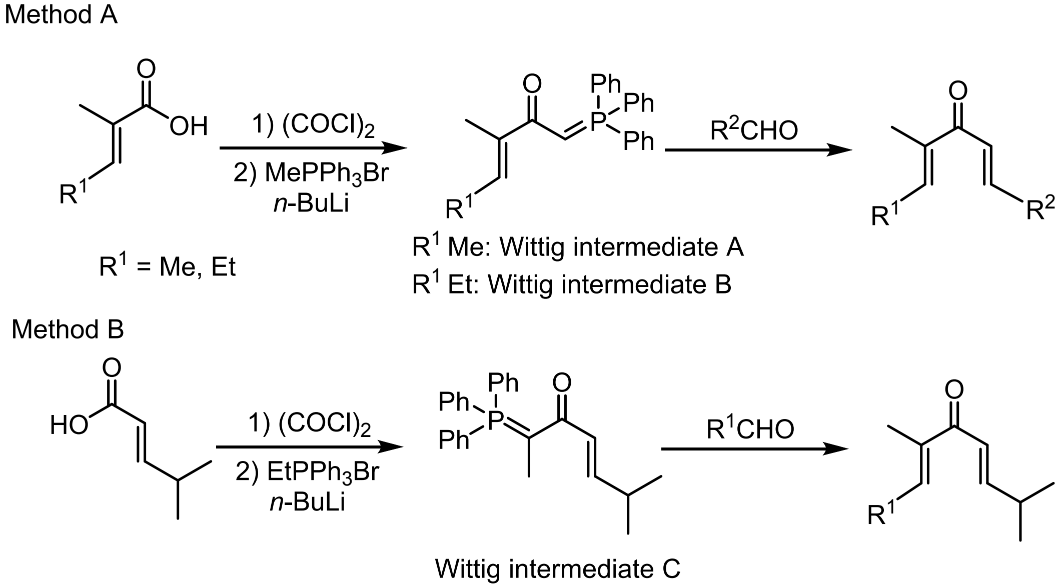
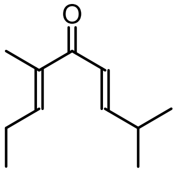


Fig. S3. Preparation of divinyl ketones

General procedure for preparation of divinyl ketones: The commercially available *E*-form carboxylic acid (50.0 mmol) was dissolved in DCM (150 mL), and then oxalyl chloride (8.7 mmol) was slowly added to the mixture at room temperature. After stirring for 2 h, the mixture was concentrated *in vacuo* to give the resulting acid chloride as a colorless liquid, which was directly used in the next step without further purification. To a solution of methyltriphenylphosphonium bromide (100 mmol, 2 equiv) in anhydrous THF (500 mL), *n*-BuLi (48 mL, 2.5 M in hexane) was added dropwise under Ar atmosphere. After stirring at room temperature for 2 h, freshly prepared acid chloride in THF (20 mL) was slowly added. The mixture was stirred overnight and was quenched with water (300 mL). The mixture was concentrated to remove THF. The residue was diluted with DCM (200 mL) and organic layer was separated. The aqueous layer was extracted with DCM (3 × 200 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the Wittig intermediate as dark brown gum (35 g), which could be used directly in the next step. The resulting Wittig intermediate was dissolved in anhydrous DCM (20 mL), and the commercially available aldehyde (40 mmol) was added at room temperature. The mixture was stirred overnight until the aldehyde was consumed (monitored by TLC, PAA stain). The solution was carefully concentrated and purified by column chromatography on silica-gel (Et_2O: Pentane = 1:100 to 1:50) to give the resulting products.

(3*E*,6*E*)-2,6-dimethylnona-3,6-dien-5-ne (**1a**)



1a was prepared following method A using isobutyraldehyde (2.4 g, 33 mmol) and Wittig intermediate B (35 g).

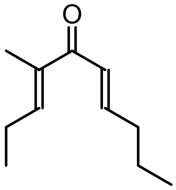
2.7g, 50%, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dd, *J* = 15.4, 6.8 Hz, 1H), 6.59 (dd, *J* = 15.6, 1.3 Hz, 1H), 6.58 (tq, *J* = 7.0 Hz, *J* = 1.5 Hz, 1H), 2.49 (dqd, *J* = 13.6, 6.8, 1.4 Hz, 1H), 2.30–2.22 (m, 2H), 1.83 (q, *J* = 1.0 Hz, 3H), 1.09 (t, *J* = 7.6 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 153.4, 144.1, 137.5, 122.4, 31.4, 22.5, 21.6, 13.3, 11.8.

HRMS (EI) (*m/z*): calculated for $C_{11}H_{18}O_1$ $[M]^+$: 166.1352; found 166.1353.

(3*E*,6*E*)-4-methyldeca-3,6-dien-5-one (**1b**)



1b was prepared following method A using butyraldehyde (1.2 g, 16.6 mmol) and Wittig intermediate B (17 g).

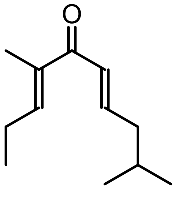
710 mg, 26%, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (dtd, *J* = 15.2, 6.9, 1.2 Hz, 1H), 6.66 (dt, *J* = 15.3, 1.3 Hz, 1H), 6.59 (t, *J* = 7.1, 1H), 2.34–2.23 (m, 2H), 2.27–2.18 (m, 2H), 1.85 (s, 3H), 1.57–1.46 (m, 2H), 1.10 (td, *J* = 7.6, 1.1 Hz, 3H), 0.96 (t, *J* = 7.4, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 147.1, 144.1, 137.4, 125.4, 34.8, 22.5, 21.7, 13.9, 13.3, 11.8.

HRMS (ESI) (*m/z*): calculated for $C_{11}H_{19}O_1$ $[M+H]^+$: 167.1430; found 167.1432.

(3*E*,6*E*)-4,9-dimethyldeca-3,6-dien-5-one (**1c**)



1c was prepared following method A using 3-methylbutanal (1.1 g, 12.8 mmol) and Wittig intermediate B (13 g).

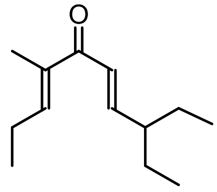
800 mg, 35 %, colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.80 (ddd, *J* = 15.3, 7.9, 7.1 Hz, 1H), 6.61 (dt, *J* = 15.3, 1.3 Hz, 1H), 6.56 (tq, *J* = 6.7, 1.3 Hz, 1H), 2.24 (td, *J* = 7.4, 1.1 Hz, 2H), 2.14–2.06 (m, 2H), 1.81 (t, *J* = 1.2 Hz, 3H), 1.75 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.06 (td, *J* = 7.6, 0.9 Hz, 3H), 0.91 (dd, *J* = 6.7, 1.0 Hz, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 192.4, 146.1, 144.1, 137.4, 126.3, 42.0, 28.1, 22.5, 22.5, 13.2, 11.7.

HRMS (EI) (*m*/*z*): calculated for $C_{12}H_{20}O_1$ $[M]^+$: 180.1509; found 180.1508.

(3*E*,6*E*)-8-ethyl-4-methyldeca-3,6-dien-5-one (**1d**)



1d was prepared following method A using 2-ethylbutanal (1.2 g, 12 mmol) and Wittig intermediate B (12.4 g).

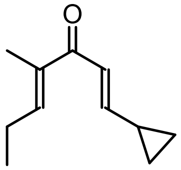
1g, 43%, colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.62–6.54 (m, 3H), 2.35–2.18 (m, 2H), 2.04–1.92 (m, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.55–1.46 (m, 2H), 1.36 (dt, *J* = 13.5, 7.7 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 192.5, 151.3, 144.0, 137.5, 125.3, 46.6, 27.1, 22.5, 13.3, 11.9, 11.8.

HRMS (ESI) (*m*/*z*): calculated for $C_{13}H_{23}O_1$ $[M+H]^+$: 195.1743; found 195.1743.

(1*E*,4*E*)-1-cyclopropyl-4-methylhepta-1,4-dien-3-one (**1e**)



1e was prepared following method A using cyclopropanecarboxaldehyde (870 mg, 12.4 mmol) and Wittig intermediate B (11 g).

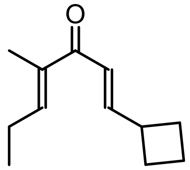
820 mg, 42%, colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.78 (d, *J* = 15.0 Hz, 1H), 6.57 (td, *J* = 7.2, 1.5 Hz, 1H), 6.33 (dd, *J* = 15.0, 10.1 Hz, 1H), 2.25 (td, *J* = 7.4, 1.0 Hz, 1H), 1.82 (d, *J* = 1.4 Hz, 2H), 1.63–1.56 (m, 2H), 1.08 (t, *J* = 7.6 Hz, 3H), 0.97–0.90 (m, 2H), 0.70–0.56 (m, 2H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 191.7, 152.4, 143.5, 137.3, 122.3, 22.5, 15.1, 13.3, 11.8, 8.8.

HRMS (EI) (*m*/*z*): calculated for $C_{11}H_{16}O_1$ $[M]^+$: 164.1196; found 164.1196.

(1*E*,4*E*)-1-cyclobutyl-4-methylhepta-1,4-dien-3-one (**1f**)



1f was prepared following method A using cyclobutanecarbaldehyde (500 mg, 4.2 mmol) and Wittig intermediate B (3.9 g).

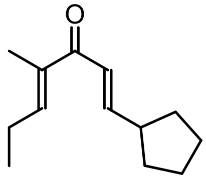
780 mg, 89%, colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.93 (dd, *J* = 15.3, 7.0 Hz, 1H), 6.57 (tq, *J* = 6.5 Hz *J* = 1.5 Hz, 1H), 6.56 (dd, *J* = 15.2, 1.4 Hz, 1H),3.21–2.99 (m, 1H), 2.30–2.23 (m, 2H), 2.19 (m, 2H), 1.97 (m, 3H), 1.86 (m, 1H), 1.83 (s, 3H), 1.08 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 192.7, 150.6, 144.1, 137.5, 122.9, 38.3, 28.2, 22.5, 18.8, 13.3, 11.8.

HRMS (EI) (*m*/*z*): calculated for $C_{12}H_{19}O_1$ $[M]^+$: 179.1430; found 179.1429.

(1*E*,4*E*)-1-cyclopentyl-4-methylhepta-1,4-dien-3-one (**1g**)



1g was prepared following method A using cyclopentanecarbaldehyde (200 mg, 2 mmol) and Wittig intermediate B (1.9 g).

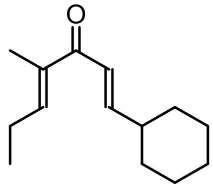
210 mg, 51%, colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.82 (dd, *J* = 15.2, 8.1 Hz, 1H), 6.62 (dd, *J* = 15.3, 1.0 Hz, 1H), 6.57 (tq, *J* = 7.1, 1.5 Hz, 1H), 2.61 (q, *J* = 8.1 Hz, 1H), 2.36–2.19 (m, 2H), 1.88–1.83 (m, 2H), 1.82 (s, 3H), 1.73–1.67 (m, 2H), 1.65–1.56 (m, 2H), 1.48–1.38 (m, 2H), 1.08 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 192.7, 151.6, 144.0, 137.5, 123.3, 43.5, 32.8, 25.5, 22.5, 13.3, 11.8.

HRMS (EI) (*m*/*z*): calculated for $C_{13}H_{21}O_1$ $[M]^+$: 193.1587; found 193.1587.

(1*E*,4*E*)-1-cyclohexyl-4-methylhepta-1,4-dien-3-one (**1h**)



1h was prepared following method A using cyclohexanecarbaldehyde (200 mg, 1.8 mmol) and Wittig intermediate B (1.6 g).

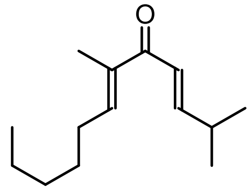
200 mg, 54%, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 15.4, 6.9 Hz, 1H), 6.60 (dd, *J* = 15.5, 1.2 Hz, 1H), 6.57 (tq, *J* = 7.0 Hz, *J* = 1.4 Hz, 1H), 2.26 (qd, *J* = 7.5, 1.0 Hz, 2H), 2.22–2.10 (m, 1H), 1.83 (q, *J* = 1.0 Hz, 3H), 1.81–1.72 (m, 4H), 1.68 (dtd, *J* = 12.4, 3.4, 1.7 Hz, 1H), 1.35–1.25 (m, 2H), 1.23–1.13 (m, 3H), 1.08 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 152.3, 144.0, 137.5, 122.7, 41.0, 32.1, 26.2, 25.9, 22.5, 13.3, 11.8.

HRMS (EI) (*m*/*z*): calculated for $C_{14}H_{22}O_1$ $[M]^+$: 206.1665; found 206.1665.

(3*E*,6*E*)-2,6-dimethyldodeca-3,6-dien-5-one (**1i**)



1i was prepared following method B using hexanal (200 mg, 2 mmol) and Wittig intermediate C (1.9 g).

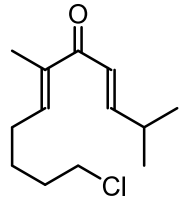
220 mg, 50%, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 15.4, 6.8 Hz, 1H), 6.63–6.54 (m, 2H), 2.49 (qd, *J* = 6.8, 1.4 Hz, 1H), 2.25 (qd, *J* = 7.3, 1.0 Hz, 2H), 1.83 (q, *J* = 1.0 Hz, 3H), 1.51–1.43 (m, 2H), 1.38–1.21 (m, 6H), 1.08 (d, *J* = 6.8 Hz, 6H), 0.92 (t, 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 192.2, 152.7, 142.1, 132.8, 121.7, 31.0, 30.7, 28.5, 27.8, 21.9, 20.9, 13.4, 11.2.

HRMS (EI) (*m*/*z*): calculated for $C_{14}H_{24}O_1$ $[M]^+$: 208.1822; found 208.1822.

(3*E*,6*E*)-11-chloro-2,6-dimethylundeca-3,6-dien-5-one (**1j**)



1j was prepared following method B using 5-chloropentanal (500 mg, 4.1 mmol) and Wittig intermediate C (3.1 g).

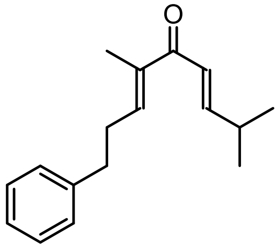
430 mg, 46%, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (dd, *J* = 15.4, 6.8 Hz, 1H), 6.50 (dd, *J* = 15.3, 1.3 Hz, 1H), 6.47 (dt,*J* = 7.0 Hz, *J* = 1.4 Hz, 1H), 3.50 (t, *J* = 6.5 Hz, 2H), 2.44–2.39(m, 1H), 2.29–2.13 (m, 2H), 1.82–1.70 (m, 5H), 1.63–1.54 (m, 2H), 1.02 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 153.8, 141.4, 138.5, 122.4, 44.8, 32.3, 31.5, 28.4, 26.1, 21.7, 12.1.

HRMS (ESI) (*m*/*z*): calculated for $C_{13}H_{21}$ $Cl_1O_1Na_1$ $[M+Na]^+$: 251.1173; found 251.1172.

(3*E*,6*E*)-4,8-dimethyl-1-phenylnona-3,6-dien-5-one (**1k**)



1k was prepared following method B using 3-phenylpropanal (1.3 g, 9.7 mmol) and Wittig intermediate C (7 g).

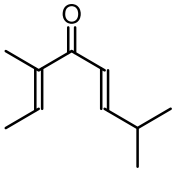
1.3 g, 54 %, colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34–7.28 (m, 2H), 7.24–7.18 (m, 3H), 6.77 (dd, *J* = 15.5, 6.7 Hz, 1H), 6.59 (tq, *J* = 7.3, 1.5 Hz, 1H), 6.52 (dd, *J* = 15.4, 1.4 Hz, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.58 (ddd, *J* = 9.1, 7.7, 6.6 Hz, 2H), 2.51–2.41 (m, 1H), 1.80 (q, *J* = 1.0 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 193.0, 153.7, 141.2, 141.2, 138.5, 128.6, 128.5, 126.3, 122.6, 34.9, 31.4, 31.0, 21.6, 12.0.

HRMS (ESI) (*m/z*): calculated for $C_{17}H_{23}O_1$ $[M+H]^+$: 243.1743; found 243.1744.

(2*E*,5*E*)-3,7-dimethylocta-2,5-dien-4-one (**1l**)



1l was prepared following method A using isobutyraldehyde (2.9 g, 40 mmol) and Wittig intermediate A (35 g).

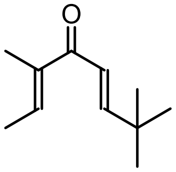
3g, 50%, colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.81 (dd, *J* = 15.4, 6.7 Hz, 1H), 6.71 (qd, *J* = 6.9, 1.4 Hz, 1H), 6.58 (dd, *J* = 15.4, 1.3 Hz, 1H), 2.48 (qd, *J* = 6.8, 1.4 Hz, 1H), 1.87 (dd, *J* = 6.9, 1.3 Hz, 3H), 1.84 (t, *J* = 1.3 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 192.7, 153.4, 139.1, 137.2, 122.4, 31.4, 21.6, 14.9, 11.7.

HRMS (EI) (*m/z*): calculated for $C_{10}H_{16}O_1$ $[M]^+$: 152.1196; found 152.1197.

(2*E*,5*E*)-3,7,7-trimethylocta-2,5-dien-4-one (**1m**)



1m was prepared following method A using pivalaldehyde (1 g, 11.6 mmol) and Wittig intermediate A (35 g).

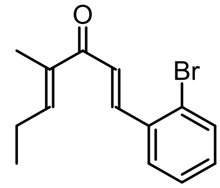
300 mg, 15%, colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.83 (d, *J* = 15.6 Hz, 1H), 6.68 (qq, *J* = 10 Hz, *J* = 1.4 Hz, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 1.87 (dd, *J* = 6.9, 1.2 Hz, 3H), 1.83 (t, *J* = 1.3 Hz, 3H), 1.09 (s, 9H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 192.9, 157.0, 139.2, 137.1, 120.2, 34.0, 29.0, 14.9, 11.7.

HRMS (ESI) (*m/z*): calculated for $C_{11}H_{19}O_1$ [M+H]$^+$: 167.1430; found 167.1432.

(1*E*,4*E*)-1-(2-bromophenyl)-4-methylhepta-1,4-dien-3-one (**1n**)



1n was prepared following method A using 2-bromobenzaldehyde (500 mg, 2.7 mmol) and Wittig intermediate B (2.5 g).

400 mg, 53%, yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.91 (d, *J* = 15.7 Hz, 1H), 7.65 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.61 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.33 (td, *J* = 7.6, 1.0 Hz, 1H), 7.21 (td, *J* = 7.8, 1.7 Hz, 1H), 7.18 (d, *J* = 15.7 Hz, 1H), 6.70 (tq, *J* = 7.3, 1.4 Hz, 1H), 2.32 (pd, *J* = 8.1, 7.5, 1.0 Hz, 1H), 1.90 (s, 3H), 1.12 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 192.1, 145.0, 141.1, 137.5, 135.4, 133.4, 130.8, 127.7, 127.6, 125.5, 125.0, 22.5, 13.2, 11.8.

HRMS (EI) (*m/z*): calculated for $C_{14}H_{15}O_1Br_1$ [M]$^+$: 278.0301; found 278.0303.

Preparation of racemate of Nazarov products

The racemic Nazarov products were prepared using 10 mol% of methanesulfonic acid at room temperature or boron trifluoride diethyl etherate in DCM at 0 °C to provide two regioisomers. Experimental: the divinyl ketone (0.2 mmol) was dissolved in DCM (1 mL). To this solution was added methanesulfonic acid (10 mol%). The mixture was stirred until the divinyl ketone was consumed (as monitored by TLC analysis) and quenched by $NaHCO_3$ (sat. aq., 0.5 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC plate (silica-gel) to afford racemic enones.

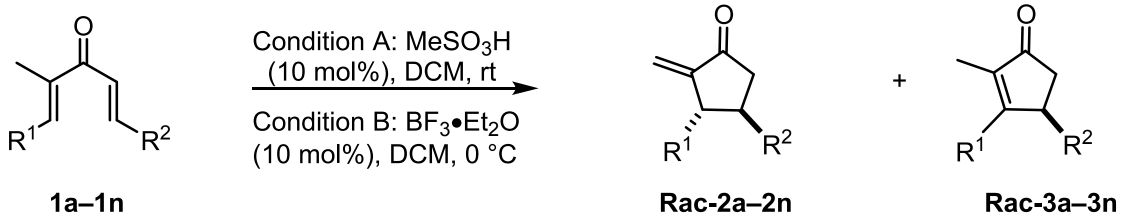


Fig. 4. Preparation of racemic product

General procedure of the asymmetric Nazarov cyclization

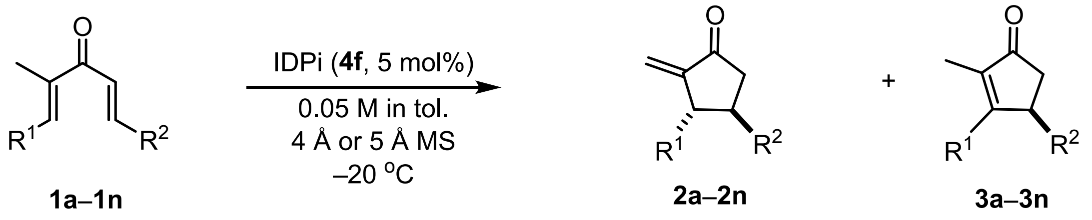
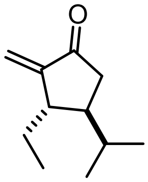


Fig. 5. The asymmetric Nazarov cyclization of simple divinyl ketones

To a flamed-dried Schlenk flask was added molecular sieves (100 mg). The flask was degassed and purged with Ar 3 times. A solution of divinyl ketone (0.2 mmol) in dried toluene (4 mL) was added to this flask under Ar. After cooling the reaction mixture with dry ice, the catalyst (**4f**, 5 mol%) was added. The reaction mixture was stirred at –20 °C until the starting material was consumed (as monitored by TLC) and was then passed through a pad of silica–gel, washing with pentane to remove the toluene. The product was eluted as a mixture with Et_2O:Pentane (3:7, 100 mL). The solvent was carefully concentrated (650 mbar, at 35 °C) to obtain a colorless residue. Before purification, a ^1H NMR was measured with Ph_3CH as internal standard (the ratio of internal standard and divinyl ketone is around 1:1 for each case) to determine the NMR yield and region-, diastereoselectivity. For volatile products (**1a–1c**, **1e**, **1f**, **1l**, **1m**), ^{1}H NMR yields are reported. Compounds that were not volatile (**1d**, **1g**, **1h**, **1i**, **1j**, **1k**) were then purified by chromatography (Et_2O: pentane 1:100 to 1:50) to afford the resulting enone products. (Note: the quality of 4 Å Molecular sieves was very important for regioselectivity. The batch of 4 Å and 5 Å Molecular sieves in this supporting information was purchased from Sigma-Aldrich, activated at 200 °C under 0.001 mbar for 2 days.)

Characterization of enones products

(3*S*,4*S*)-3-ethyl-4-isopropyl-2-methylenecyclopentan-1-one (**2a**)



Divinyl ketone **1a** (33 mg, 0.2 mmol) was subjected to the general procedure. 4 Å molecular sieves were used. After 7 days, the reaction had reached full conversion. The ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (72 %). The regioisomeric ratio was >20:1. (Note: the product is volatile.) The catalyst could be recovered (95%) via flash column chromatography following completion of the reaction.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (dd, *J* = 2.5, 1.1 Hz, 1H), 5.24 (dd, *J* = 2.3, 1.1 Hz, 1H), 2.55 (dq, *J* = 6.0, 3.0 Hz, 1H), 2.42 (ddd, *J* = 18.8, 8.6, 0.9 Hz, 1H), 2.17 (dd, *J* = 18.8, 6.0 Hz, 1H), 1.86 (dq, *J* = 8.6, 5.5 Hz, 1H), 1.76–1.67 (m, 1H), 1.62 (ddd, *J* = 15.0, 7.6, 6.2 Hz, 1H), 1.58–1.48 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

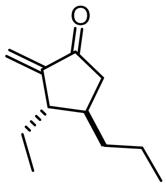
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 149.0, 117.4, 45.4, 43.4, 39.6, 30.6, 26.9, 21.0, 18.3, 10.9.

$[\alpha]_D^{25}$ = 12.8 (*c* = 0.25, $CDCl_3$)

HRMS (ESI) (*m/z*): calculated for $C_{11}H_{18}O_1Na_1$ $[M+Na]^+$: 189.1250; found 189.1252.

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 350 °C (detector), 80 °C (oven, 3 min, iso) to 130 °C (15 °C/min, 27 min iso); Gas: H_2 (0.5 bar); t_R = 14.94 min (minor), t_R = 16.97 min (major), e.r. = 3:97.

(3*S*,4*R*)-3-ethyl-2-methylene-4-propylcyclopentan-1-one (**2b**)



Divinyl ketone **1b** (33 mg, 0.2 mmol) was subjected to the general procedure. 5 Å molecular sieves were used. After 14 days, the reaction had reached full conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (62%). The regioisomeric ratio was 10:1. (Note: the product is volatile.)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 2.7, 1.1 Hz, 1H), 5.23 (dd, *J* = 2.4, 1.1 Hz, 1H), 2.54 (ddd, *J* = 18.2, 7.8, 0.7 Hz, 1H), 2.38 (qt, *J* = 5.8, 2.4 Hz, 1H), 2.00 (dd, *J* = 18.2, 6.9 Hz, 1H), 1.95–1.87 (m, 1H), 1.70–1.61 (m, 1H), 1.61–1.56 (m, 1H), 1.54–1.48 (m, 1H), 1.41–1.35 (m, 1H), 1.35–1.27 (m, 1H), 1.26–1.17 (m, 1H), 0.97–0.90 (t, 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H).

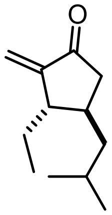
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 148.6, 117.4, 48.6, 43.5, 37.6, 25.6, 20.9, 14.3, 10.9.

HRMS (ESI) (*m*/*z*): calculated for $C_{11}H_{18}O_1Na_1$ [M+Na] 189.1250; found 189.1251.

$[\alpha]_D^{25} = -38.8$ (c = 0.5, $CDCl_3$)

GC: The enantiomeric ratio is measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 350 °C (detector), 80 °C (oven, 3 min, iso) to 130 °C (15 °C/min, 30 min iso) to 220 °C (15 °C/min, 10 min iso); Gas: H_2 (0.5 bar); t_R = 15.39 min (minor), t_R = 17.11 min (major), e.r. = 7:93.

(3*S*,4*R*)-3-ethyl-4-isobutyl-2-methylenecyclopentan-1-one (**2c**)



Divinyl ketone **1c** (36 mg, 0.2 mmol) was subjected to the general procedure. 4 Å molecular sieves were used. After 13 days, the reaction had reached 89% conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (67 %). The regioisomeric ratio was >20:1. (Note: the product is volatile.)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 2.7, 1.1 Hz, 1H), 5.24 (dd, *J* = 2.4, 1.1 Hz, 1H), 2.55 (dd, *J* = 10.4, 0.8 Hz, 1H), 2.40–2.30 (m, 1H), 2.03–1.91 (m, 2H), 1.72–1.53 (m, 3H), 1.41–1.32 (m, 1H), 1.21–1.12 (m, 1H),0.92 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H).

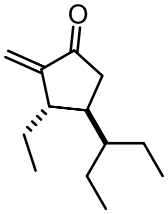
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 148.5, 117.4, 48.8, 44.8, 43.7, 35.6, 26.2, 25.3, 23.7, 22.1, 10.9.

$[\alpha]_D^{25} = -60$ (c = 0.25, $CHCl_3$)

HRMS (EI) (*m*/*z*): calculated for $C_{12}H_{20}O_1$ $[M]^+$: 180.1509; found 180.1510.

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 350 °C (detector), 80 °C (oven, 3 min, iso) to 130 °C (15 °C/min, 27 min iso); Gas: H_2 (0.5 bar); t_R = 18.41 min (minor), t_R = 20.23 min (major), e.r. = 7:93.

(3*S*,4*S*)-3-ethyl-2-methylene-4-(pentan-3-yl)cyclopentan-1-one (**2d**)



Divinyl ketone **1d** (39 mg, 0.2 mmol) was subjected to the general procedure. 4 Å molecular sieves were used. After 12 days, the reaction had reached 86% conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (80%). The regioisomeric ratio was >20:1. The residue was purified by chromatography on silica-gel to afford **2d** (30 mg, 0.15 mmol, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (dd, *J* = 2.6, 1.1 Hz, 1H), 5.23 (dd, *J* = 2.3, 1.1 Hz, 1H), 2.62–2.51 (m, 1H), 2.39 (dd, *J* = 18.3, 8.4 Hz, 1H), 2.19–2.04 (m, 2H), 1.64 (dqd, *J* = 15.0, 7.5, 5.7 Hz, 1H), 1.61–1.50 (m, 1H), 1.46–1.29 (m, 2H), 1.29–1.07 (m, 3H), 0.95–0.85 (m, 9H).

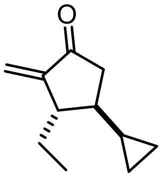
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 149.2, 117.1, 45.2, 43.9, 39.7, 39.3, 26.7, 24.1, 22.2, 12.3, 12.0, 10.8.

$[\alpha]_D^{25} = -10.0$ (*c* = 0.54, $CHCl_3$)

HRMS (ESI) (*m/z*): calculated for $C_{13}H_{22}O_1Na_1$ $[M+Na]^+$: 217.1563; found 217.1563.

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 350 °C (detector), 80 °C (oven, 3 min, iso) to 130 °C (15 °C/min, 30 min iso) to 220 °C (15 °C/min, 10 min iso); t_R = 25.61 min (minor), t_R = 27.85 min (major), e.r. = 5:95.

(3*S*,4*S*)-4-cyclopropyl-3-ethyl-2-methylenecyclopentan-1-one (**2e**)

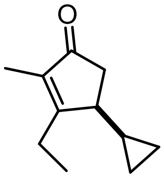


Divinyl ketone **1e** (33 mg, 0.2 mmol) was subjected to the general procedure. 5 Å molecular sieves were used. After 14 days, the reaction had reached full conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (51% of **2e** and 48% of **3e**). The regioisomeric ratio was 1:1. (Note: the products are volatile.)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (dd, *J* = 2.5, 1.1 Hz, 1H), 5.26 (dd, *J* = 2.3, 1.1 Hz, 1H), 2.61 (dt, *J* = 5.7, 2.7 Hz, 1H), 2.51 (dd, *J* = 18.4, 7.9 Hz, 1H), 2.18 (dd, *J* = 18.4, 6.5 Hz, 1H), 1.70–1.58 (m, 2H), 1.32 (ddt, *J* = 11.3, 9.0, 4.4 Hz, 1H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.71–0.63 (m, 1H), 0.58–0.49 (m, 1H), 0.49–0.41 (m, 1H), 0.20 (dt, *J* = 9.6, 4.8 Hz, 1H), 0.12 (dt, *J* = 9.4, 4.8 Hz, 1H).

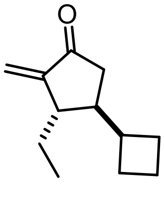
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 148.7, 117.5, 49.5, 43.4, 42.7, 29.9, 25.7, 16.2, 10.9, 4.7, 3.1.
$[\alpha]_D^{25} = 23.1$ (c = 0.20, $CDCl_3$)
HRMS (EI) (*m*/*z*): calculated for $C_{11}H_{16}O_1$ $[M]^+$: 164.1196; found 164.1197.
GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 220 °C (injector), 350 °C (detector), 80 °C (3 min, iso) to 130°C (15 °C/min, 27 min iso); Gas: H_2 (0.5 bar); t_R = 18.32 min (minor), t_R = 21.35 min (major), e.r. = 8:92.

(*S*)-4-cyclopropyl-3-ethyl-2-methylcyclopent-2-en-1-one (**3e**)



^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70–2.46 (m, 3H), 2.24–2.09 (m, 2H), 1.70 (dd, *J* = 1.8, 0.6 Hz, 3H), 1.12 (t, *J* = 7.7 Hz, 3H), 0.72–0.54 (m, 1H), 0.51–0.43 (m, 1H), 0.43–0.33 (m, 1H), 0.16–0.11 (m, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 178.0, 135.6, 45.2, 41.0, 22.5, 15.1, 12.3, 7.9, 5.4, 2.2.
HRMS (EI) (*m*/*z*): calculated for $C_{11}H_{16}O_1$ $[M]^+$: 164.1197; found 164.1197.
$[\alpha]_D^{25} = 15$ (c = 0.54, $CDCl_3$)
GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 220 °C (injector), 350 °C (detector), 80 °C (3 min, iso) to 130 °C (15 °C/min, 27 min iso); Gas: H_2 (0.5 bar); t_R = 27.52 min (minor), t_R = 29.47 min (major), e.r. = 0.3:99.7.

(3*S*,4*S*)-4-cyclobutyl-3-ethyl-2-methylenecyclopentan-1-one (**2f**)



Divinyl ketone **1f** (36 mg, 0.2 mmol) was subjected to the general procedure. 4 Å molecular sieves were used. After 2.5 days, the reaction had reached full conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (64%). The regioisomeric ratio was >20:1. (Note: the products is volatile.)

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.08–5.94 (m, 1H), 5.24 (t, *J* = 1.5 Hz, 1H), 2.43 (dd, *J* = 18.5, 8.0 Hz, 1H), 2.36 (m, 1H), 2.18–2.08 (m, 1H), 2.08–1.92 (m, 4H), 1.88–1.73 (m, 2H), 1.72–1.54 (m, 3H), 1.47 (dt, *J* = 14.1, 7.2 Hz, 1H), 0.94 (t, *J* = 7.4 Hz, 3H).

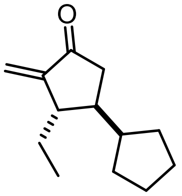
^{13}C NMR (125 MHz, CDCl$_3$) δ 207.5, 148.6, 118.1, 46.6, 43.6, 40.3, 40.0, 27.2, 27.1, 26.4, 17.8, 11.3.

HRMS (ESI) (*m/z*): calculated for $C_{12}H_{19}O_1$ $[M+H]^+$: 179.1430; found 179.1433.

$[\alpha]_D^{25}$ = 41 (*c* = 0.53, CHCl$_3$).

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm).Temperature: 220 °C (injector), 350 °C (detector), 80 °C (3 min, iso) to 150 °C (15 °C/min, 60 min iso); Gas: H$_2$ (0.5 bar); tR = 16.80 min (minor), tR = 18.14 min (major), e.r. = 4:96.

(1*S*,5*S*)-5-ethyl-4-methylene-[1,1'-bi(cyclopentan)]-3-one (**2g**)



Divinyl ketone **1g** (38 mg, 0.2 mmol) was subjected to the general procedure. 4 Å molecular sieves were used. After 4.5 days, the reaction had reached full conversion. ^{1}H NMR yield of this mixture was measured with Ph$_3$CH as an internal standard (79%). The regioisomeric ratio was >20:1. The residue was purified by chromatography on silica-gel to afford **2g** (30 mg, 0.15 mmol, 78%) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.03 (d, *J* = 1.8 Hz, 1H), 5.25 (d, *J* = 1.5 Hz, 1H), 2.55 (q, *J* = 2.9 Hz, 1H), 2.50 (dd, *J* = 18.7, 8.3 Hz, 2H), 2.18 (dd, *J* = 18.7, 4.4 Hz, 1H), 1.90 (dt, *J* = 8.2, 4.1 Hz, 1H), 1.83–1.77 (m, 1H), 1.77–1.67 (m, 2H), 1.67–1.55 (m, 3H), 1.52 (m, 3H), 1.20–1.06 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

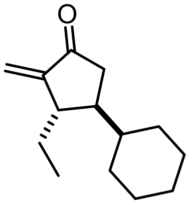
^{13}C NMR (125 MHz, CDCl$_3$) δ 207.5, 148.6, 117.6, 47.7, 44.2, 42.5, 41.6, 31.1, 30.2, 27.1, 25.4, 25.2, 11.0.

HRMS (ESI) (*m/z*): calculated for $C_{13}H_{20}O_1Na_1$ $[M+Na]^+$: 215.1406; found 215.1408.

$[\alpha]_D^{25}$ = 39 (*c* = 0.21, CHCl$_3$)

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm).Temperature: 350 °C (detector), 80 °C (Oven, 3 min, iso) to 150 °C (20 °C/min, 5 min iso) to 180 °C (15 °C/min, 20 min iso); Gas: H$_2$ (0.5 bar); t_R = 17.59 min (minor), t_R = 18.12 min (major), e.r. = 4:96.

(3*S*,4*S*)-4-cyclohexyl-3-ethyl-2-methylenecyclopentan-1-one (**2h**)



Divinyl ketone **1h** (41 mg, 0.2 mmol) was subjected to the general procedure. 4 Å molecular sieves were used. After 4.5 days, the reaction had reached full conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (87%). The regioisomeric ratio was >20:1. The residue was purified by chromatography on silica-gel to afford **2h** (35 mg, 0.17 mmol, 85%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (dt, *J* = 2.5, 1.1 Hz, 1H), 5.28–5.18 (m, 1H), 2.61 (q, *J* = 6.1 Hz, 1H), 2.42 (dd, *J* = 18.7, 8.7 Hz, 1H), 2.20 (dd, *J* = 18.7, 5.8 Hz, 1H), 1.84 (dq, *J* = 10.6, 5.4 Hz, 1H), 1.74 (m, 2H), 1.69–1.58 (m, 4H), 1.53 (dt, *J* = 14.1, 7.1 Hz, 1H), 1.41–1.29 (m, 1H), 1.27–1.07 (m, 3H), 1.03–0.90 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

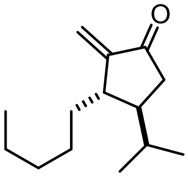
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 149.1, 117.1, 45.1, 42.8, 41.1, 40.1, 31.3, 28.9, 27.1, 26.6, 26.5, 26.4, 10.8.

HRMS (ESI) (*m*/*z*): calculated for $C_{14}H_{22}O_1Na_1$ $[M+Na]^+$: 229.1563; found 229.1565.

$[\alpha]_D^{25}$ = 14 (*c* = 0.28, $CHCl_3$)

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 350 °C (detector), 80 °C (Oven, 3 min, iso) to 150 °C (20 °C/min, 5 min iso) to 180 °C (15 °C/min, 20 min iso); Gas: H_2 (0.5 bar); t_R = 21.60 min (minor), t_R = 22.07 min (major), e.r. = 4:96.

(3*S*,4*S*)-4-isopropyl-2-methylene-3-pentylcyclopentan-1-one (**2i**)



Divinyl ketone **1i** (41 mg, 0.2 mmol) was subjected to the general procedure. 5 Å molecular sieves were used. After 14 days, the reaction reached 93% conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (74%). The regioisomeric ratio was >20:1. The residue was purified by chromatography on silica-gel to afford **2i** (30 mg, 0.144 mmol, 72%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 2.6, 1.0 Hz, 1H), 5.24 (dd, *J* = 2.3, 1.1 Hz, 1H), 2.71–2.54 (m, 1H), 2.42 (dd, *J* = 18.8, 8.6 Hz, 1H), 2.17 (dd, *J* = 18.8, 5.8 Hz, 1H), 1.89–1.79 (m, 1H), 1.78–1.67 (m, 1H), 1.58–1.43 (m, 2H), 1.41–1.23 (m, 6H), 0.90 (m, 6H), 0.85 (d, *J* = 6.7 Hz, 3H).

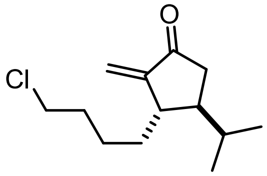
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 149.7, 117. 1, 44.3, 44.3, 39.6, 34.8, 32.2, 30.7, 26.4, 22.7, 21.0, 18.4, 14.2.

HRMS (ESI) (*m/z*): calculated for $C_{14}H_{24}O_1Na_1$ $[M+Na]^+$: 231.1719; found 231.1716.

$[\alpha]_D^{25} = 17$ (c = 0.52, $CHCl_3$)

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 350 °C (detector), 80 °C (Oven, 3 min, iso) to 150 °C (20 °C/min, 5 min iso) to 180 °C (15 °C/min, 20 min iso); t_R = 16.30 min (minor), t_R = 16.64 min (major), e.r. = 6:94.

(3*S*,4*S*)-3-(4-chlorobutyl)-4-isopropyl-2-methylenecyclopentan-1-one (**2j**)



Divinyl ketone **1j** (41 mg, 0.18 mmol) was subjected to the general procedure. 5 Å molecular sieves were used. After 14 days, the reaction had reached 94% conversion. ^1H NMR yield of this mixture was measured with Ph_3CH as an internal standard (76%). The regioisomeric ratio was >20:1. The residue was purified by chromatography on silica-gel to afford **2j** (30 mg, 0.13 mmol, 73%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (dd, J = 2.5, 1.0 Hz, 1H), 5.25 (dd, J = 2.2, 1.0 Hz, 1H), 3.55 (t, J = 6.6 Hz, 2H), 2.62 (tq, J = 5.8, 2.7 Hz, 1H), 2.43 (ddd, J = 18.8, 8.6, 0.8 Hz, 1H), 2.18 (dd, J = 18.8, 5.8 Hz, 1H), 1.89–1.74 (m, 3H), 1.72 (qd, J = 6.8, 5.4 Hz, 1H), 1.65–1.46 (m, 4H), 0.91 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H).

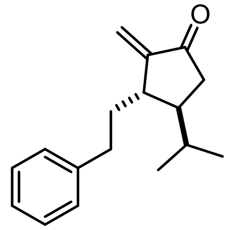
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 149.3, 117.4, 44.9, 44.2, 44.1, 39.6, 34.0, 32.8, 30.7, 24.0, 21.0, 18.4.

HRMS (EI) (*m/z*): calculated for $C_{13}H_{21}O_1Cl_1$ $[M]^+$: 228.1275; found 228.1277.

$[\alpha]_D^{25} = 15$ (c = 0.55, $CDCl_3$)

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 350 °C (detector), 80 °C (Oven, 3 min, iso) to 150 °C (20 °C/min, 5 min iso) to 180 °C (15 °C/min, 20 min iso); Gas: H_2 (0.5 bar); t_R = 24.94 min (minor), t_R = 25.67 min (major), e.r. = 6:94.

(3*S*,4*S*)-4-isopropyl-2-methylene-3-phenethylcyclopentan-1-one (**2k**)



Divinyl ketone **1k** (48 mg, 0.18 mmol) was subjected to the general procedure. 5 Å molecular sieves were used. After 15 days, the reaction had reached 93% conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (77%). The regioisomeric ratio was 12:1. The residue was purified by chromatography on silica-gel to afford **2k** (35 mg, 0.13 mmol, 72%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.24 (m, 2H), 7.23–7.16 (m, 3H), 6.07 (d, *J* = 2.2 Hz, 1H), 5.31 (dd, *J* = 2.3, 0.9 Hz, 1H), 2.77–2.59 (m, 3H), 2.45 (dd, *J* = 18.7, 8.6 Hz, 1H), 2.20 (dd, *J* = 18.8, 5.9 Hz, 1H), 1.90 (m, 1H), 1.83 (ddd, *J* = 14.0, 7.0, 3.5 Hz, 1H), 1.75 (pd, *J* = 6.8, 5.4 Hz, 1H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H).

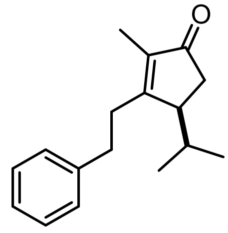
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 149.3, 142.0, 128.6, 128.5, 126.1, 117.4, 44.3, 44.0, 39.5, 36.5, 33.1, 30.7, 21.0, 18.3.

$[\alpha]_D^{25} = 15$ ($c = 0.53$, $CHCl_3$)

HRMS (EI) (*m/z*): calculated for $C_{17}H_{22}O_1$ $[M]^+$: 242.1665; found 242.1665.

HPLC: AD-3R, Acetonitrile/water = 50/50, 1 mL/min, 25 °C, 220 nm, t_R (minor) = 21.91 min; t_R (major) = 40.97 min, e.r. = 7:93

(*S*)-4-isopropyl-2-methyl-3-phenethylcyclopent-2-en-1-one (**3k**)



The ^{1}H NMR yield of regioisomer **3k** is 6 %. After purification, ca 1 mg (isolated yield: 2 %) colorless **3k** product was obtained.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.24–7.16 (m, 3H), 2.93–2.81 (m, 2H), 2.84–2.77 (m, 1H), 2.73 (ddd, *J* = 12.5, 9.1, 6.1 Hz, 1H), 2.56 (ddd, *J* = 13.9, 9.0, 5.5 Hz, 1H), 2.24 (dd, *J* = 18.8, 6.6 Hz, 1H), 2.24–2.15 (m, 1H), 2.13 (dd, *J* = 18.8, 2.3 Hz, 1H), 1.64–1.60 (m,3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.59 (d, *J* = 6.9 Hz, 3H).

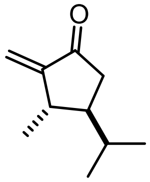
^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 174.4, 140.8, 137.6, 128.5, 128.2, 126.4, 45.9, 34.8, 33.4, 30.6, 27.7, 21.8, 14.8, 7.9.

HRMS (EI) (*m*/*z*): calculated for $C_{17}H_{22}O_1$ $[M]^+$: 242.1665; found 242.1666.

$[\alpha]_D^{25}$ = –84 (*c* = 0.1, $CDCl_3$)

HPLC: AS-H, *iso*propanol/heptane = 2/98, 1 mL/min, 25 °C, 229 nm, t_R (major) = 22.07 min; t_R (minor) = 28.68 min, e.r. = 98:2

(3*S*,4*S*)-4-isopropyl-3-methyl-2-methylenecyclopentan-1-one (**2l**)



Divinyl ketone **1l** was subjected to the general procedure. 5 Å molecular sieves were used. After 3.5 days, the reaction had reached full conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (66%). The regiomeric ratio was > 20:1.(Note: the product is volatile.)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 3.2, 0.9 Hz, 1H), 5.20 (dd, *J* = 2.8, 0.9 Hz, 1H), 2.54 (ddt, *J* = 9.6, 6.3, 3.1 Hz, 1H), 2.36 (dd, *J* = 18.2, 7.8 Hz, 1H), 2.09 (dd, *J* = 18.3, 10.9 Hz, 1H), 1.95–1.85 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

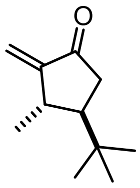
^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 151.4, 116.1, 47.8, 39.2, 39.0, 28.7, 21.8, 18.2, 17.2.

HRMS (EI) (*m*/*z*): calculated for $C_{10}H_{16}O_1$ $[M]^+$: 152.1197; found 152.1194.

$[\alpha]_D^{25}$ = –55.2 (*c* = 0.5, $CDCl_3$)

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm).Temperature: 350 °C (detector), 100 °C (oven, 40 min, iso) to 230 °C (15 °C/min, 10 min iso); Gas: H_2 (0.5 bar); t_R = 23.05 min (minor), t_R = 25.36 min (major), e.r. = 5:95.

(3*S*,4*R*)-4-(tert-butyl)-3-methyl-2-methylenecyclopentan-1-one (**2m**)



Divinyl ketone **1m** (33 mg, 0.2 mmol) was subjected to the general procedure. 4 Å molecular sieves were used. After 13 days, the reaction had reached full conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (72 %). The regioisomeric ratio was >20:1. (Note: the product is volatile.)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (dd, *J* = 2.7, 0.9 Hz, 1H), 5.23 (dd, *J* = 2.4, 0.9 Hz, 1H), 2.76 (t, *J* = 1.2 Hz, 1H), 2.46 (ddd, *J* = 19.2, 9.2, 1.0 Hz, 1H), 2.26 (dd, *J* = 19.2, 7.1 Hz, 1H), 1.66 (ddd, *J* = 9.2, 7.1, 5.7 Hz, 1H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H).

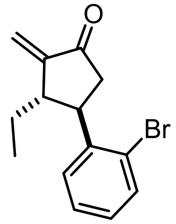
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 151.7, 116.9, 51.2, 40.0, 37. 3, 33.3, 27.8, 23. 1.

HRMS (ESI) (*m*/*z*): calculated for $C_{11}H_{19}O_1$ $[M+H]^+$ 167.1430; found 167.1432.

$[\alpha]_D^{25}$ = 1.2 (*c* = 0.66, $CDCl_3$)

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 350 °C (detector), 80 °C (oven, 3 min, iso) to 130 °C (15 °C/min, 27 min iso); Gas: H_2 (0.5 bar); t_R = 13.46 min (minor), t_R = 14.73 min (major), e.r. = 3:97.

(3*S*,4*R*)-4-(2-bromophenyl)-3-ethyl-2-methylenecyclopentan-1-one (**2n**)



Divinyl ketone **1n** (56 mg, 0.2 mmol) was subjected to the general procedure. 4 Å molecular sieves were used. After 5 days, the reaction had reached 97% conversion. ^{1}H NMR yield of this mixture was measured with Ph_3CH as an internal standard (71%). The regioisomeric ratio was >20:1. The residue was purified by chromatography on silica-gel to afford **2n** (29 mg, 0.103 mmol, 53%). The isolated yield was poor due to a technical mistake.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.28 (td, *J* = 7.6, 1.4 Hz, 1H), 7.19 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.13–7.04 (m, 1H), 6.16 (dd, *J* = 2.8, 0.9 Hz, 1H), 5.33 (dd, *J* = 2.4, 0.9 Hz, 1H), 3.65 (q, *J* = 7.8 Hz, 1H), 2.94–2.83 (m, 2H), 2.38 (dd, *J* = 18.6, 7.9 Hz, 1H), 1.75 (dtd, *J* = 14.9, 7.4, 5.7 Hz, 1H), 1.65 (dt, *J* = 14.1, 7.1 Hz, 1H), 0.92 (t, *J* = 7.4 Hz, 3H).

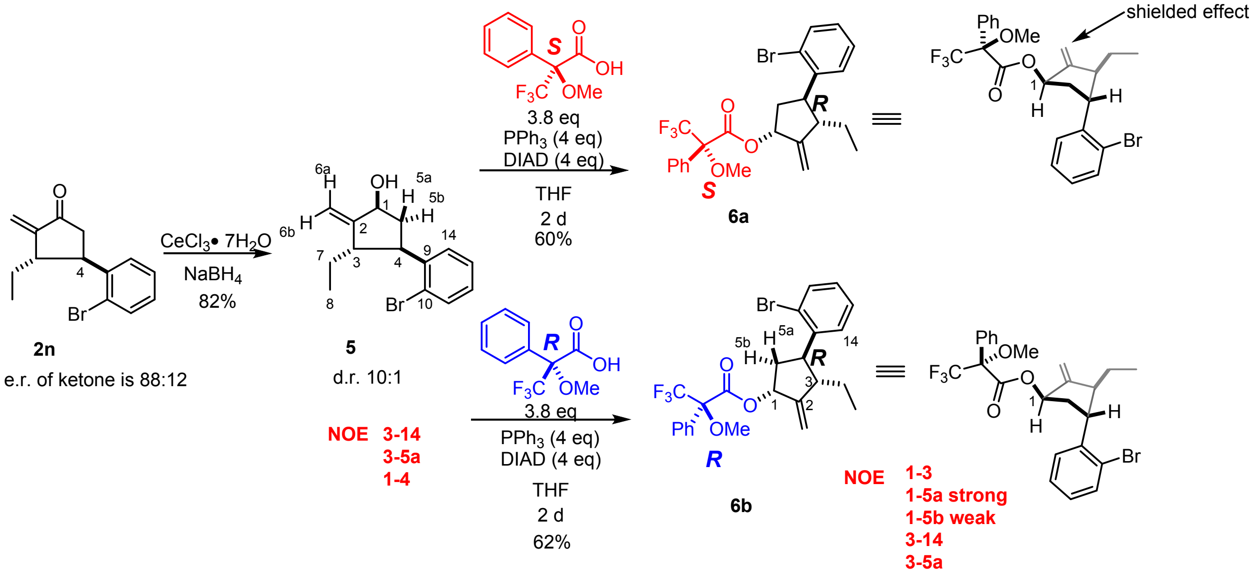
^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 147.7, 142.8, 133.3, 128.3, 128.1, 127.2, 125.2, 118.3, 49.4, 44.8, 43.1, 25.9, 11.2.

HRMS (EI) (*m*/*z*): calculated for $C_{14}H_{15}O_1Br_1$ $[M]^+$: 278.0301; found 278.0303.

$[\alpha]_D^{25}$ = –16 (*c* = 0.44, CHCl3)

HPLC: AS-H, *iso*propanol/heptane = 1.3/98.7, 0.8 mL/min, 25 °C, 230 nm, t_R (minor) = 13.84 min; t_R (major) = 15.34 min, e.r. = 12:88

Determination[5] of the absolute configuration of enone 2n

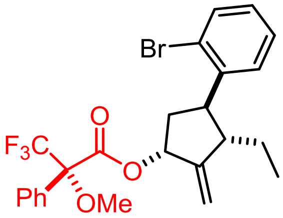


Scheme 3. Preparation of Mosher's ester **6a** and **6b**

Experimental: To a solution of **2n** (18 mg, 0.065 mmol) in MeOH (1 mL) was added $CeCl_3$• $7H_2O$ (24 mg, 0.065 mmol, 1 equiv). The mixture was cooled to 0 °C and $NaBH_4$ (2.4 mg, 0.065 mmol, 1 equiv) was added. The reaction was stirred until the starting material was consumed (as monitored by TLC) and subsequently quenched with water (1 mL) followed by dilution with diethyl ether (5 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified by column chromatography to give **5** (15 mg, 82%) following removal of the solvent under reduced pressure. To a solution of **5** (7.5 mg, 0.027 mmol) in dry THF (0.5 mL) was added triphenylphosphine (26.9 mg, 0.12 mmol, 4.5 equiv) and *S*–Mosher's acid (25 mg, 0.11 mmol, 4 equiv). The reaction mixture was cooled to 0 °C, and to this solution diisopropyl azodicarboxylate (DIAD, 24 mg, 0.12 mmol, 4 equiv) was added dropwise. The mixture was then allowed to warm to room temperature and was stirred for 2 days. The volatiles were then removed *in vacuo*. A crude ^1H NMR of resulting residue was performed, and the mixture was purified by column on silica-gel to give *S*–Mosher's ester **6a** (8 mg, 0.016 mmol, 60%, d.r. 7:1 from 76% e.e. of **2n**).

The *R*–Mosher's ester **6b** was prepared by similar procedure (8.2 mg, 0.017 mmol, 62 %).

S–Mosher's ester **6a**



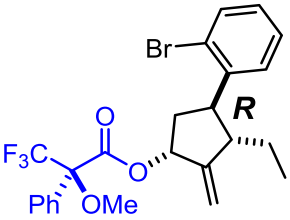
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.53 (m, 2H), 7.43–7.37 (m, 3H), 7.31–7.20 (m, 3H), 7.07 (t, *J* = 1.0 Hz, 1H), 5.86 (dd, *J* = 5.4, 1.4 Hz, 1H), 5.47 (dd, *J* = 2.7, 1.0 Hz, 1H), 5.19 (dd, *J* = 2.4, 1.1 Hz, 1H), 3.67 (ddt, *J* = 13.4, 10.2, 6.7 Hz, 1H), 3.59 (s, 3H), 2.68 (dtd, *J* = 9.2, 5.8, 2.7 Hz, 1H), 2.33 (ddd, *J* = 14.2, 6.7, 1.5 Hz, 1H), 1.91 (ddd, *J* = 14.1, 11.3, 5.5 Hz, 1H), 1.59–1.48 (m, 2H), 0.72 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 151.3, 142.5, 133.0, 129.5, 128.4, 127.9, 127.8, 127.5, 125.2, 114.3, 79.0, 50.4, 46.5, 40.1, 30.3, 29.7, 25.4, 10.64.

^{19}F NMR (470 MHz, $CDCl_3$) δ –71.62.

HRMS (ESI) (*m*/*z*): calculated for $C_{24}H_{24}O_3F_3Br_1Na_1$ $[M+Na]^+$: 519.0753; found 519.0756.

R–Mosher's ester **6b**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2H), 7.54 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.44–7.36 (m, 3H), 7.30–7.14 (m, 1H), 7.06 (ddd, *J* = 8.0, 6.9, 2.0 Hz, 1H), 5.87 (dd, *J* = 5.5, 1.4 Hz, 1H), 5.52 (dd, *J* = 2.7, 1.0 Hz, 1H), 5.24 (dd, *J* = 2.4, 1.1 Hz, 1H), 3.71–3.60 (m, 1H), 3.57 (s, 3H), 2.76–2.60 (m, 1H), 2.25 (ddd, *J* = 14.1, 6.6, 1.6 Hz, 1H), 1.88 (ddd, *J* = 14.2, 11.2, 5.4 Hz, 1H), 1.61–1.56 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 3H).

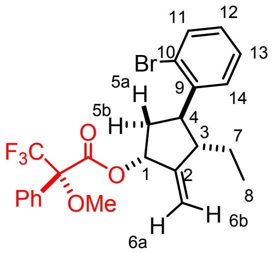
^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 151.6, 142.5, 133.0, 129.5, 128.4, 127.9, 127.7, 127.5, 127.4, 125.3, 114.3, 79.1, 55.4, 50.5, 46.5, 40.1, 29.7, 25.4, 10.7.

^{19}F NMR (470 MHz, $CDCl_3$) δ –71.49.

HRMS (ESI) (*m*/*z*): calculated for $C_{24}H_{24}O_3F_3Br_1Na_1$ $[M+Na]^+$: 519.0753; found 519.0756.

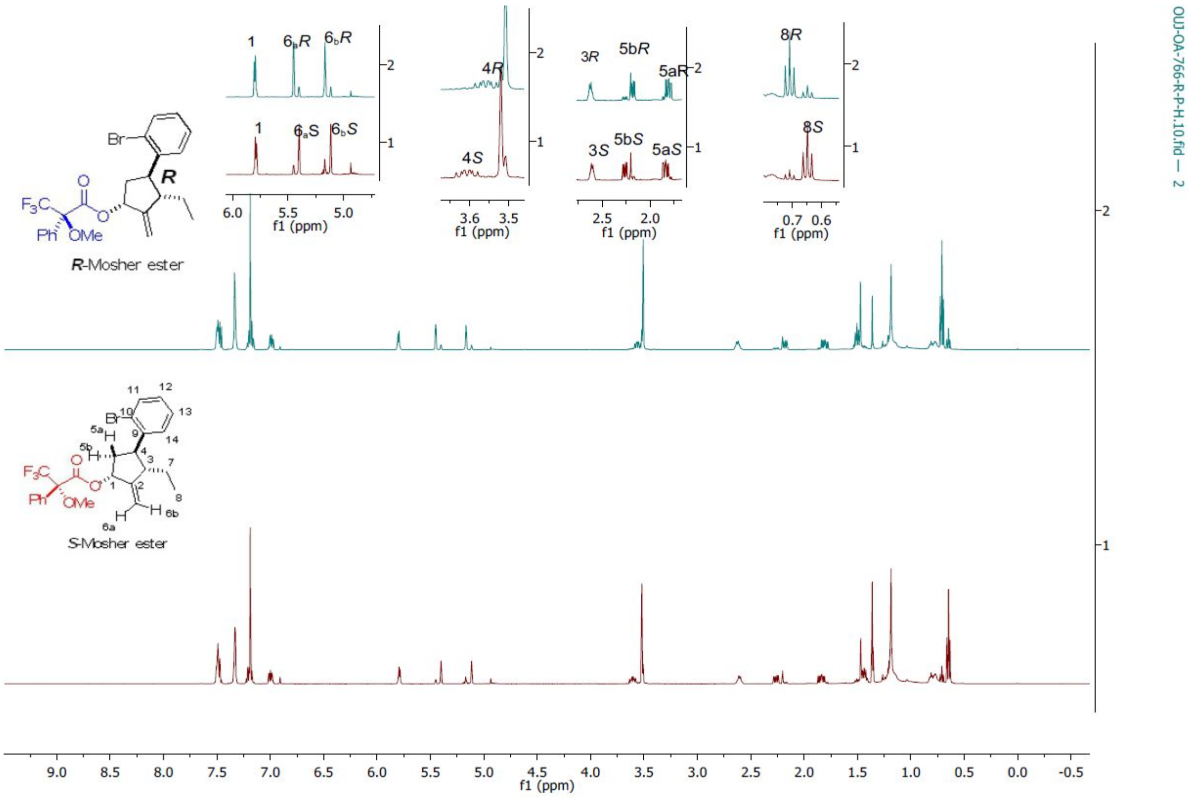
Table S3: Δδ (=δ$_{S}$–δ$_{R}$) data for the (*S*)- and (*R*)-MTPA (Mosher esters **6a** and **6b**)

	S-MTPA Ester **16a**	*R*-MTPA Ester **16b**	(*S*)-(*R*)
C6a	5.40	5.45	– 0.05
C6b	5.12	5.17	– 0.05
C3	2.60	2.62	– 0.02
C4	3.61	3.56	0.05
C5a	1.84	1.81	0.03
C5b	2.26	2.18	0.08
C8	0.65	0.71	– 0.06

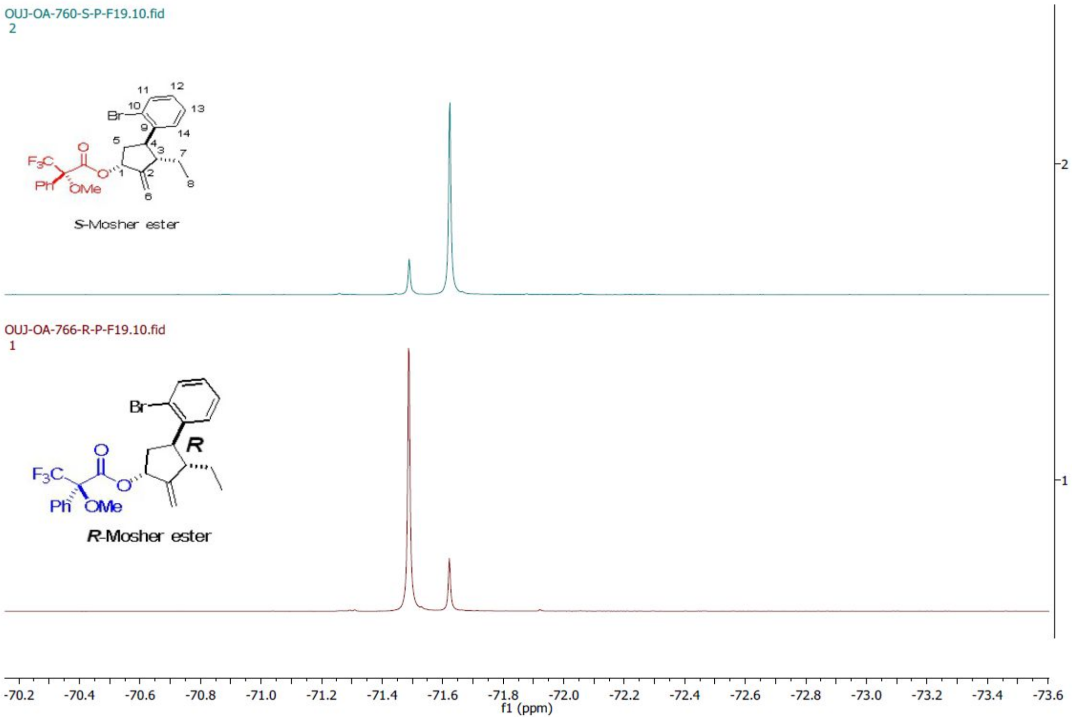


***S*-Mosher ester 6a**

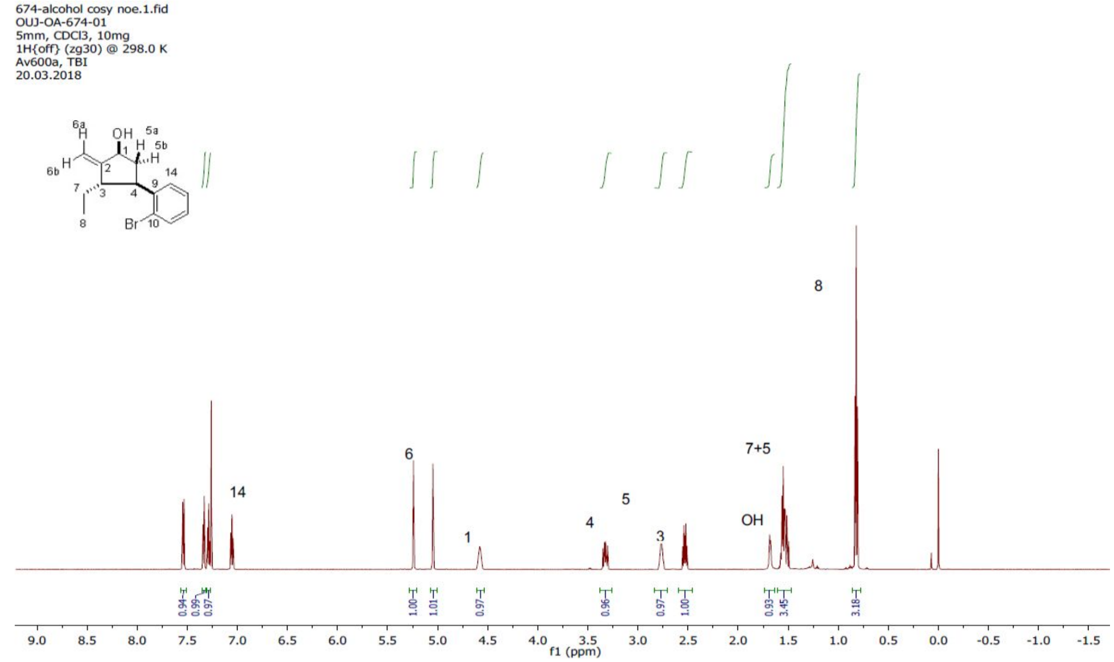
^{1}H NMR difference between (*S*)–MTPA ester and (*R*)–MTPA ester

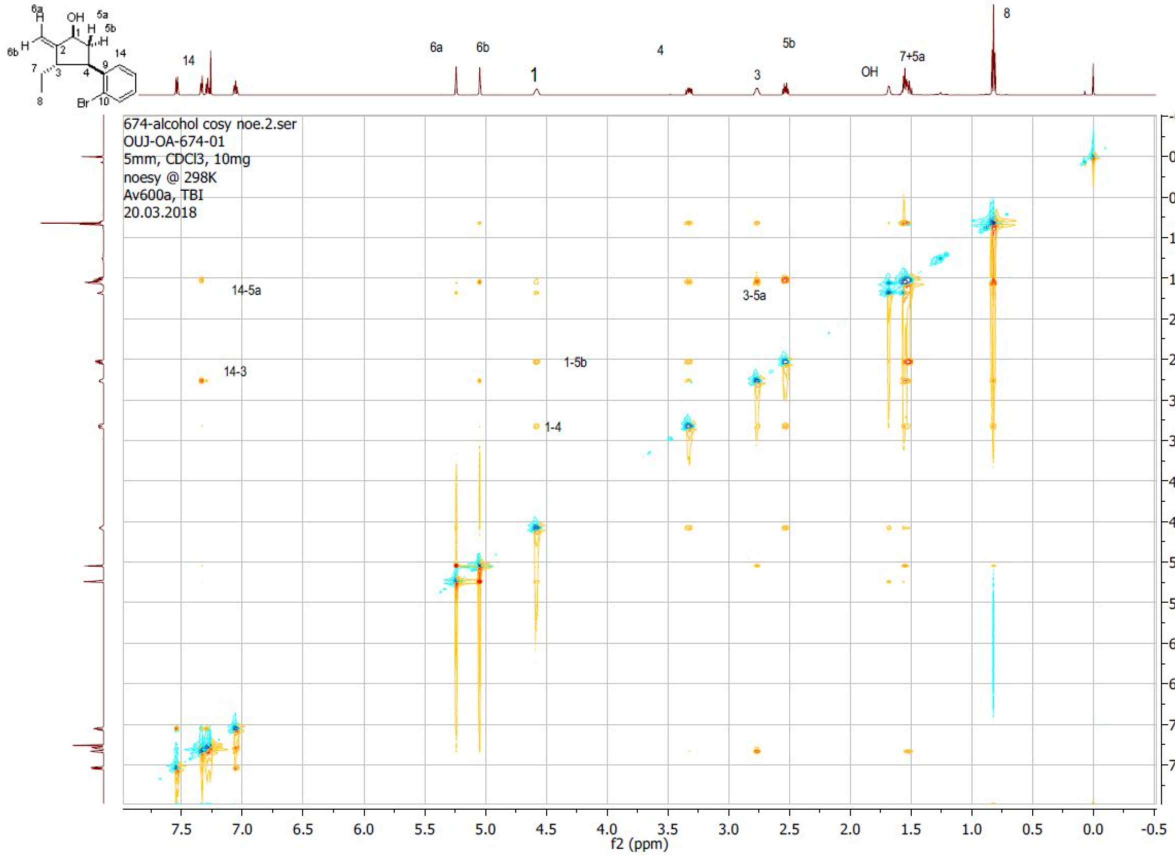


^{19}F NMR difference between (*S*)–MTPA ester and (*R*)–MTPA ester

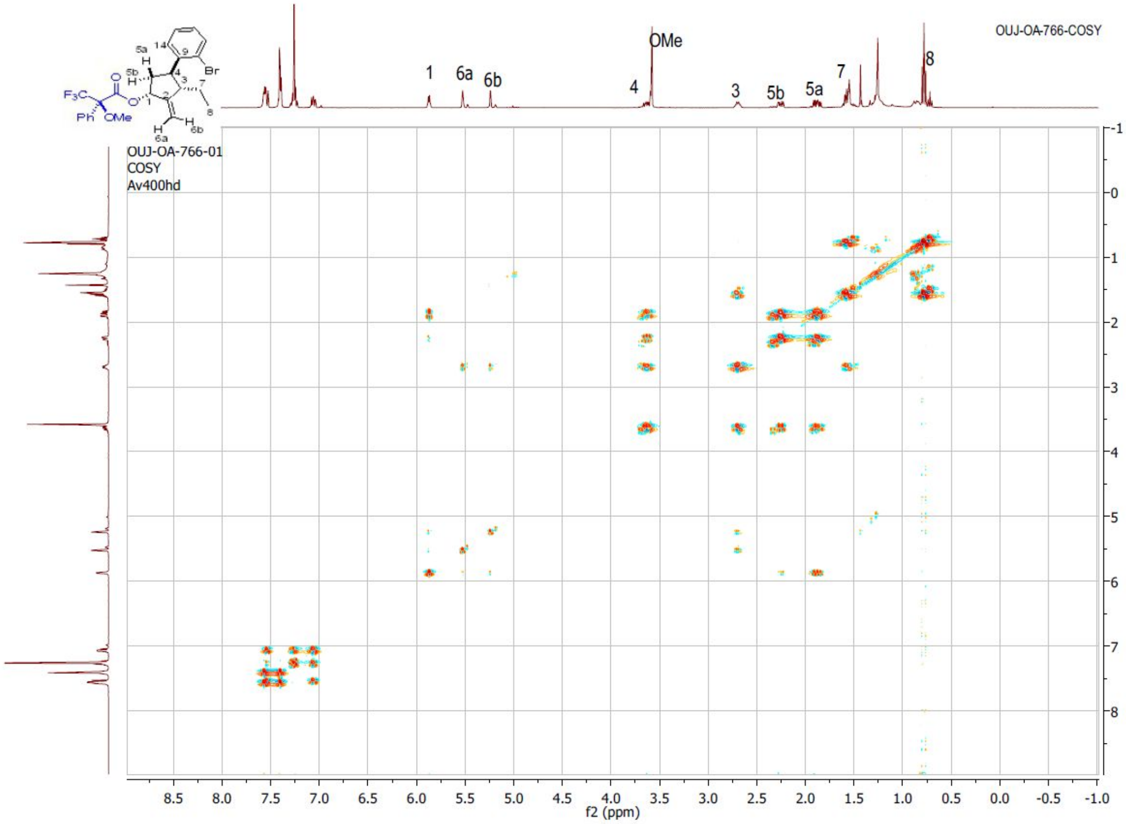


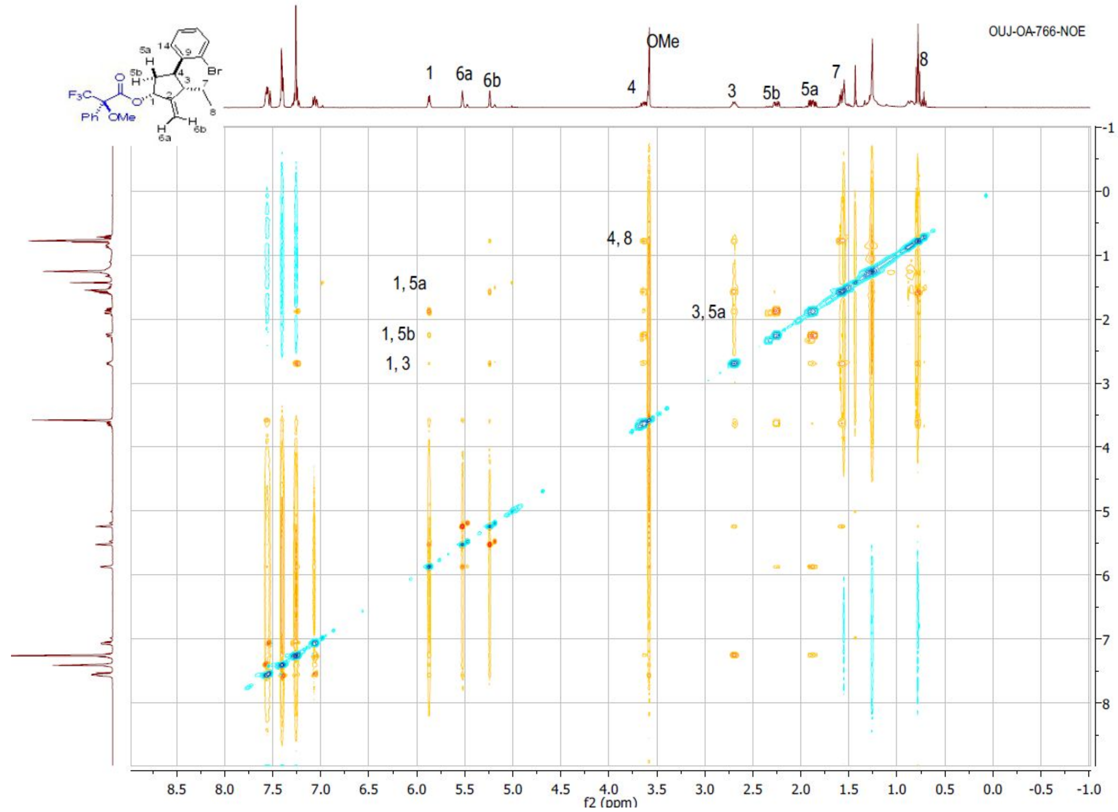
Alcohol **5** COSY and NOE



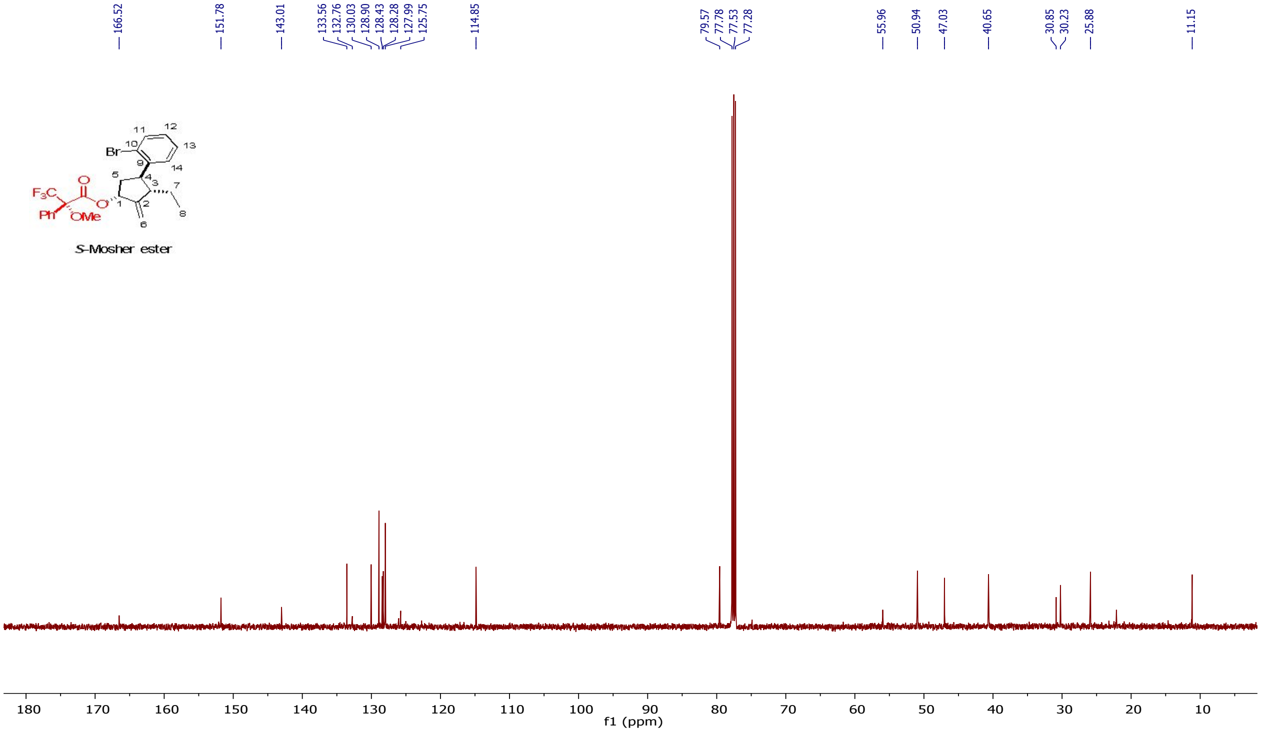


R–Mosher' ester **6b** H–H COSY and H–H NOESY

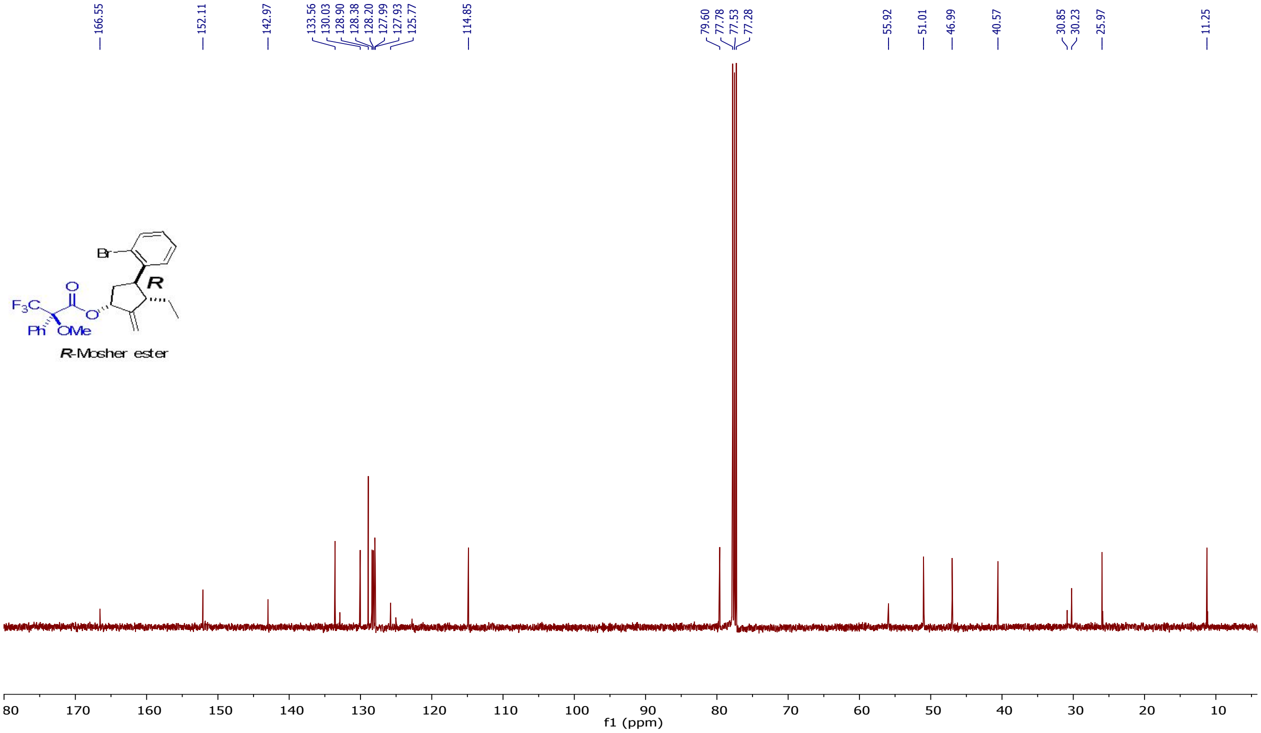




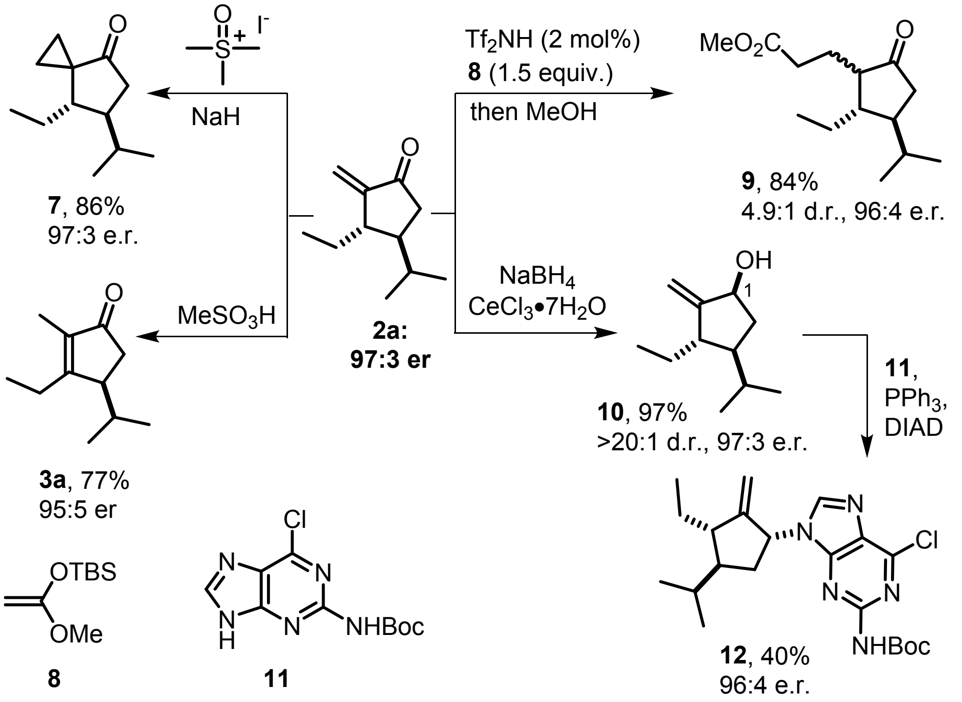
^{13}C NMR (125 MHz, CDCl$_3$) of **6a**



^{13}C NMR (125 MHz, CDCl$_3$) of **6b**

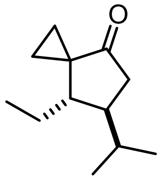


Functionalization of 2a



Scheme 4. Functionalization of **2a**

(6*S*,7*S*)-7-ethyl-6-isopropylspiro[2.4]heptan-4-one (**7**)



To a solution of trimethyloxosulfonium iodide (13 mg, 0.06 mmol) in dry THF (0.2 mL) was added NaH (60% mineral oil dispersion, 2.9 mg, 1.2 equiv) under Ar, followed by addition of anhydrous DMSO (0.4 mL). After stirring for nearly 30 min at room temperature, the mixture was clear and gas evolution had ceased. The mixture was cooled to 0 °C. After addition of a solution of **2c** (10 mg, 0.06 mmol) in DMSO (0.2 mL), the solution was warmed to room temperature with vigorous stirring for another 20 min and then quenched with NH_4Cl (sat. aq., 1 mL), followed by addition of diethyl ether (2 mL). The organic phase was separated and the aqueous layer was extracted with diethyl ether (3 x 5 mL). All organic portions were combined and washed with brine (3 x 5 mL) to remove DMSO, dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to give a colorless residue, which was further purified by flash chromatography on silica-gel to provide **7** (9.3 mg, 86%) .

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (dd, J = 18.6, 8.6 Hz, 1H), 2.14 (dd, J = 18.6, 5.7 Hz, 1H), 1.89 (dtd, J = 8.6, 5.7, 4.6 Hz, 1H), 1.79 (dt, J = 7.3, 5.1 Hz, 1H), 1.76–1.70 (m, 1H), 1.34–1.25

(m, 2H), 1.09 (ddd, *J* = 9.8, 6.9, 2.9 Hz, 1H), 1.05–1.00 (m, 1H), 0.95 (ddd, *J* = 9.3, 6.8, 3.7 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H), 0.78–0.69 (m, 1H).

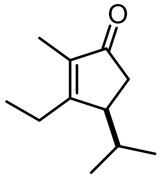
^{13}C NMR (125 MHz, $CDCl_3$) δ 220.1, 45.0, 45.0, 40.1, 34.2, 30.4, 25.6, 21.3, 20.3, 18.8, 14.1, 11.9.

$[\alpha]_D^{25} = 34.7$ (*c* = 0.45, $CDCl_3$)

HRMS (ESI) (*m/z*): calculated for $C_{12}H_{30}O_1Na_1$ [M+Na]$^+$ 203.1406; found 203.1407.

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm). Temperature: 350 °C (detector), 80 °C (oven, 3 min, iso) to 130 °C (15 °C/min, 27 min iso); Gas: H_2 (0.5 bar); t_R = 19.45 min (minor), t_R = 20.14 min (major), e.r. = 3:97.

(*S*)-3-ethyl-4-isopropyl-2-methylcyclopent-2-en-1-one (**3a**)



To a solution of **2a** (8.7 mg, 0.052 mmol) in anhydrous DCM (1 mL) was added methylsulfonic acid (18.5 mg, 0.19 mmol, 3.6 equiv) at room temperature. The solution was stirred for 3 h and then quenched with *N*,*N*-diisopropylethylamine (50 μL). The reaction mixture was directly purified by column chromatography on silica-gel (Et_2O: pentane=1:10 to 1:6) to give **3a** (6.7 mg, 77%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.80 (broad, 1H), 2.47 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.26–2.13 (m, 2H), 2.13–2.00 (m, 2H), 1.63 (d, *J* = 1.8 Hz, 3H), 1.04 (td, *J* = 7.7, 1.4 Hz, 3H), 0.93 (dd, *J* = 6.9, 1.4 Hz, 3H), 0.51 (dd, *J* = 6.9, 1.5 Hz, 3H).

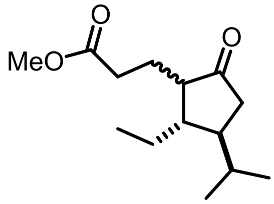
^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 177.3, 136.6, 45.7, 34.9, 27.7, 22.0, 14.9, 11.8, 8.0. (One missing carbon overlapped at 22.0 ppm)

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25mm). Temperature: 350 °C (detector), 80 °C (oven, 3 min, iso) to 130 °C (15 °C/min, 27 min iso); Gas: H_2 (0.5 bar); t_R = 17.00 min (minor), t_R = 18.71 min (major), e.r. = 5:95.

HRMS (EI) (*m/z*): calculated for $C_{11}H_{18}O_1$ [M]$^+$ 166.1352; found 166.1355.

$[\alpha]_D^{25} = 9.5$ (*c* = 0.4, $CDCl_3$)

Methyl 3-((2*S*,3*S*)-2-ethyl-3-isopropyl-5-oxocyclopentyl)propanoate (**9**)



To a solution of **2a** (13 mg, 0.078 mmol) in dry Et_2O was added silyl ketene acetal **8** (22 mg, 0.12 mmol, 1.5 equiv) under Ar. After cooling the solution to –78 °C, Tf_2NH (0.1 M in $CHCl_3$, 16 μL, 2 mol%) was added. The mixture stirred for 10 min at this temperature and was then quenched with MeOH (0.5 mL), and concentrated at 35 °C to afford a colorless residue, which was purified by column on silica-gel to afford **9** (16 mg, 84%, d.r. 83:17).

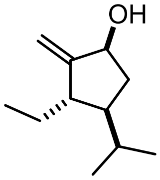
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.55 (ddd, *J* = 16.2, 9.0, 5.7 Hz, 1H), 2.44 (ddd, *J* = 16.1, 8.9, 6.9 Hz, 1H), 2.30–2.21 (m, 1H), 1.99–1.84 (m, 3H), 1.82–1.71 (m, 1H), 1.68–1.51 (m, 3H), 0.97–0.90 (m, 8H), 0.82 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.7, 172.9, 52.7, 52.0, 44.8, 44.3, 39.2, 31.2, 28.0, 26.1, 25.0, 23.8, 22.6, 16.7.

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (C-DEXTRIN H G632: 25.0 m; i.D. 0.25 mm).Temperature: 230 °C (injector), 350 °C (detector), 100 °C (0.3 min, iso) to 150 °C (9 min iso); Gas: H_2 (0.4 bar); for major diastereoisomer t_R = 85.13 min (minor), t_R = 86.85 min (major), e.r. = 4:96, for minor diastereoisomer t_R = 90.04 min (minor), t_R = 90.54 min (major), e.r. = 4:96.

HRMS (ESI) (*m*/*z*): calculated for $C_{14}H_{24}O_3Na_1$ $[M+Na]^+$ 263.1617; found 263.1619.

(1*S*,3*S*,4*S*)-3-ethyl-4-isopropyl-2-methylenecyclopentan-1-ol (**10**)



To a solution of **2a** (15 mg, 0.09 mmol) in MeOH (1 mL) was added $CeCl_3•7H_2O$ (33.6 mg, 0.09 mmol, 1 equiv). The solution was cooled in a dry ice bath for 10 min, and then $NaBH_4$ (4 mg, 0.11 mmol, 1.2 equiv) was added. The mixture was stirred for 20 min until the **2a** was consumed (as monitored by TLC) and was then quenched with water (1 mL) and diluted with diethyl ether (5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 3 mL). All organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography to afford **10** (15 mg, 97%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (s, 1H), 4.87 (d, *J* = 2.2 Hz, 1H), 4.44–4.35 (m, 1H), 2.21 (dtq, *J* = 7.0, 4.1, 2.1 Hz, 1H), 2.16 (dt, *J* = 11.9, 6.9 Hz, 1H), 1.67–1.48 (m, 2H, OH), 1.45–1.32

(m, 2H), 1.14 (q, *J* = 11.0 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H).

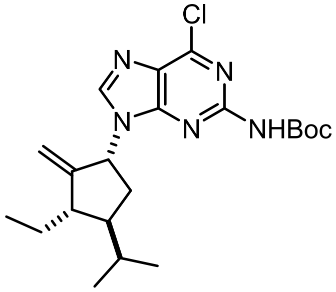
^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 105.1, 74.5, 46.9, 45.8, 38.2, 31.9, 28.2, 21.8, 19.2, 11.1.

HRMS (EI) (*m*/*z*): calculated for $C_{11}H_{20}O_1$ $[M]^+$ 168.1508; found 168.1508.

$[\alpha]_D^{25}$ = 64 (*c* = 0.5, $CDCl_3$)

GC: The enantiomeric ratio was measured by GC analysis on a chiral column (BGB 176 column: 25.0 m; i.D. 0.25 mm).Temperature: 350 °C (detector), 80 °C (oven, 3 min, iso) to 105 °C (15 °C/min, 40 min iso); Gas: H_2 (0.5 bar); t_R = 45.31 min (minor), t_R = 46.41 min (major), e.r. = 3:97.

Tert-butyl(6-chloro-9-((1*R*,3*S*,4*S*)-3-ethyl-4-isopropyl-2-methylenecyclopentyl)-9H-purin-2-yl)carbamate (**12**)



To a solution of **10** (15 mg, 0.089 mmol) in dry THF (1 mL) was added triphenylphosphine (108 mg, 0.41 mmol, 4.5 equiv) and *tert*-butyl (6-chloro-9H-purin-2-yl)carbamate (**11**, 29 mg, 0.11 mmol, 1.2 equiv) under Ar. The reaction mixture was cooled in an ice-water bath, and then diisopropyl azodicarboxylate (72 mg, 0.36 mmol, 4 equiv) was added. The reaction mixture was stirred for 15 min and warmed to room temperature until **10** was consumed (as monitored by TLC). Subsequently, the mixture was concentrated *in vacuo* and directly purified by column chromatography (ALOX, EtOAc: isohexane= 1:4) to afford **12** (15 mg, 40%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.44 (s, 1H), 5.50–5.37 (m, 1H), 5.16 (t, *J* = 2.3 Hz, 1H), 4.86 (t, *J* = 2.4 Hz, 1H), 2.38 (tq, *J* = 5.9, 3.0, 2.3 Hz, 1H), 2.20 (ddd, *J* = 13.7, 8.4, 6.6 Hz, 1H), 2.03 (dt, *J* = 14.0, 7.4 Hz, 1H), 1.83 (p, *J* = 6.8 Hz, 1H), 1.75 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.71–1.61 (m, 2H), 1.54 (s, 9H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (12 MHz, $CDCl_3$) δ 153.4, 153.3, 152.4, 151.2, 150.3, 143.3, 128.0, 125.7, 110.9, 81.7, 57.3, 47.4, 33.6, 30.5, 29.6, 26.1, 21.7, 18.6, 11.3.

$[\alpha]_D^{25}$ = –18.9 (*c* = 0.75, DCM)

HPLC: AD-3, isopropanol/heptane = 1.5/98.5, 1.1 mL/min, 25 °C, 289 nm, t_R (major) = 20.26 min; t_R (minor) = 30.23 min, e.r. = 96:4

HRMS (ESI) (*m*/*z*): calculated for $C_{21}H_{31}N_5O_2Cl_1$ $[M+H]^+$ 420.2161; found 420.2161.

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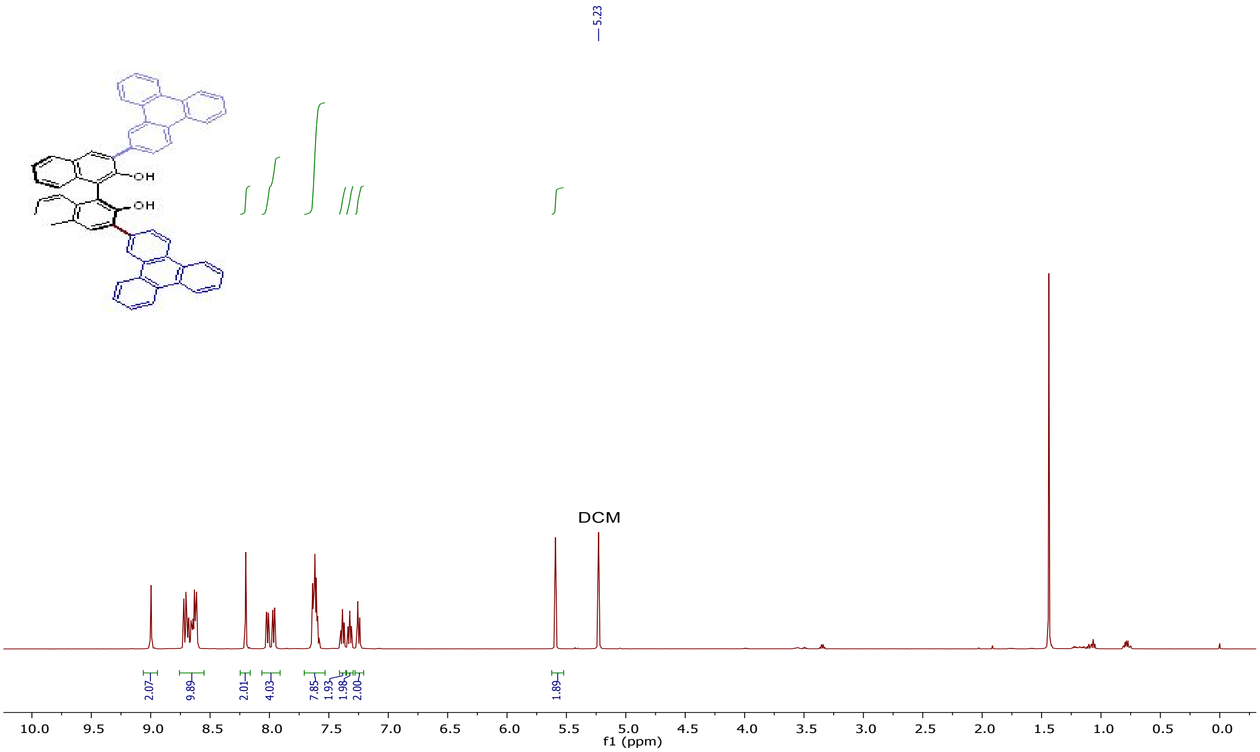
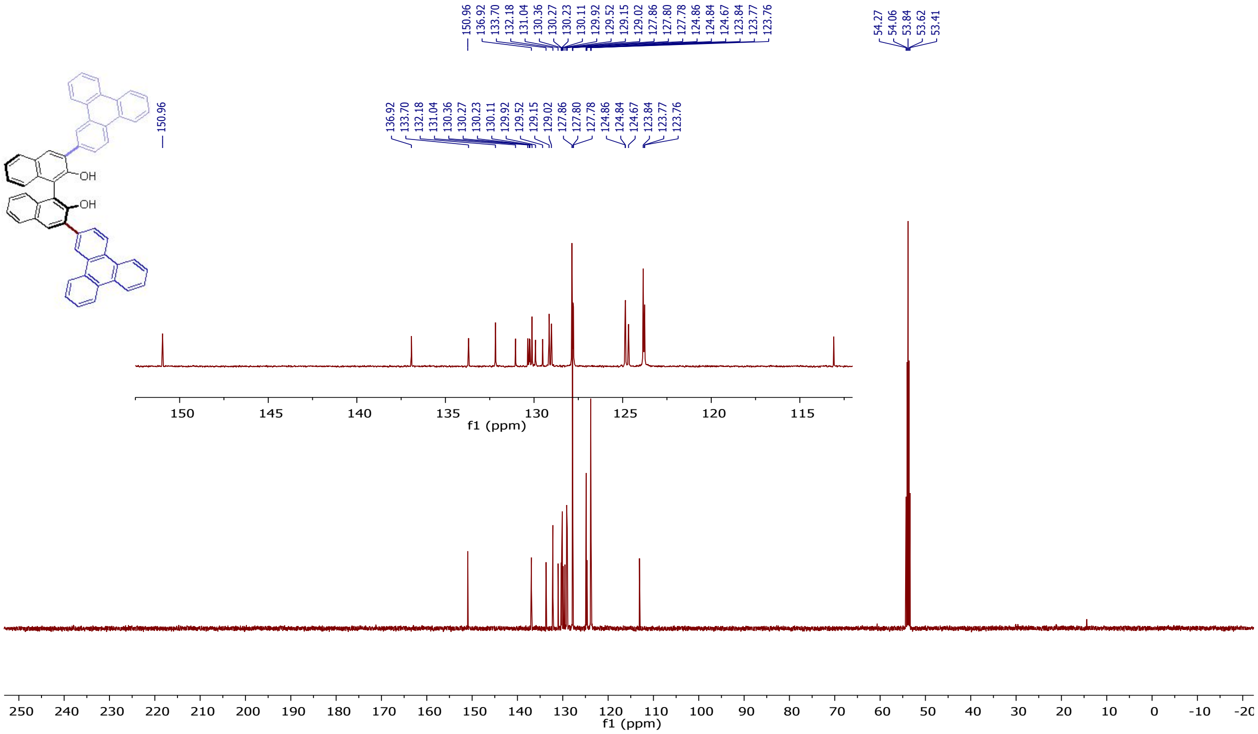
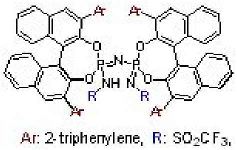
NMR spectra

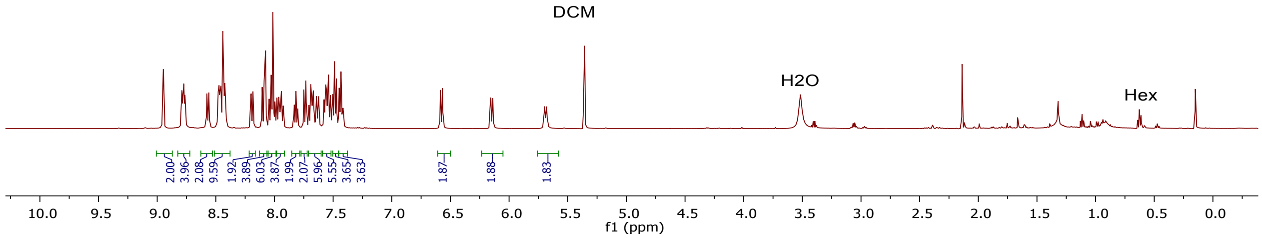
^{1}H NMR (500 MHz, CD_2Cl_2) and **^{13}C NMR** (125 MHz, CD_2Cl_2) of diol

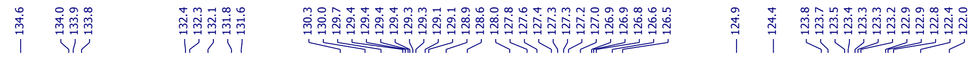


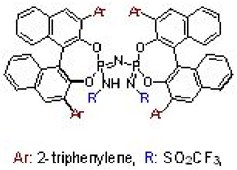


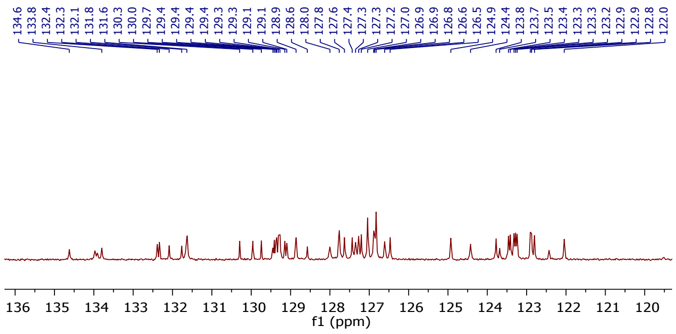
^{1}H **NMR** (500 MHz, CD_2Cl_2) and ^{13}**C NMR** (125 MHz, CD_2Cl_2) of catalyst **4e**

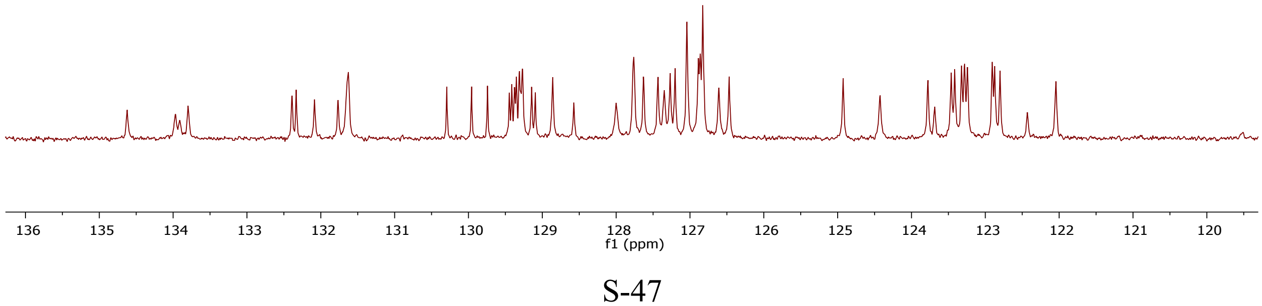




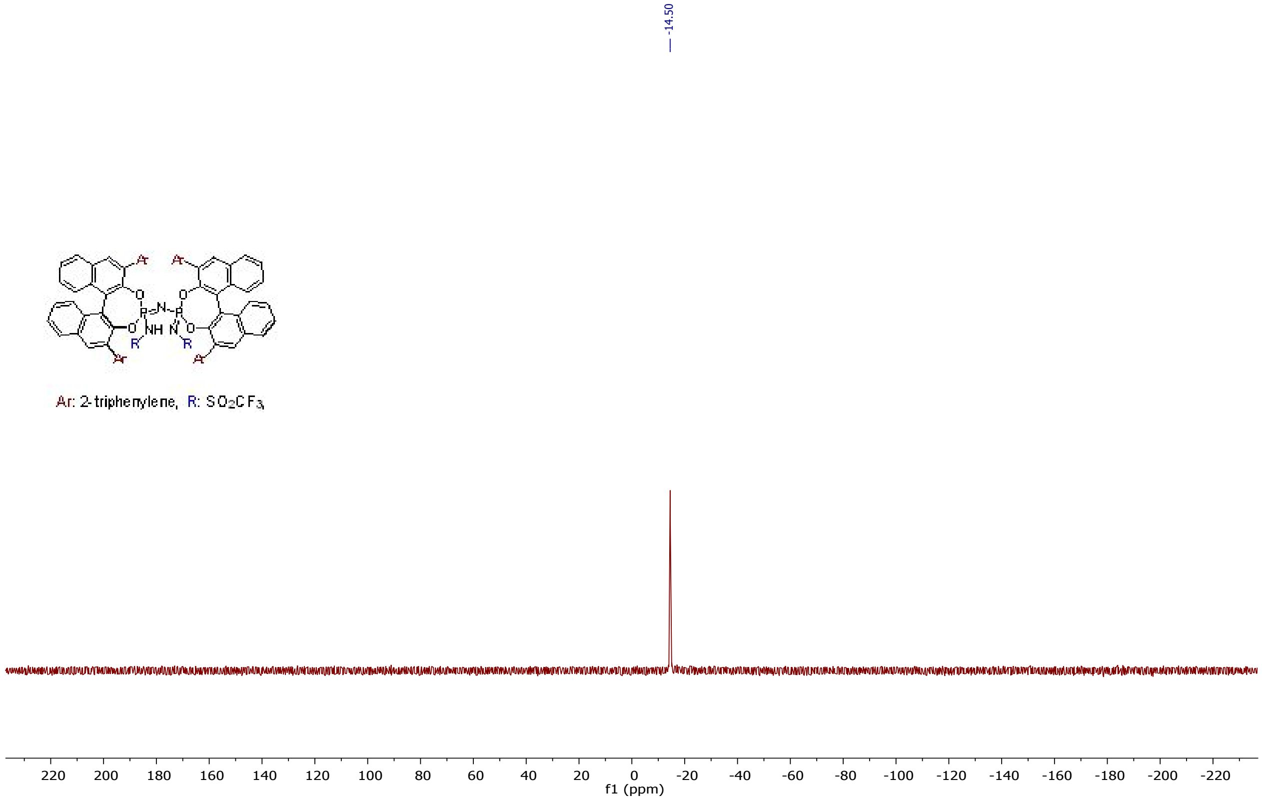


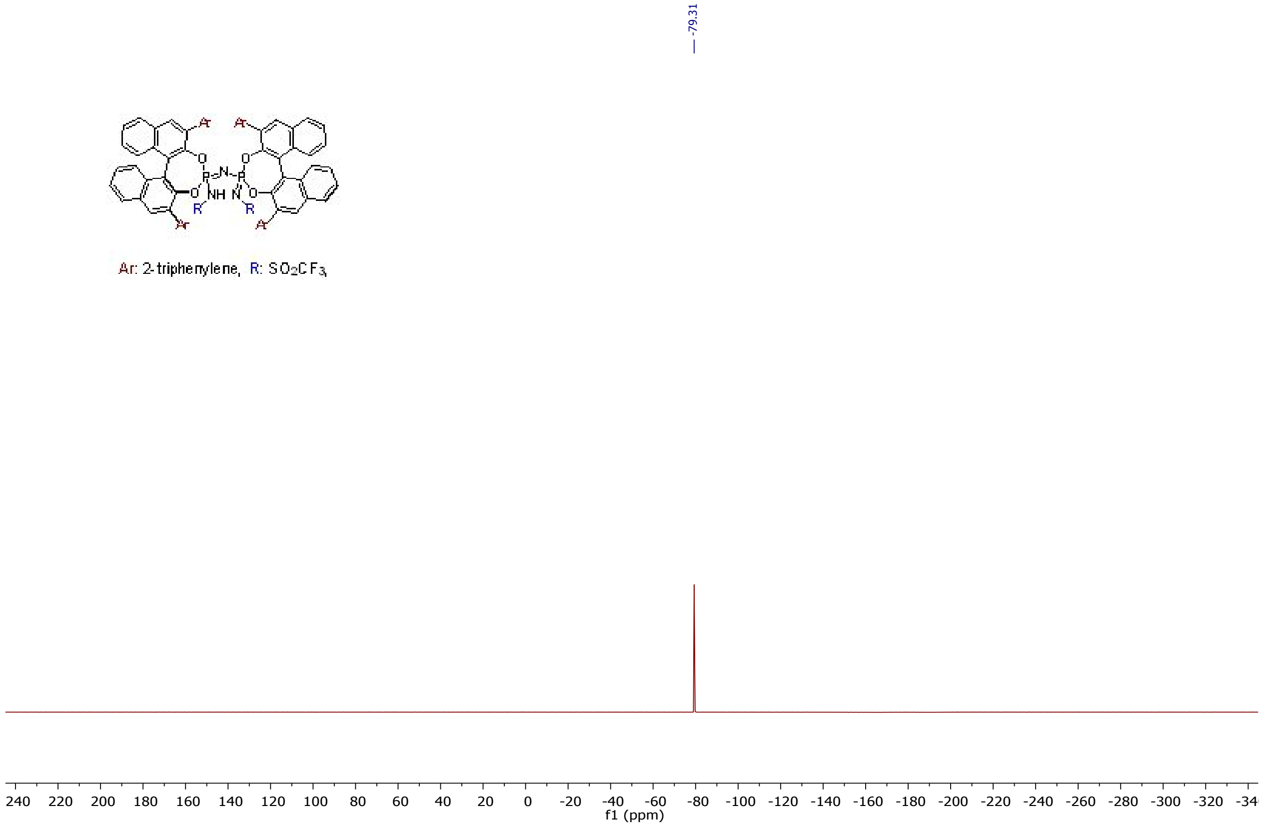




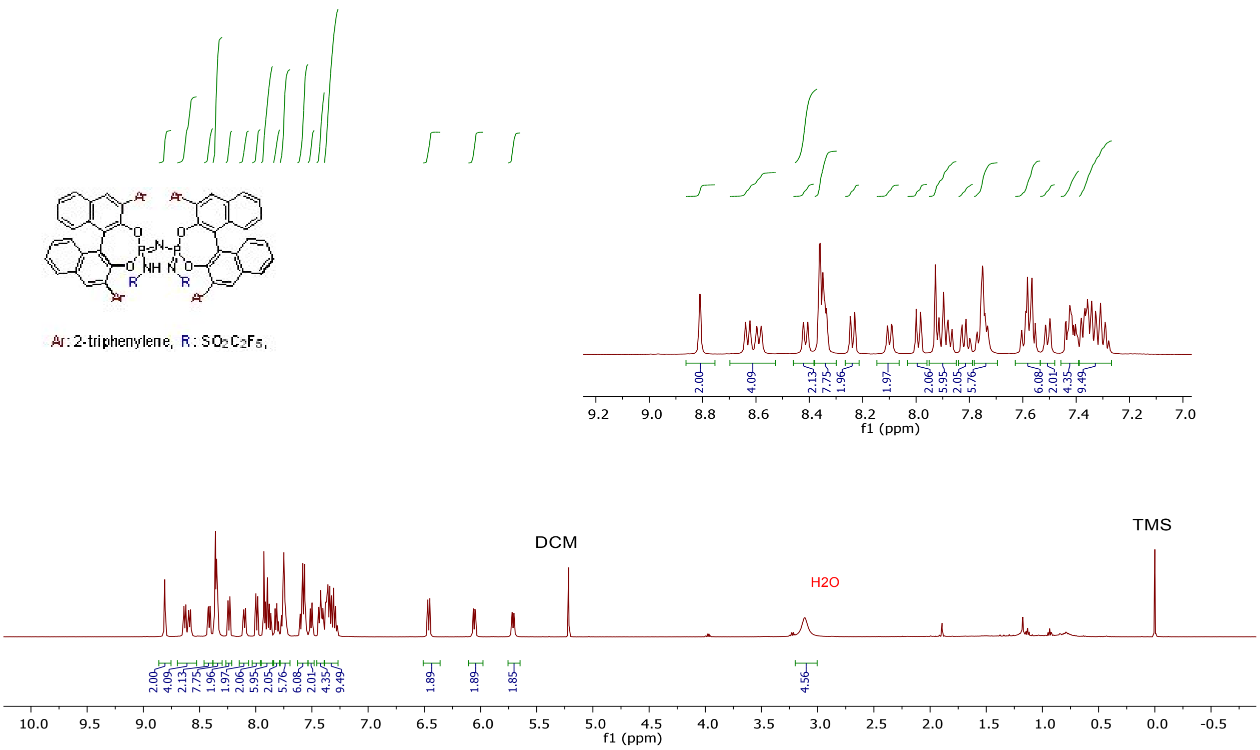


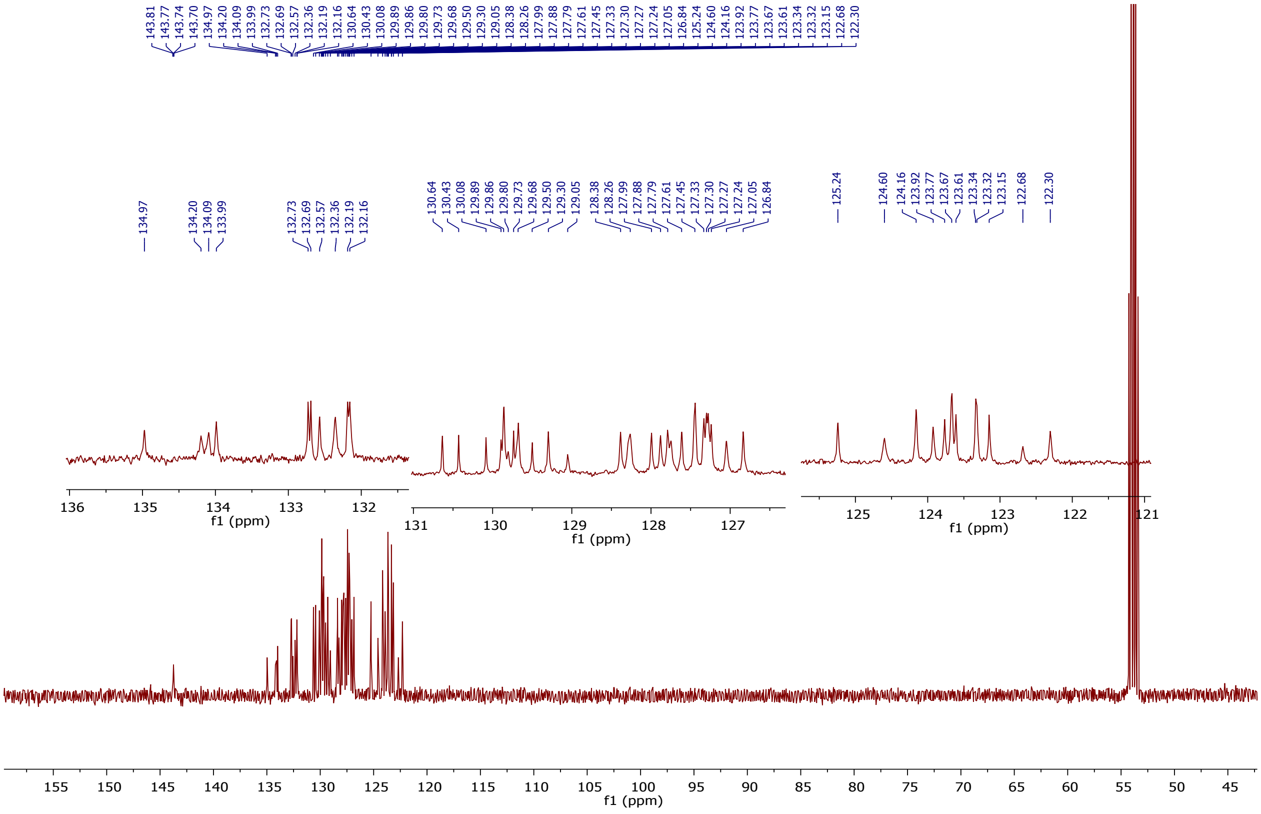
^{31}P NMR (203 MHz, CD_2Cl_2) and **^{19}F NMR** (470 MHz, CD_2Cl_2) of catalyst **4e**



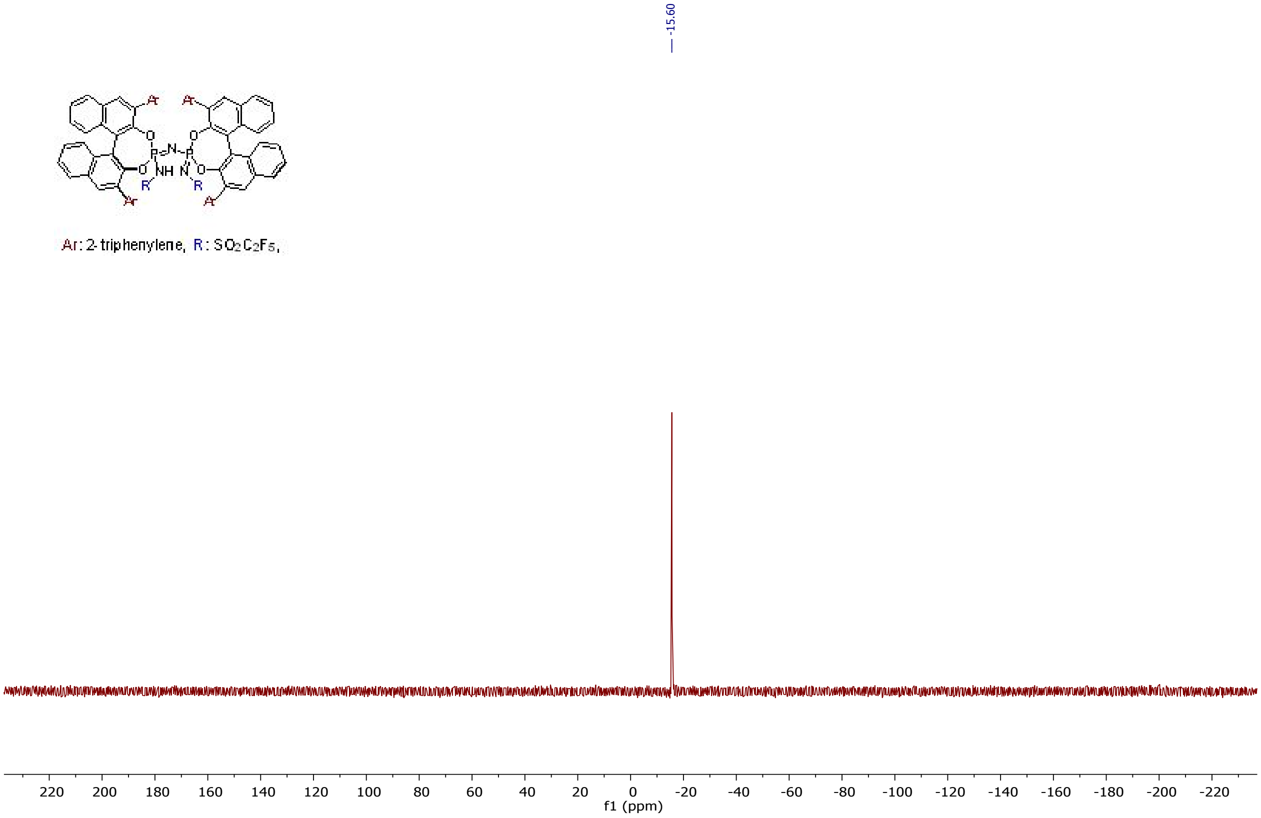


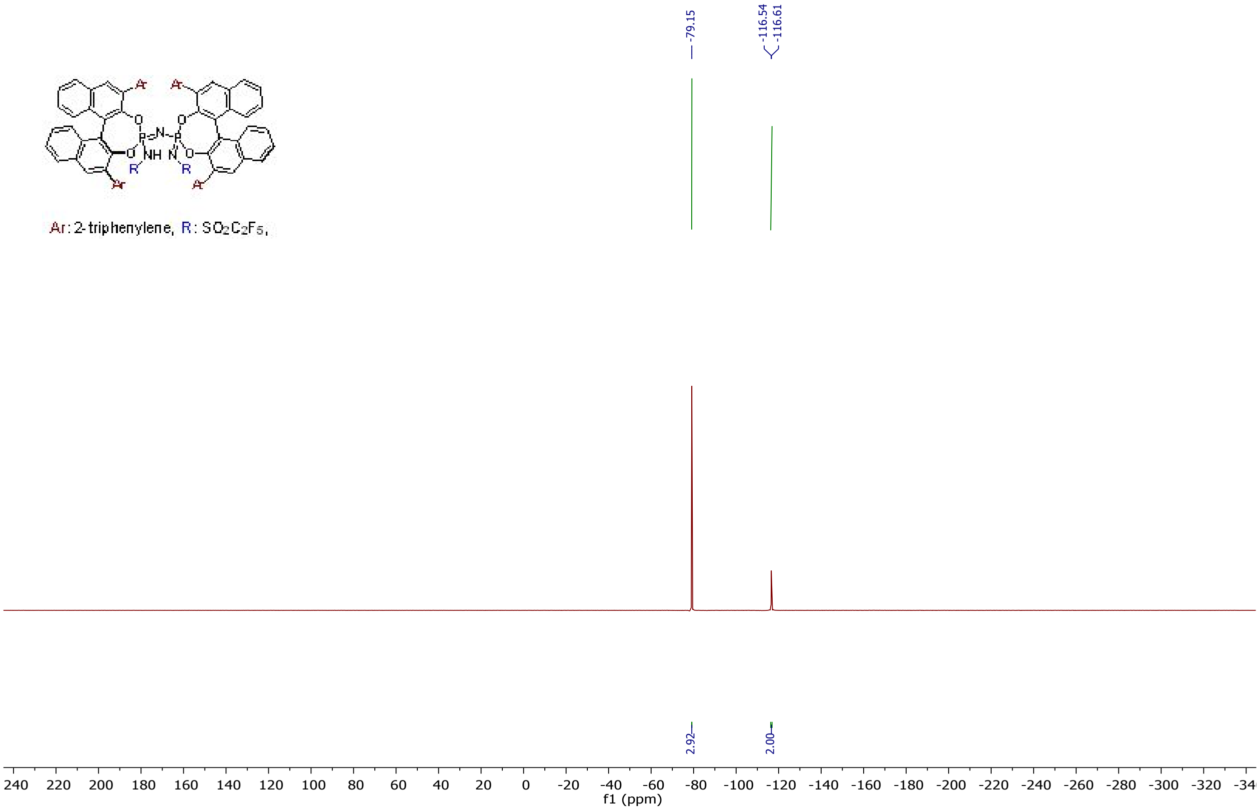
^{1}H NMR (500 MHz, CD_2Cl_2) and ^{13}C NMR (125 MHz, CD_2Cl_2) of catalyst **4f**



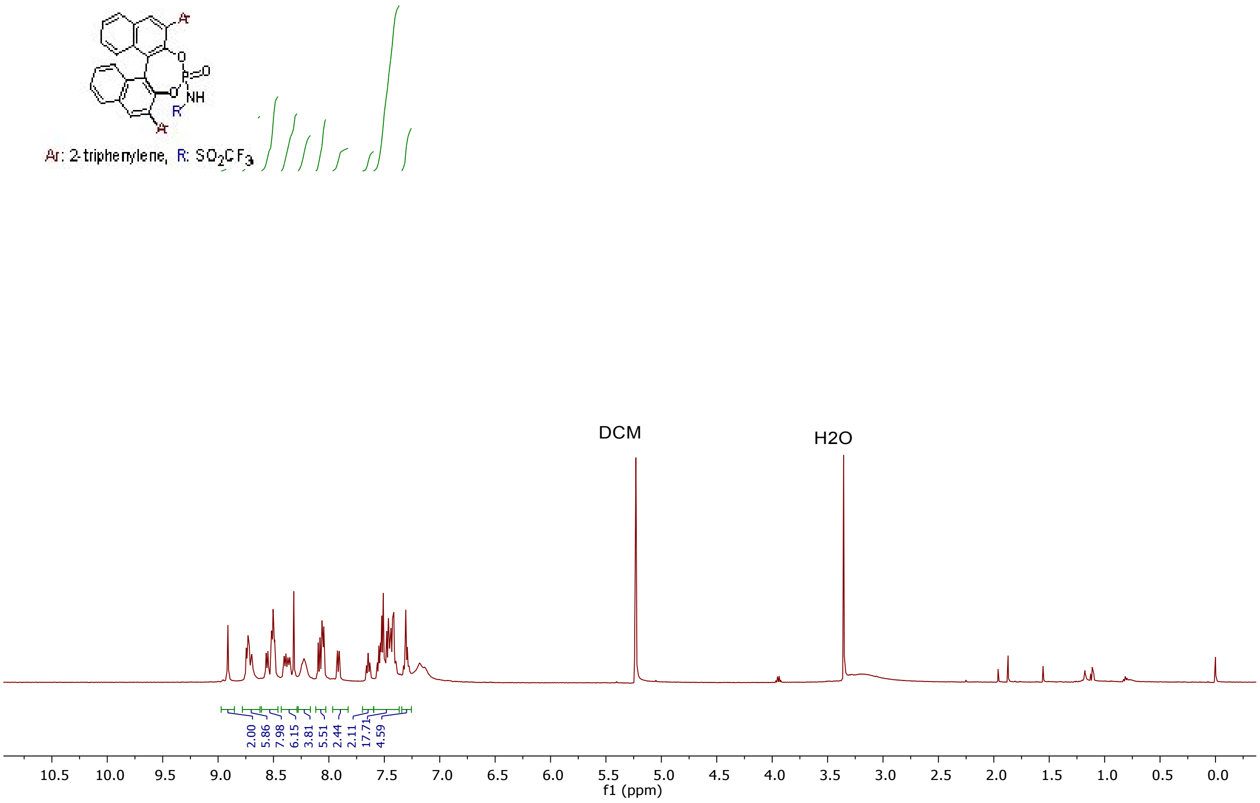


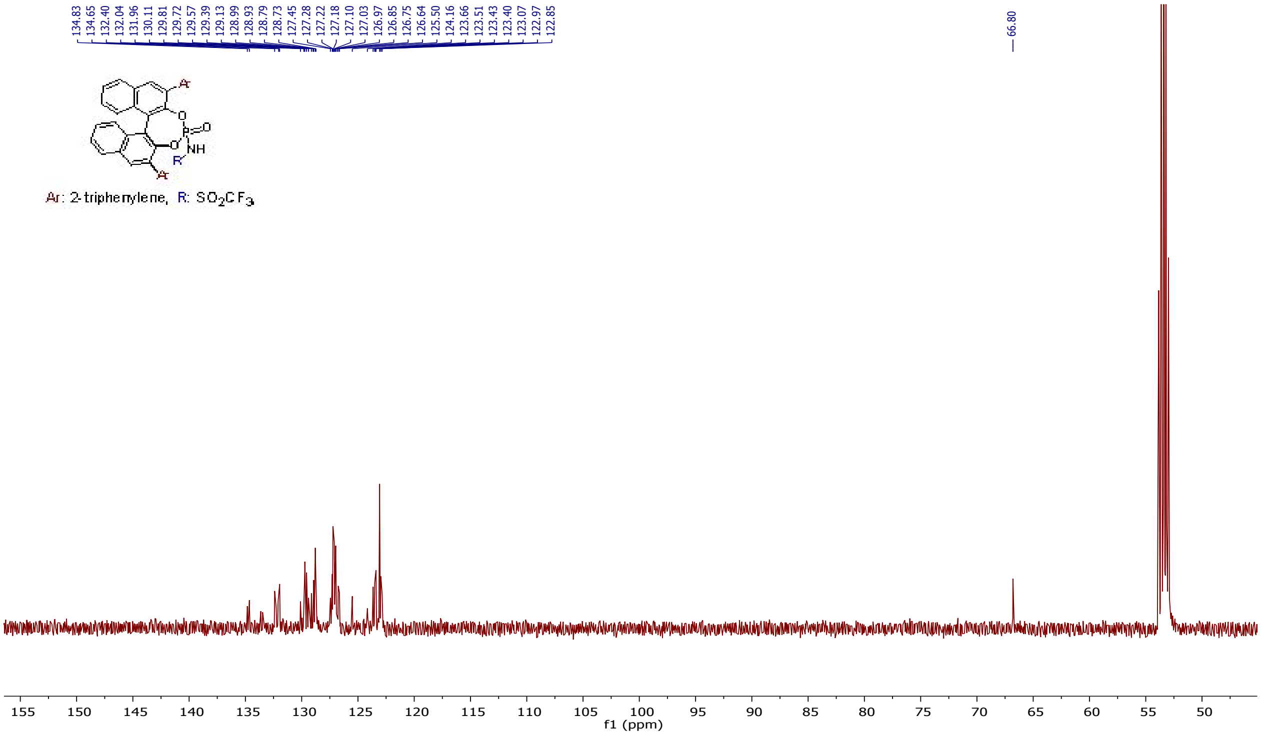
^{31}**P NMR** (203 MHz, CD_2Cl_2) and ^{19}**F NMR** (470 MHz, CD_2Cl_2) of catalyst **4f**





^{1}H NMR (500 MHz, CD_2Cl_2) and **^{13}C NMR** (125 MHz, CD_2Cl_2) of catalyst **4g**





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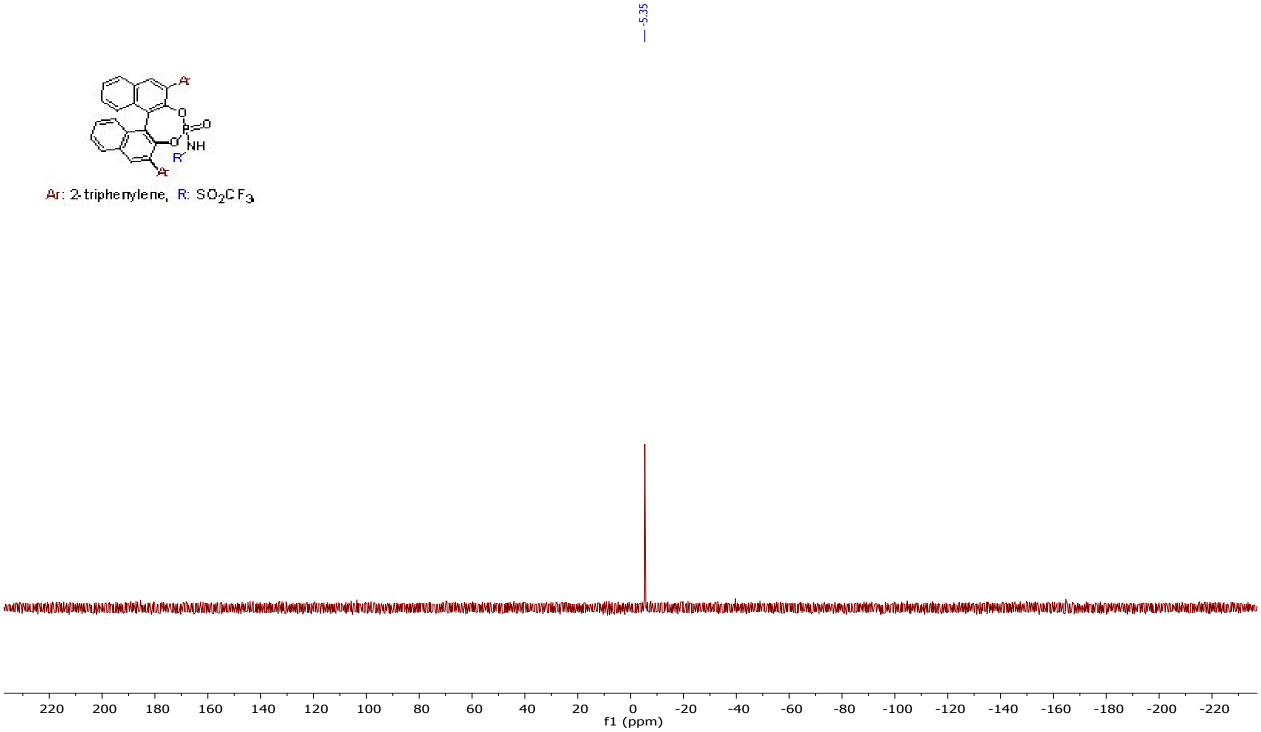
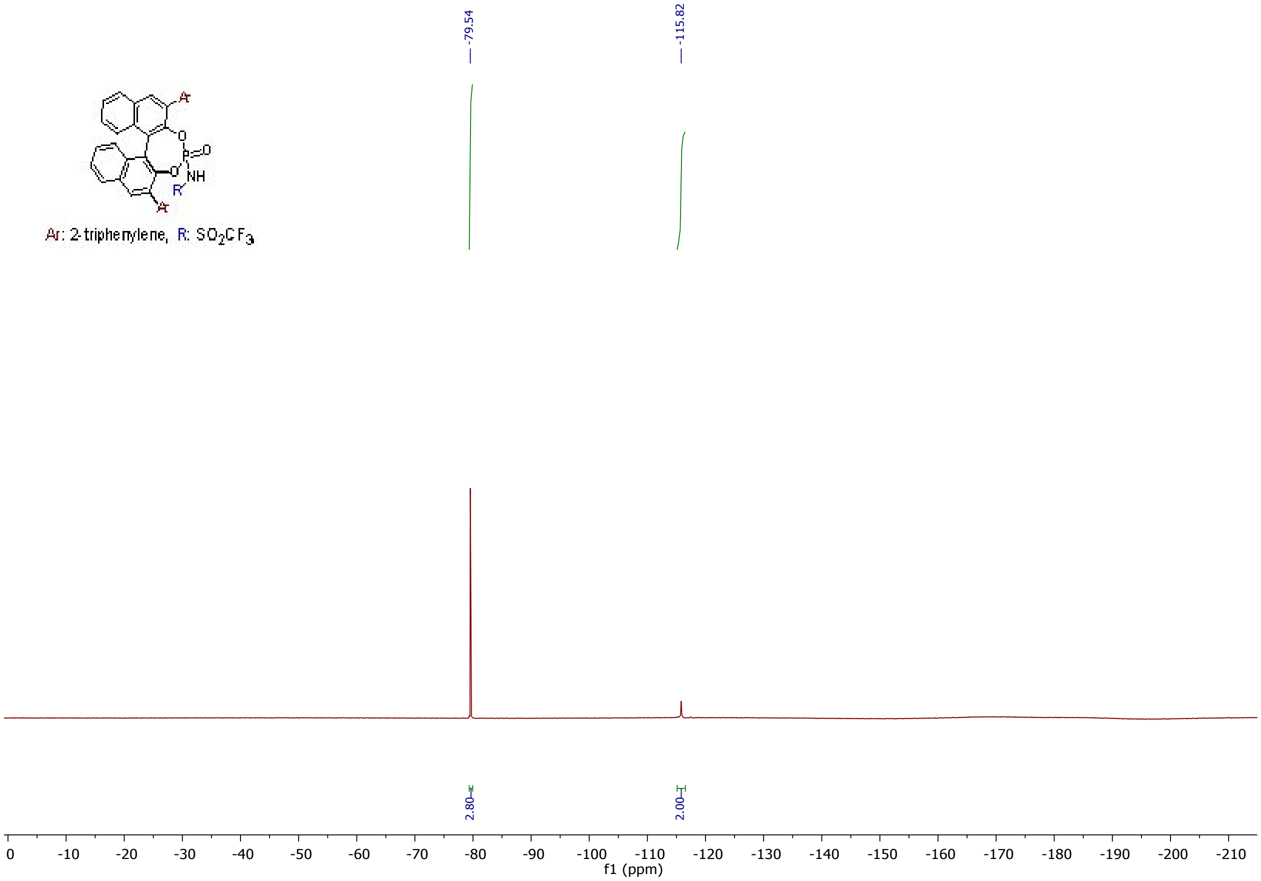
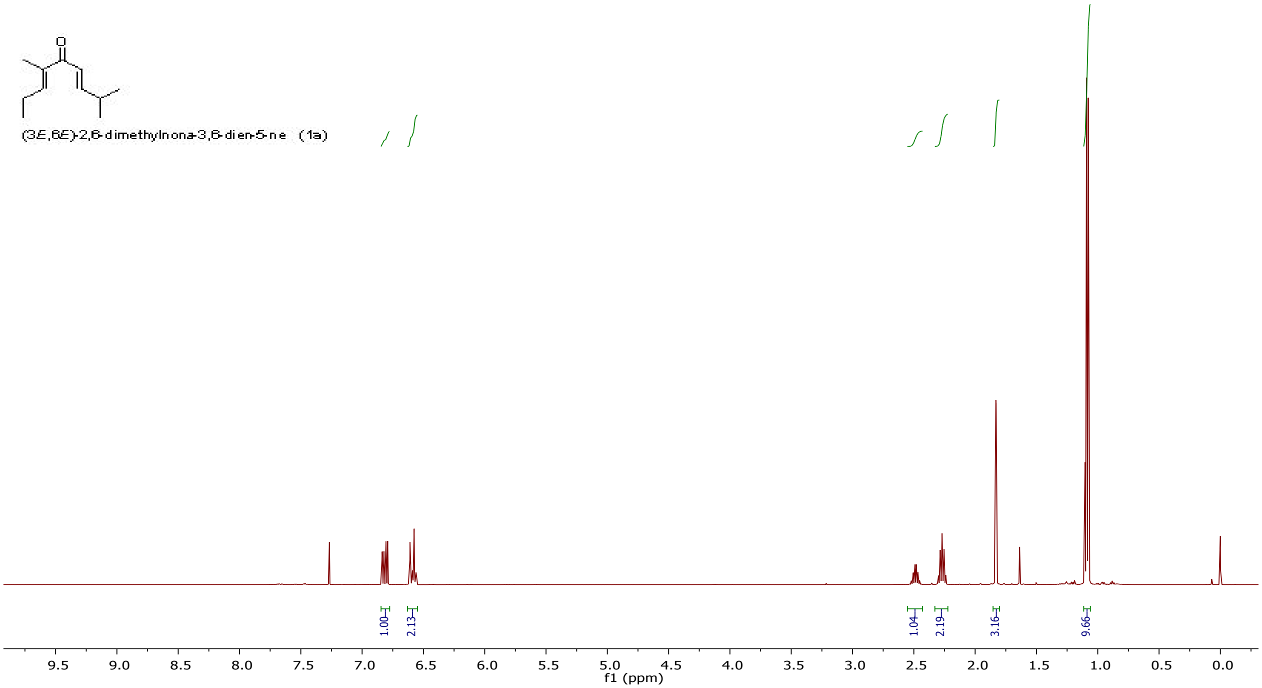
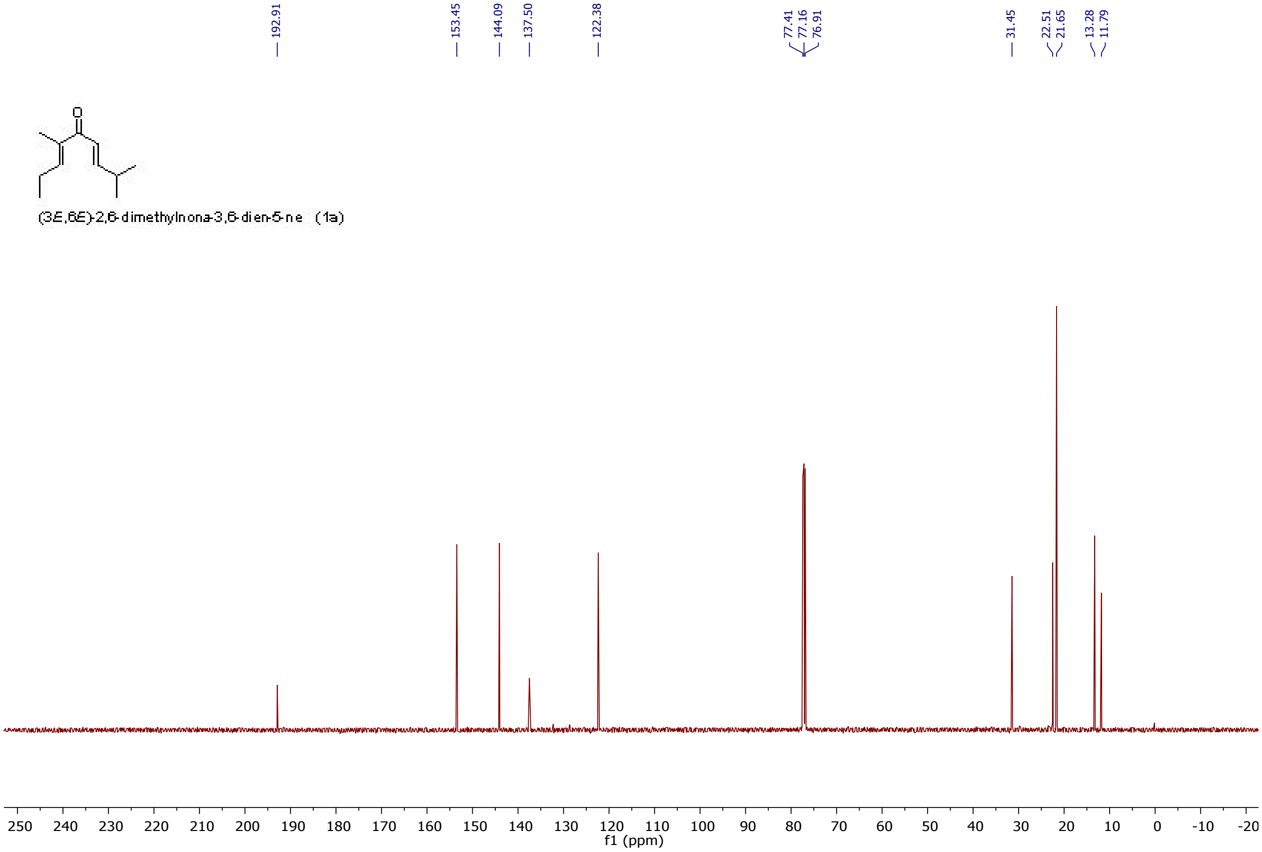




^{1}H NMR (500 MHz, $CDCl_3$) and **^{13}C NMR** (125 MHz, $CDCl_3$) of **1a**





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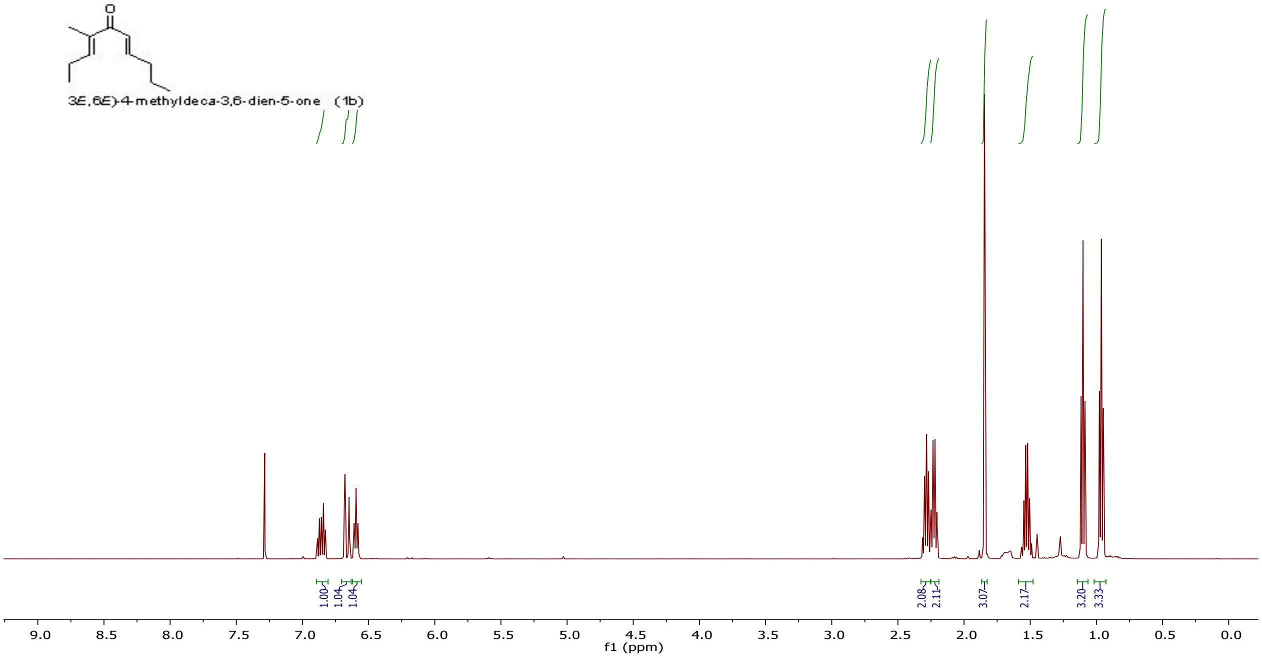
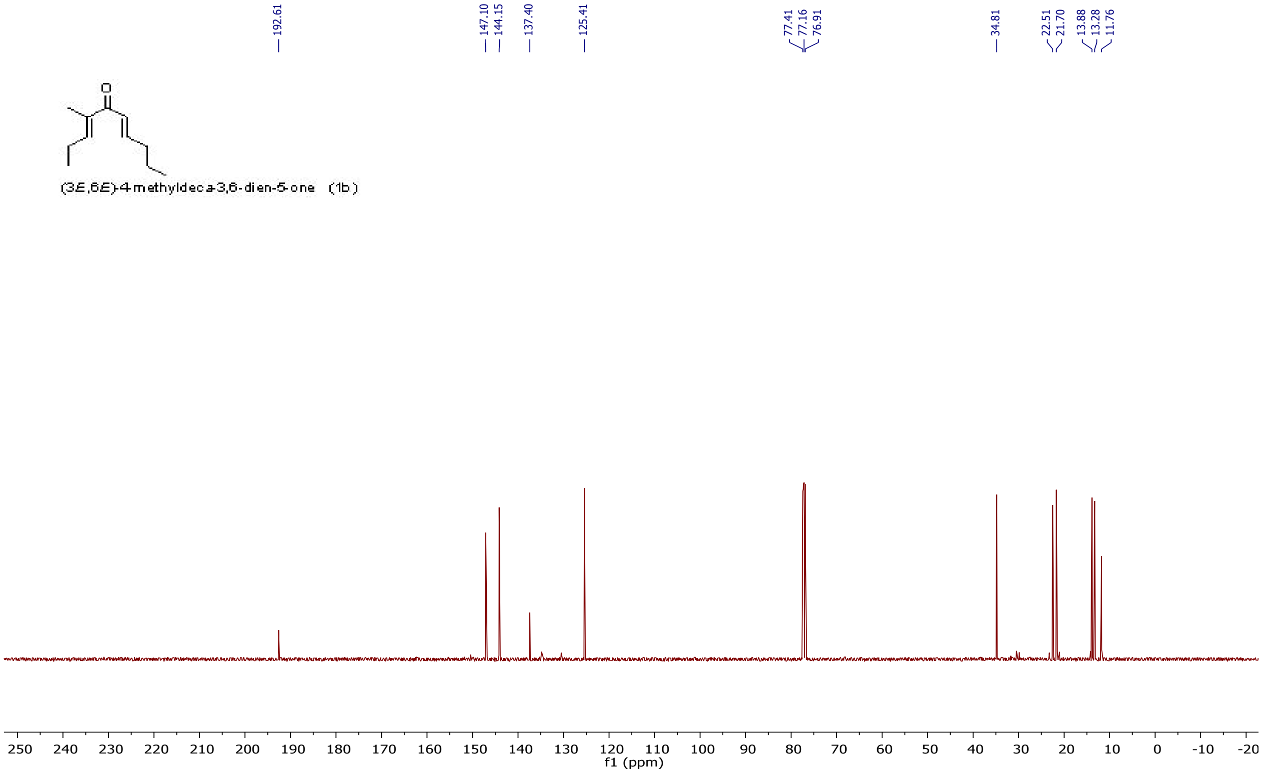
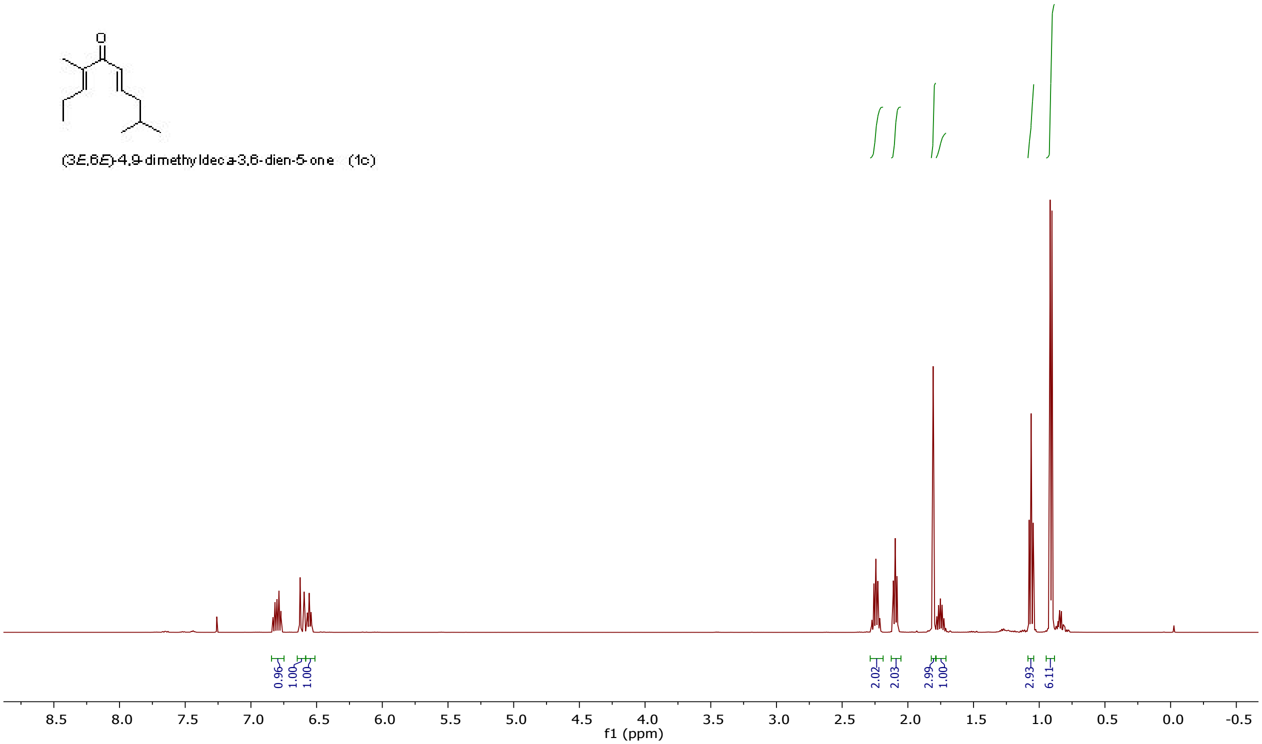
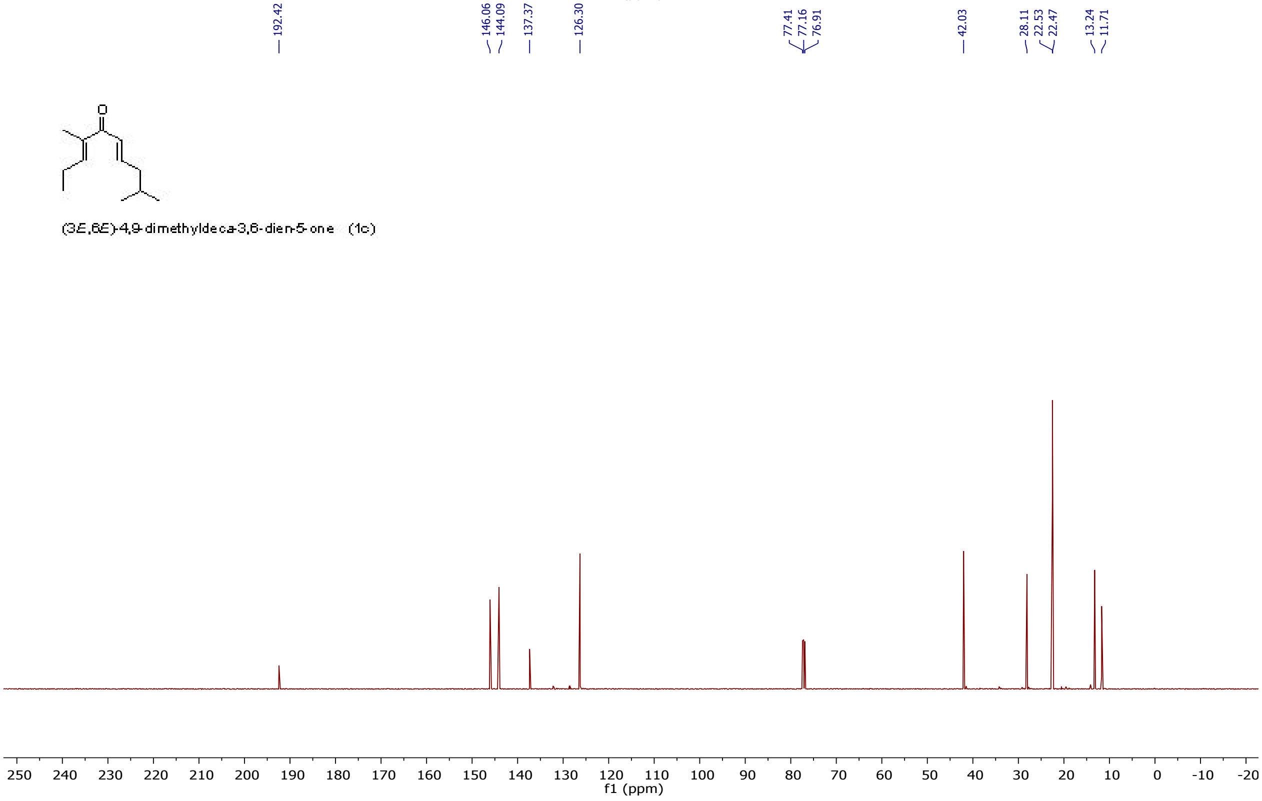




^{1}H NMR (500 MHz, CDCl$_3$) and **^{13}C NMR** (125 MHz, CDCl$_3$) of **1c**





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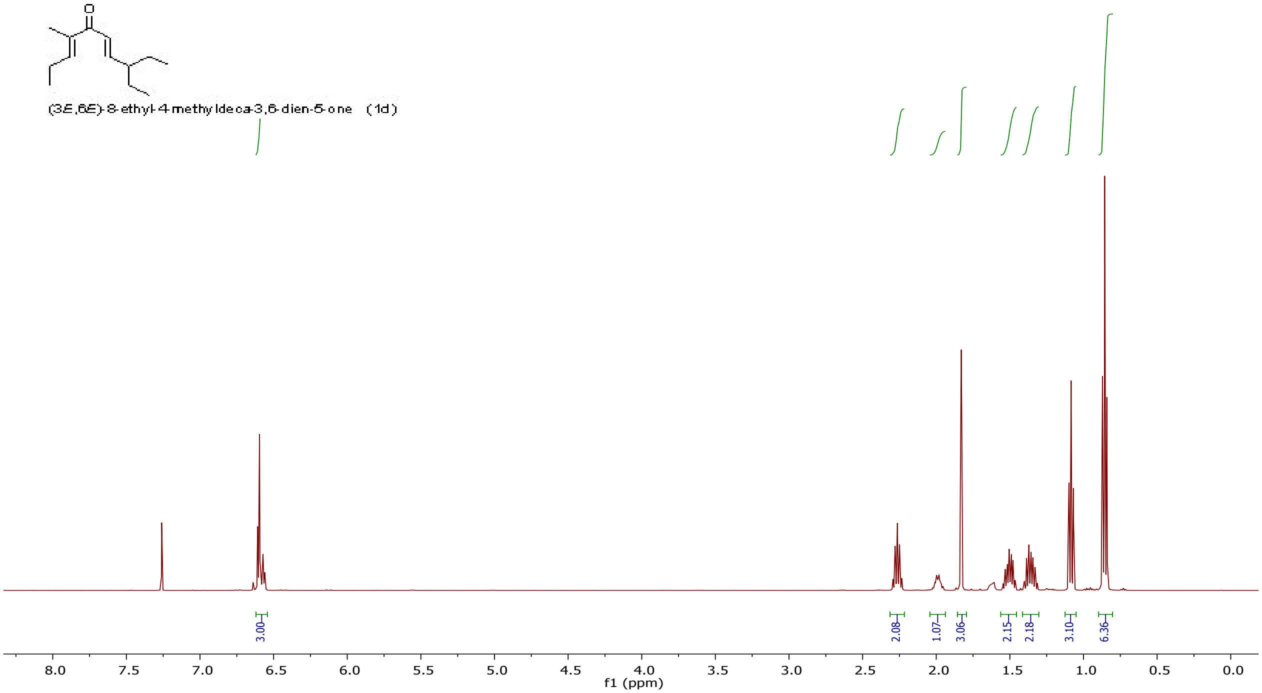
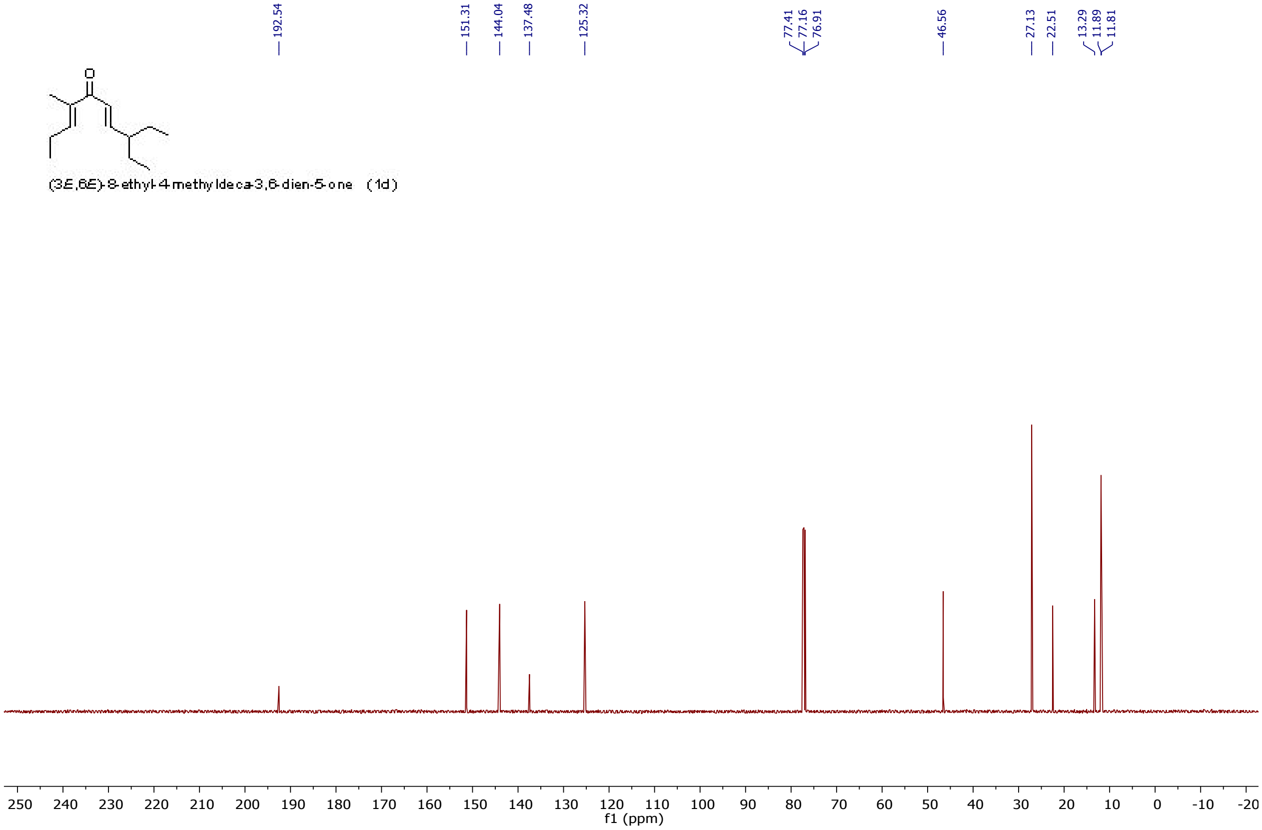
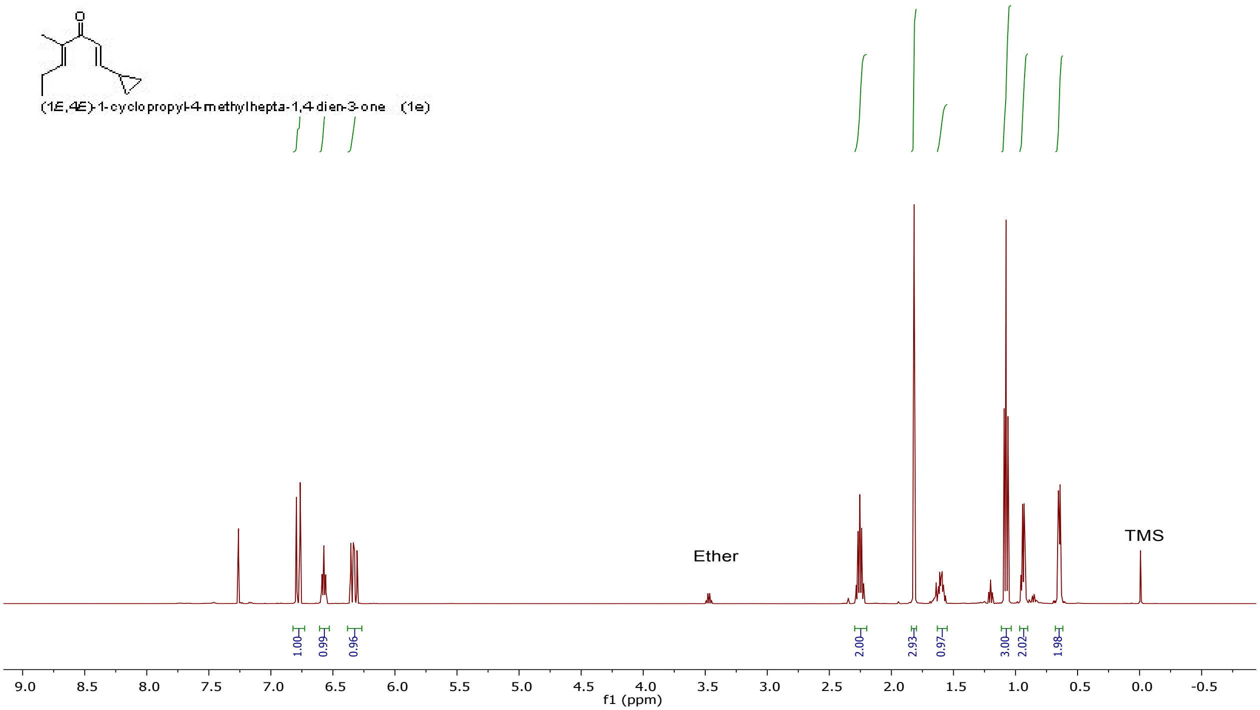
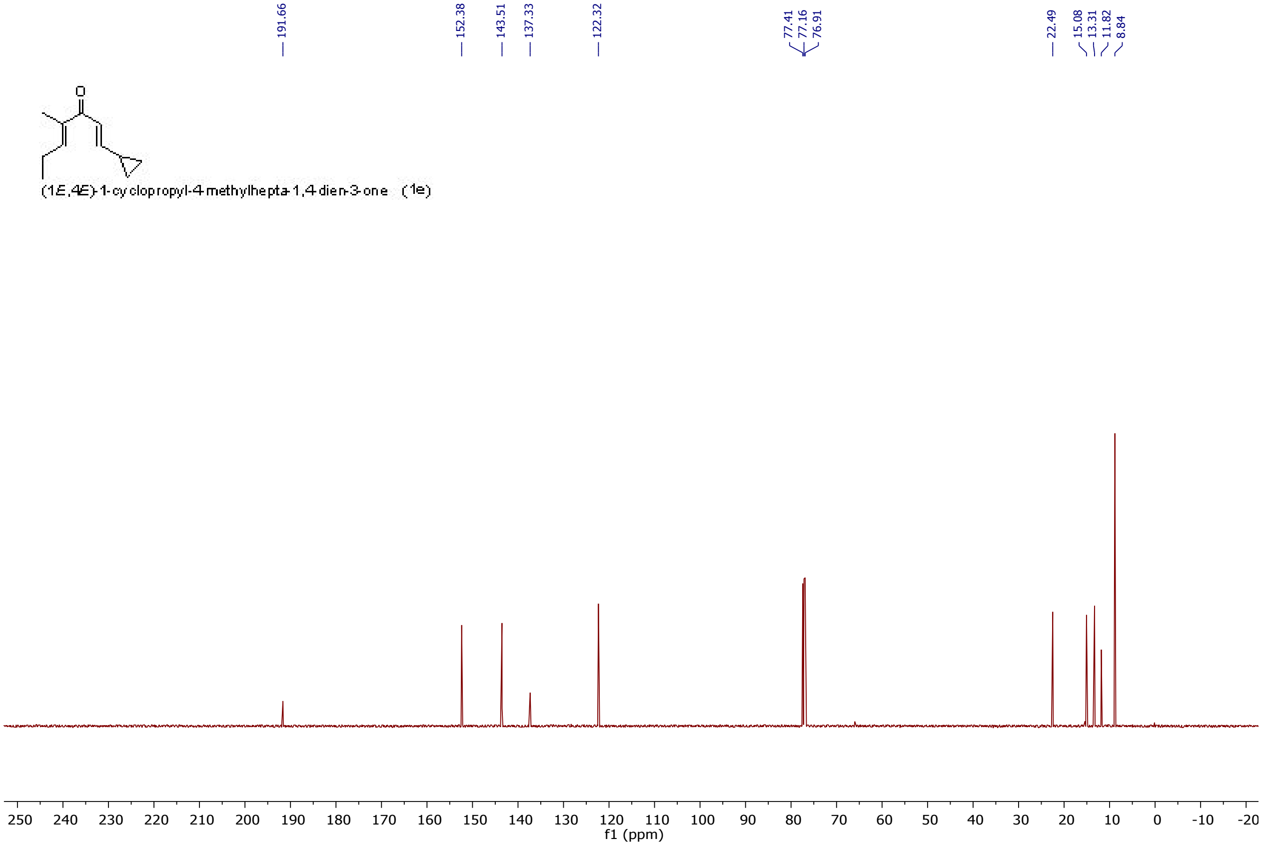


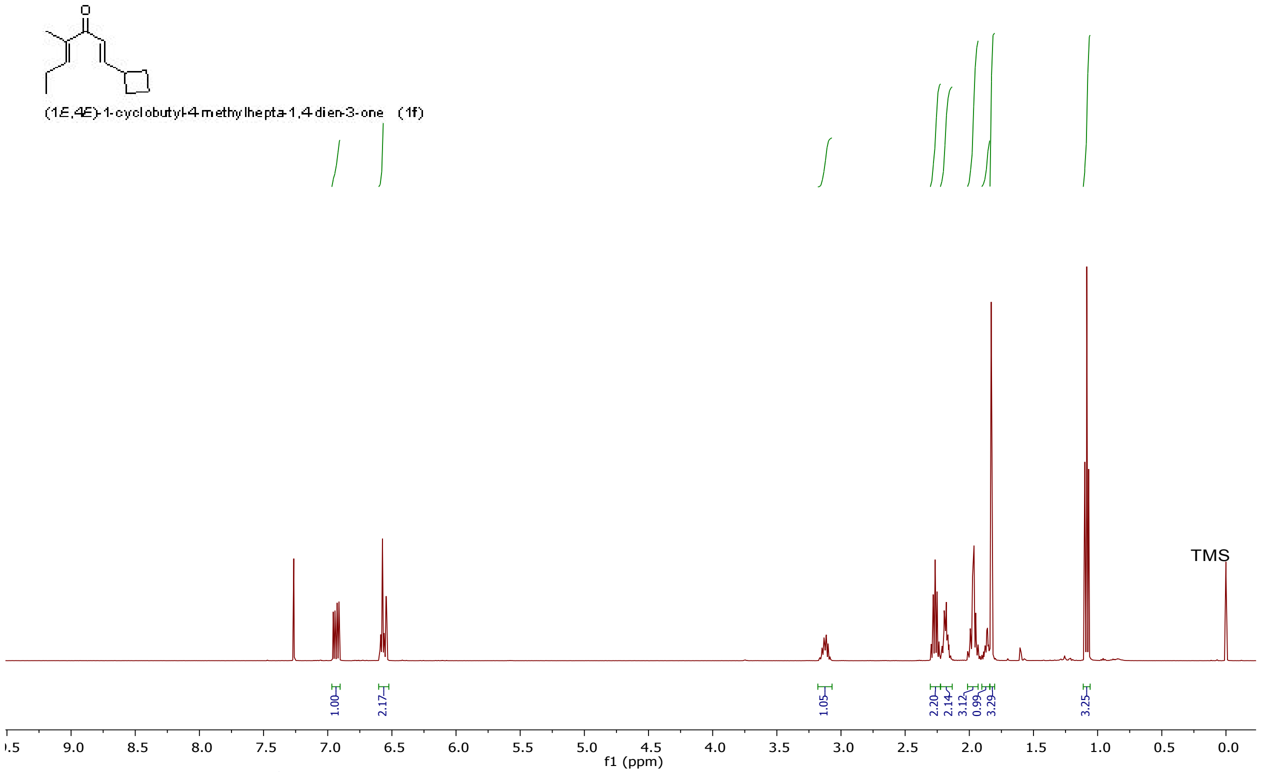


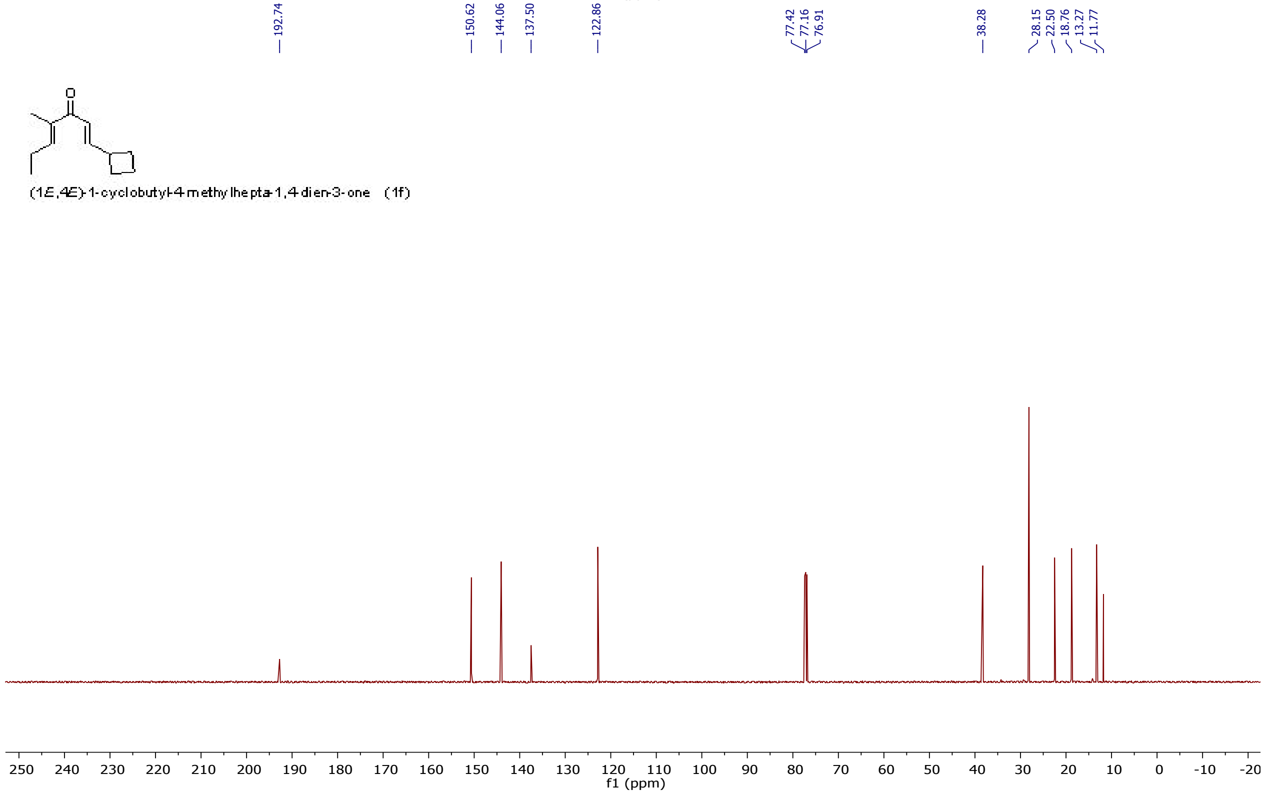
^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **1e**



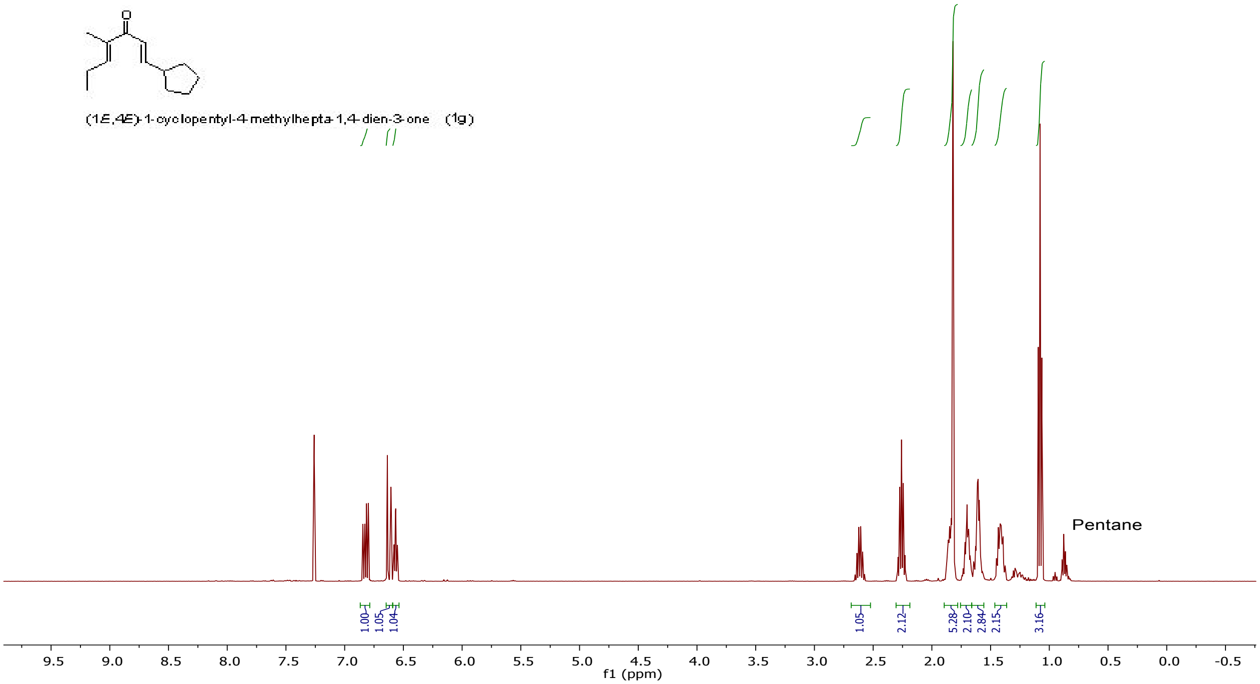


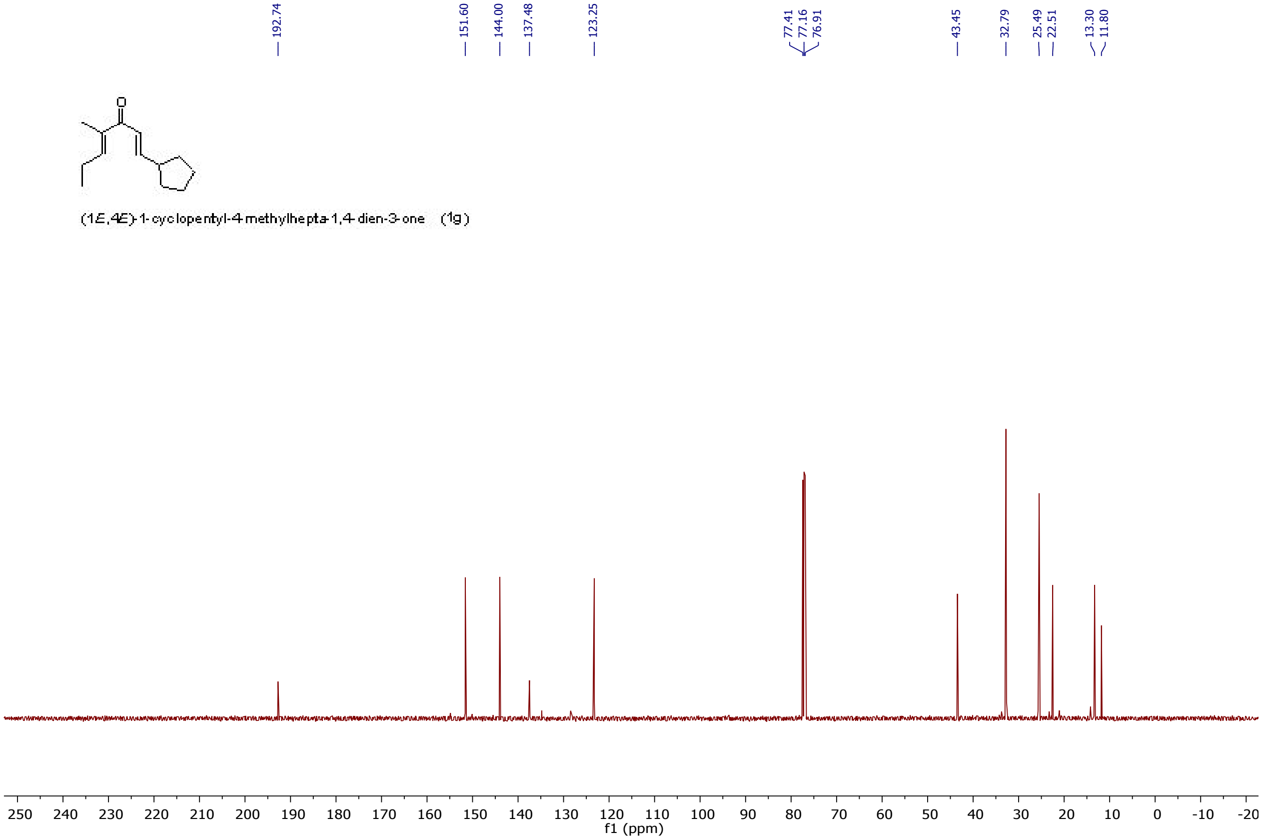
^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **1f**



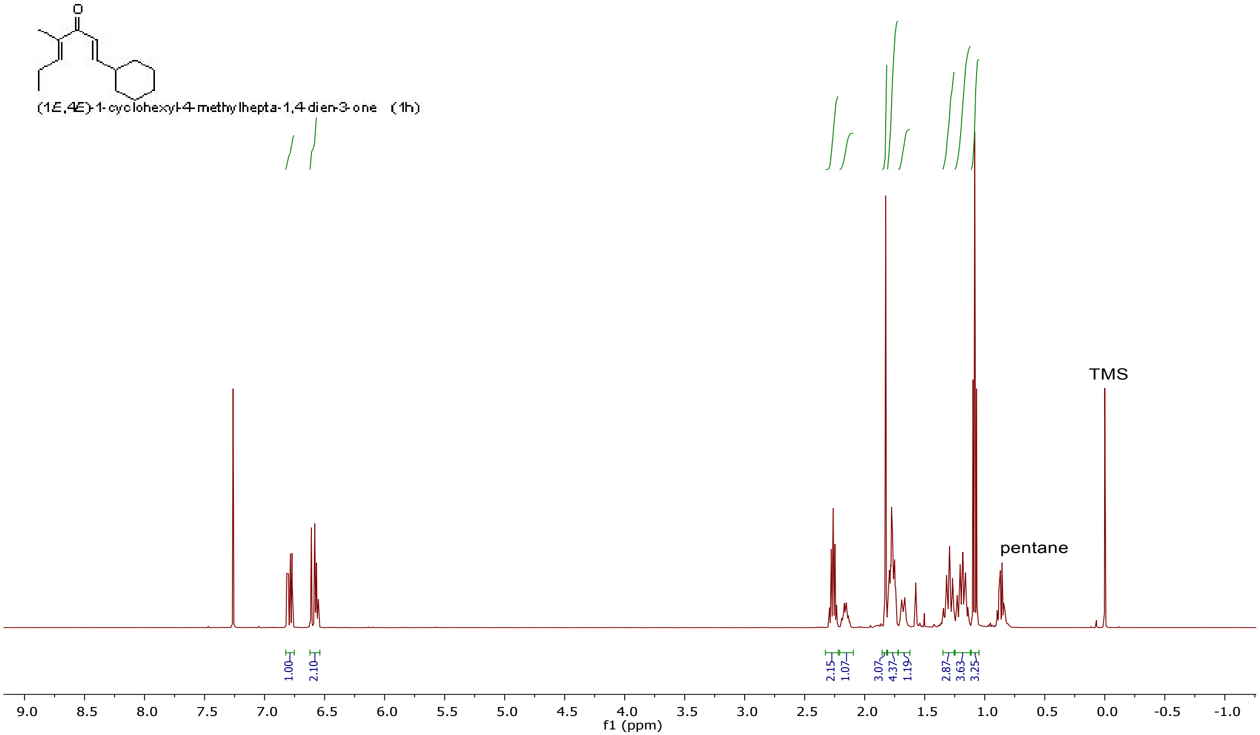


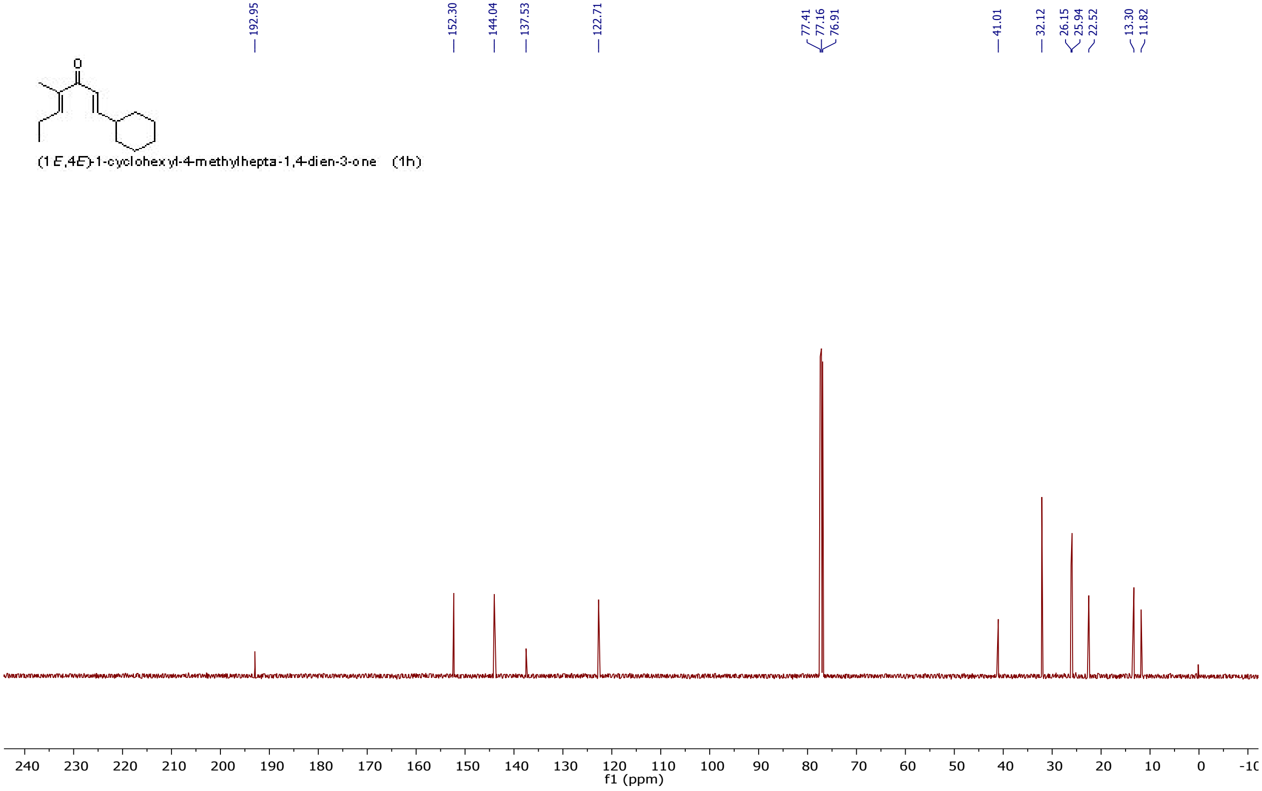
^{1}H NMR (500 MHz, $CDCl_3$) and **^{13}C NMR** (125 MHz, $CDCl_3$) of **1g**





^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **1h**





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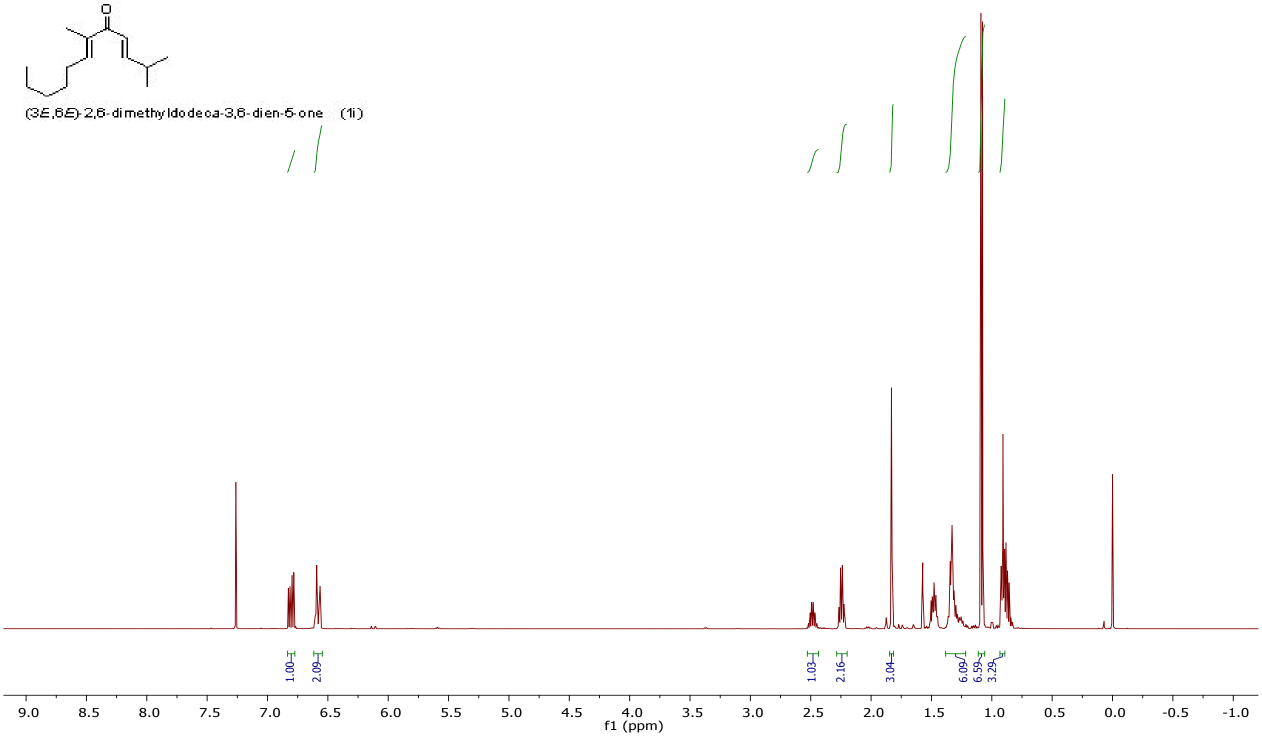
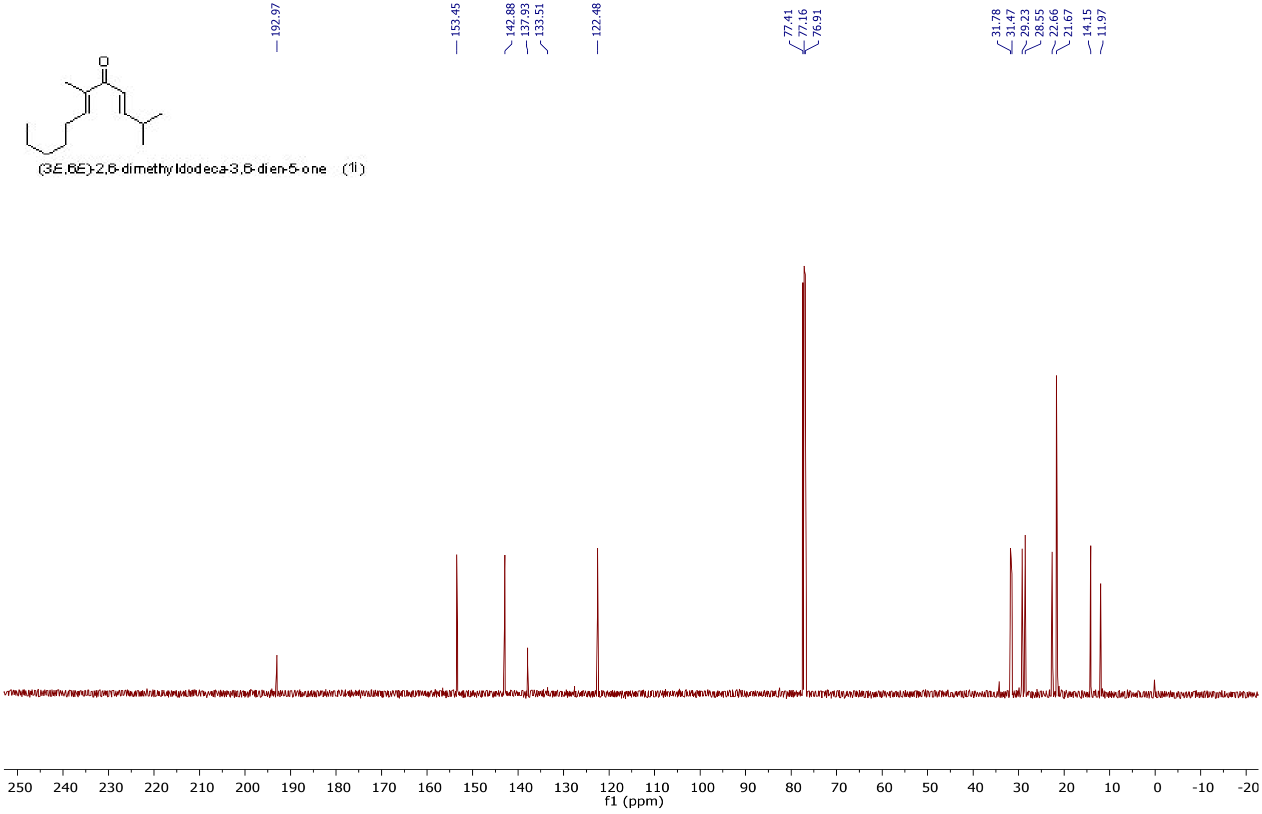
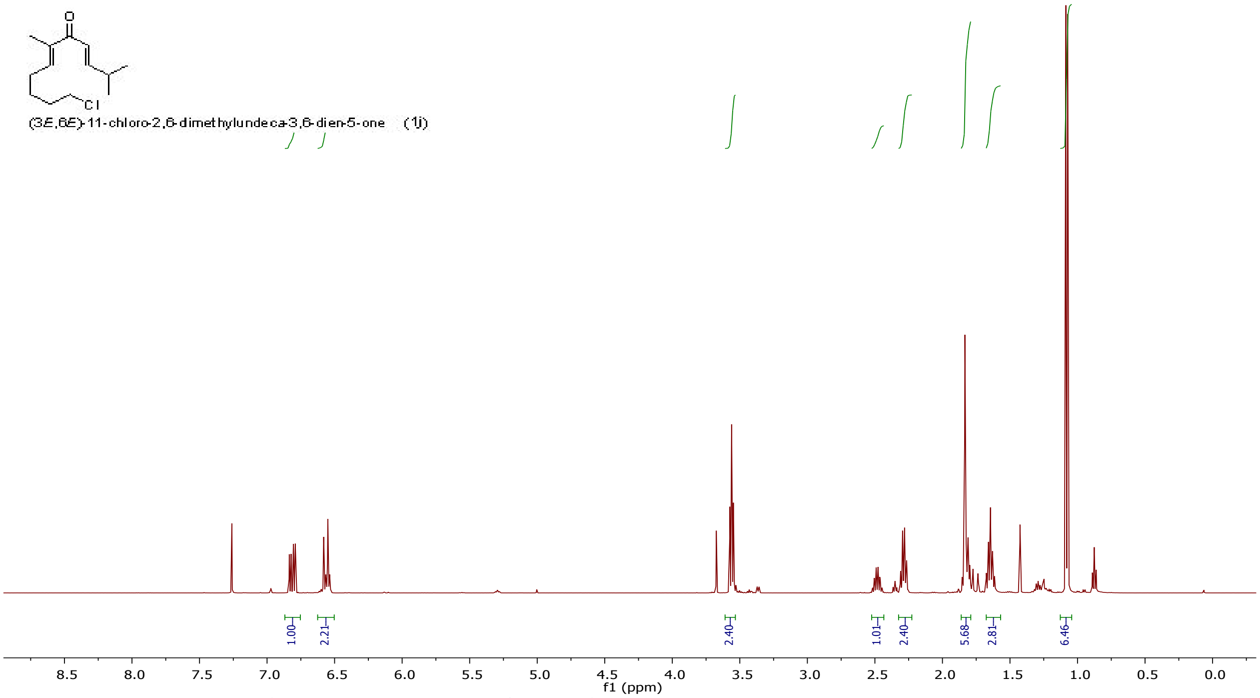
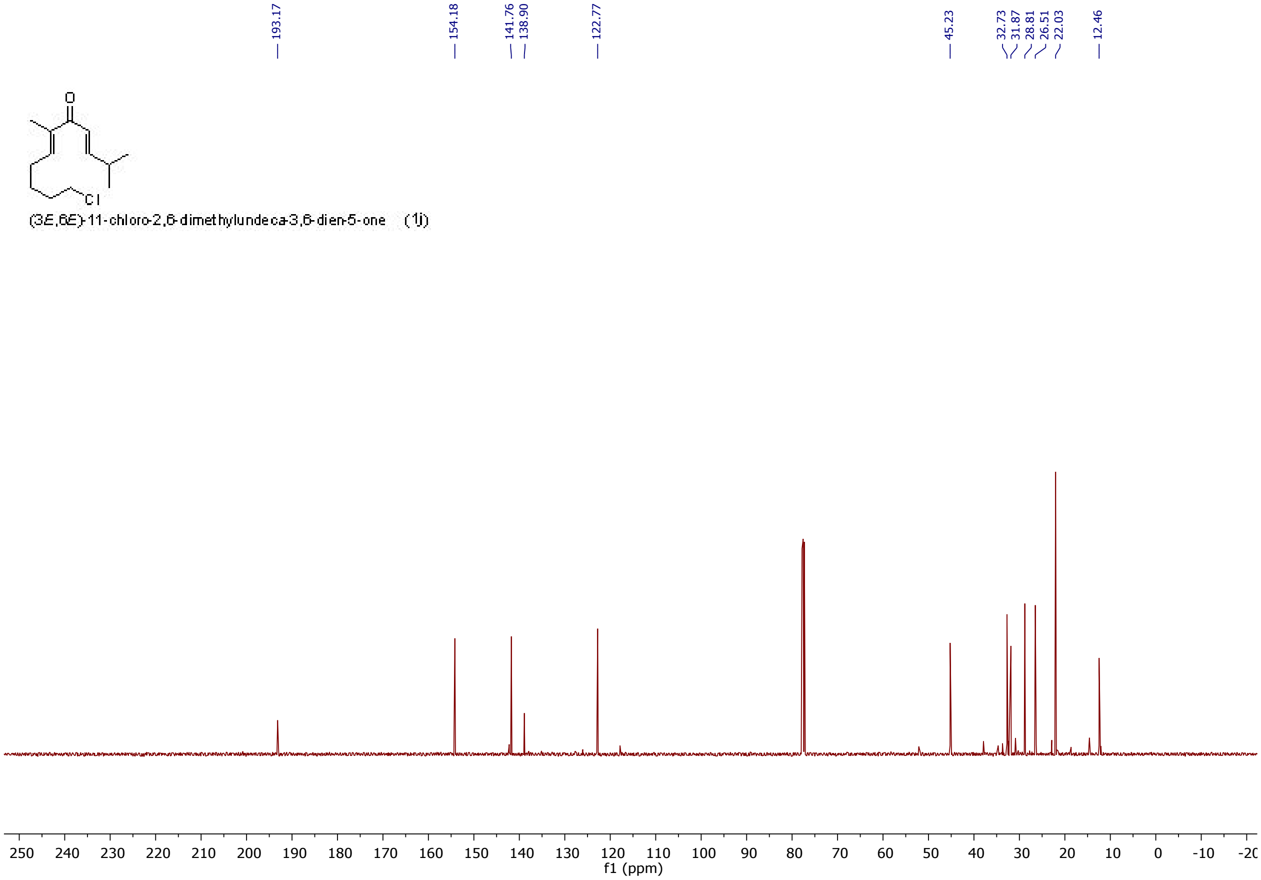


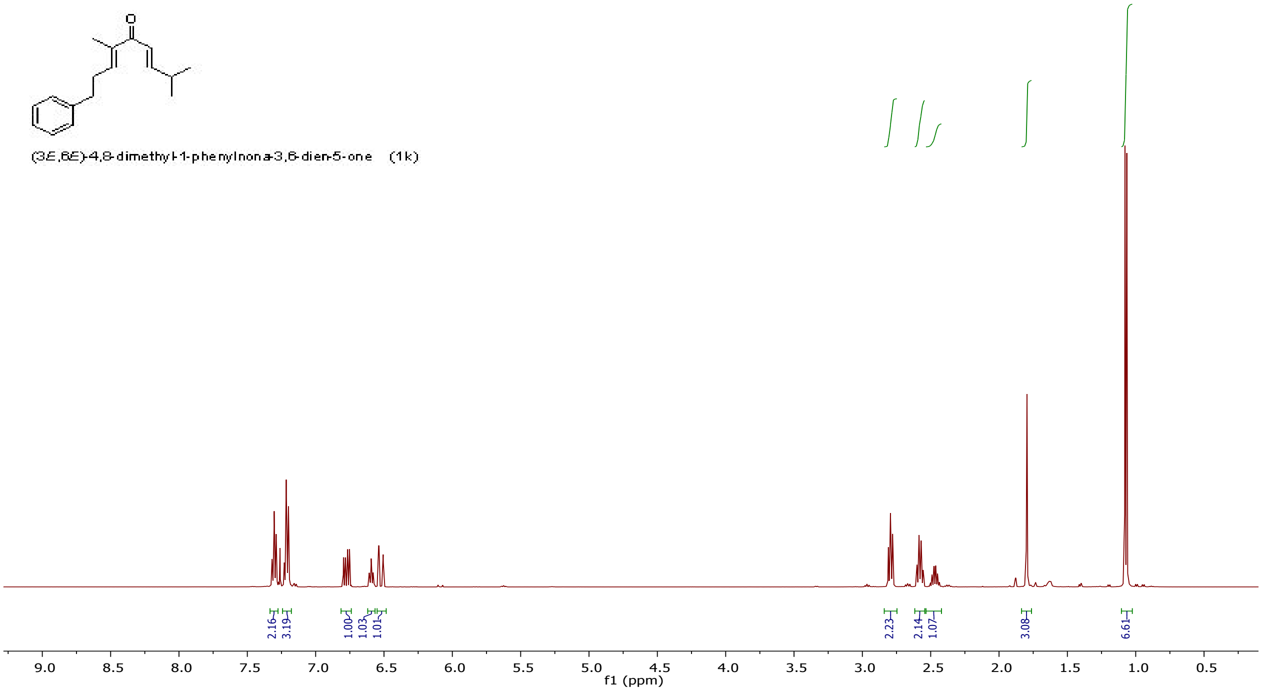


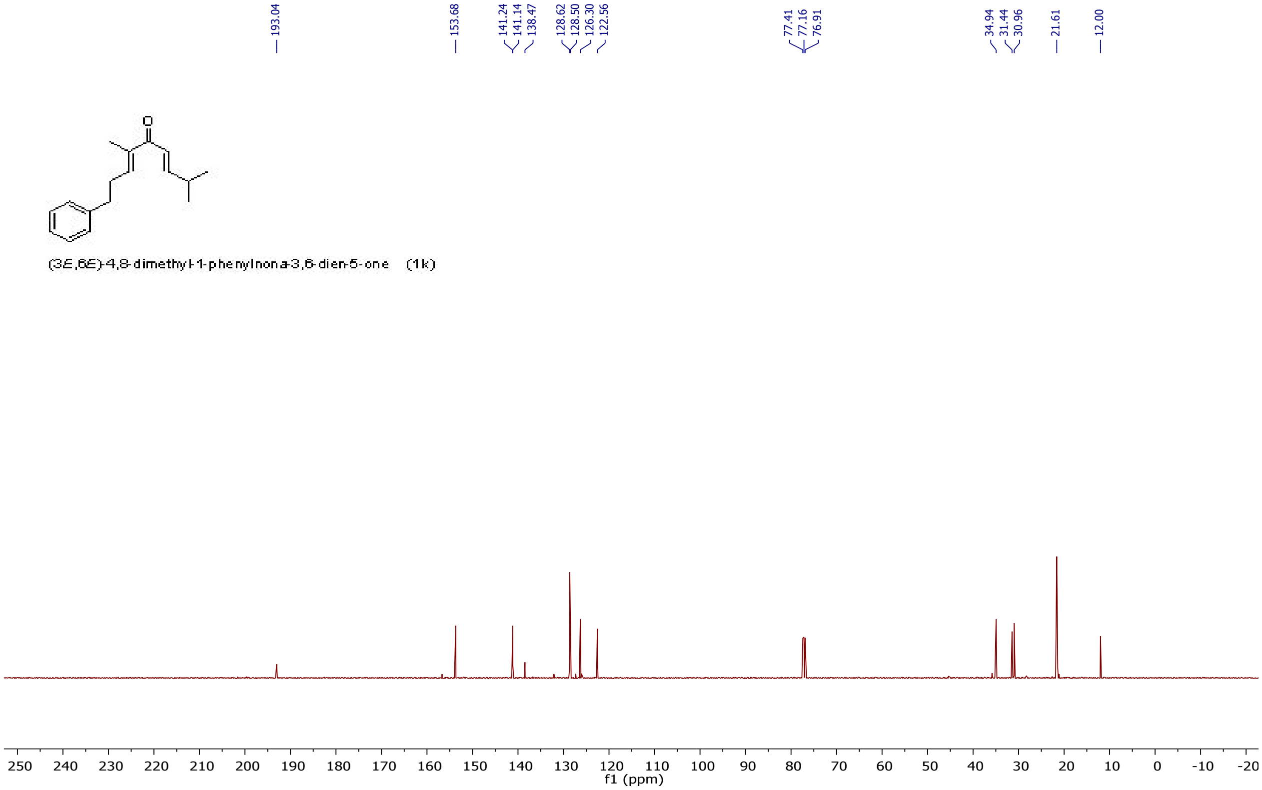
^{1}H NMR (500 MHz, CDCl$_3$) and **^{13}C NMR** (125 MHz, CDCl$_3$) of **1j**



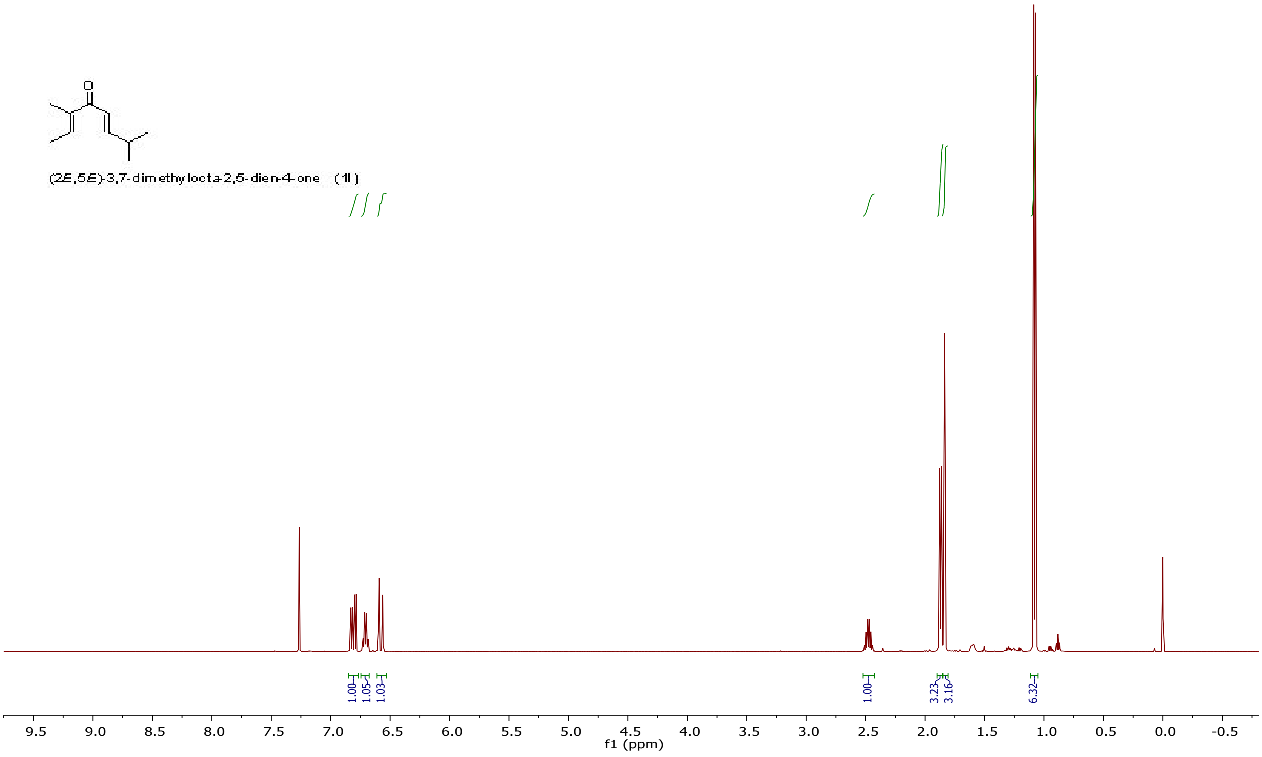


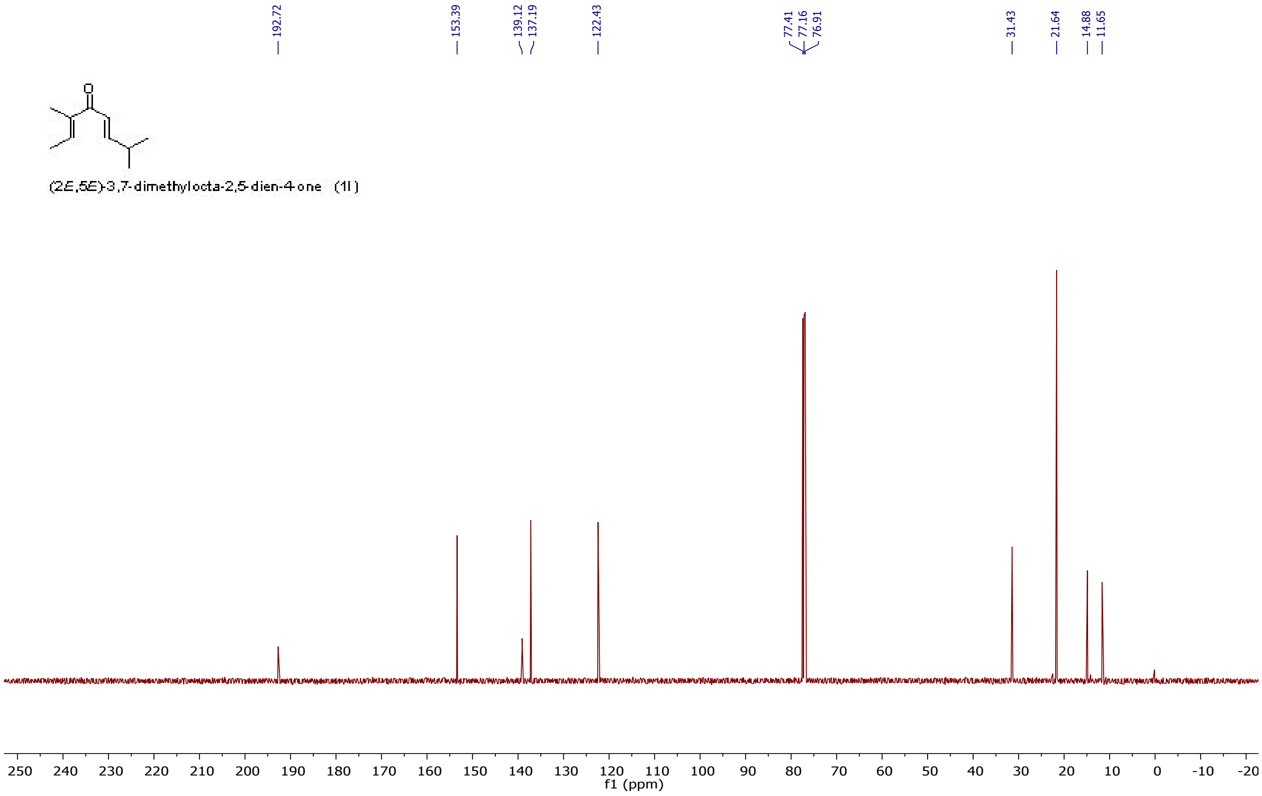
^{1}H NMR (500 MHz, CDCl$_3$) and ^{13}C NMR (125 MHz, CDCl$_3$) of **1k**



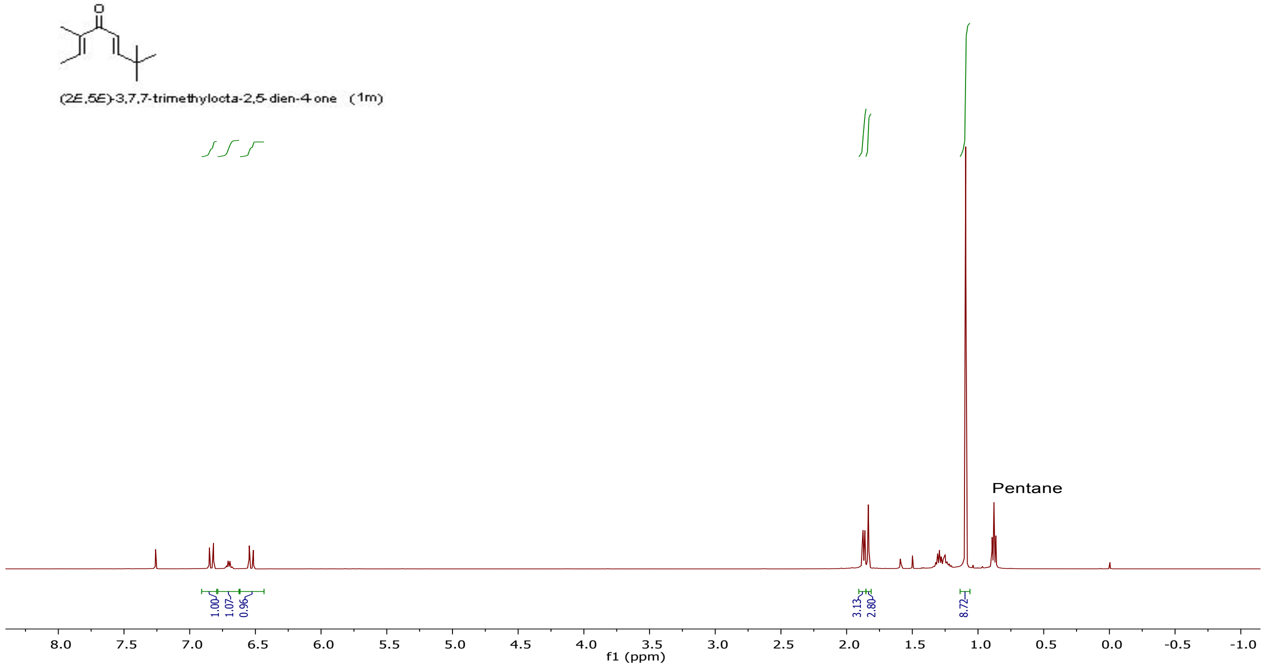


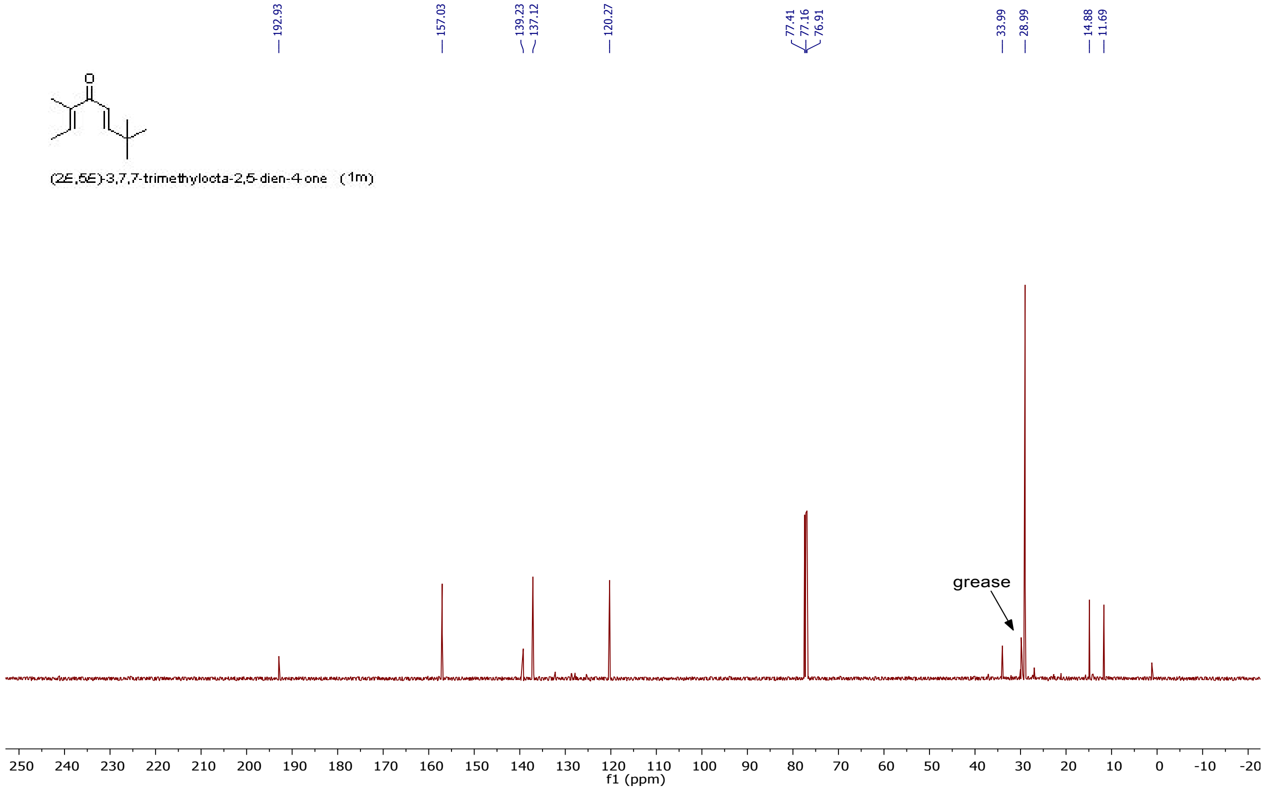
^{1}H NMR (500 MHz, $CDCl_3$) and **^{13}C NMR** (125 MHz, $CDCl_3$) of **1l**



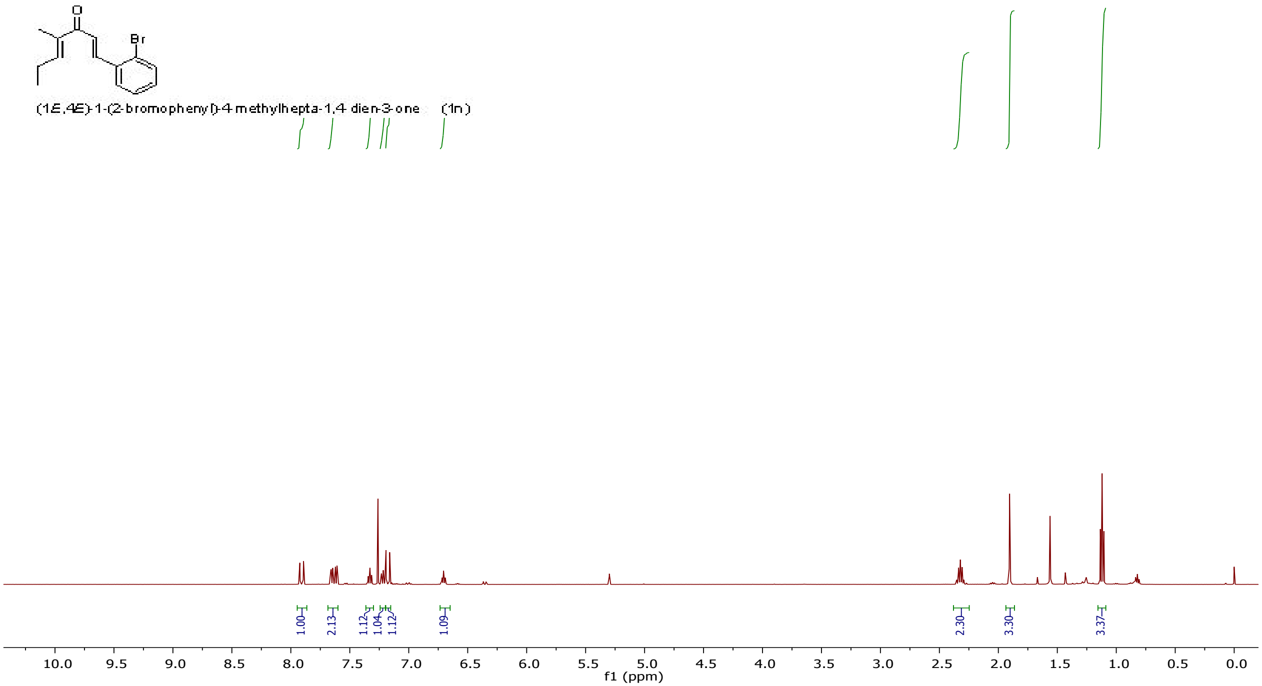


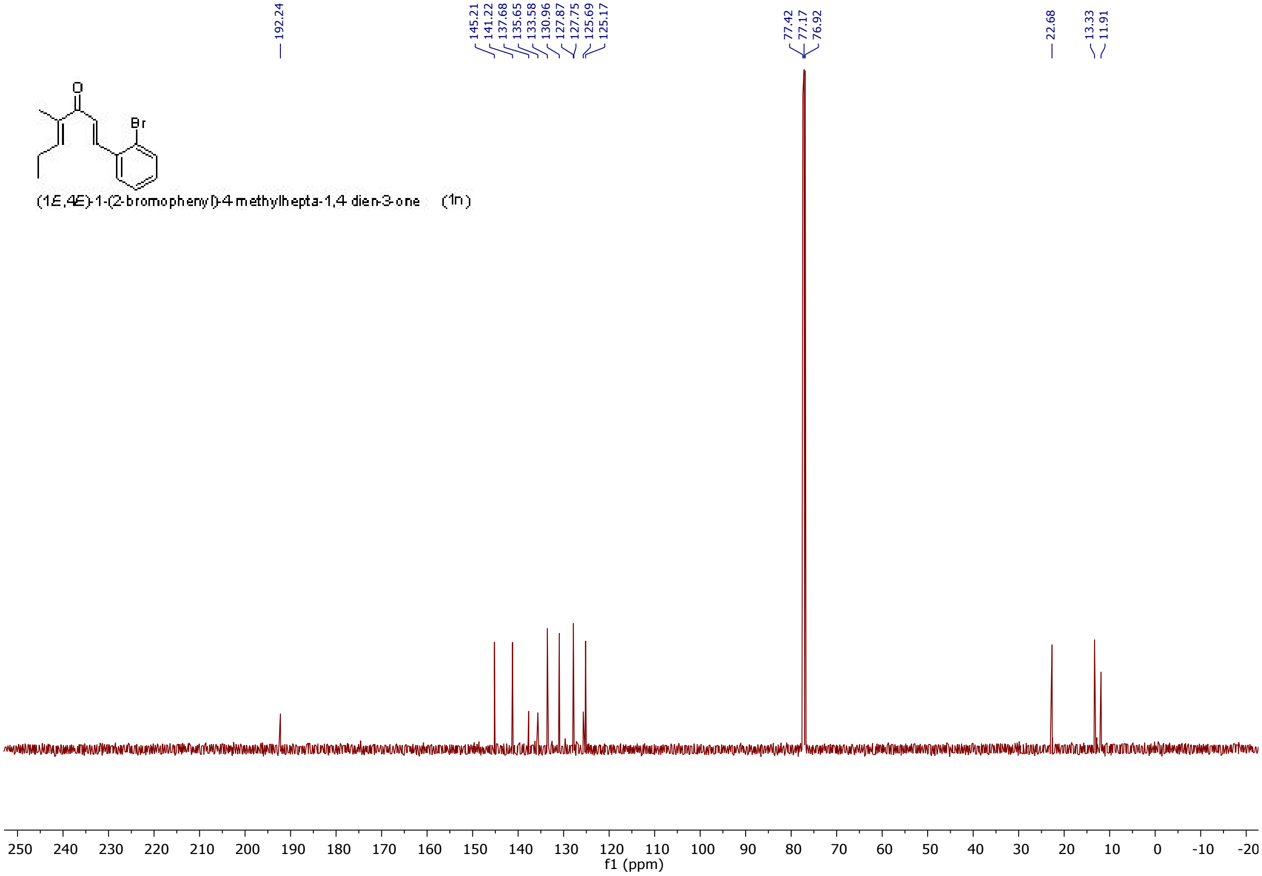
^{1}H NMR (500 MHz, $CDCl_3$) and **^{13}C NMR** (125 MHz, $CDCl_3$) of **1m**



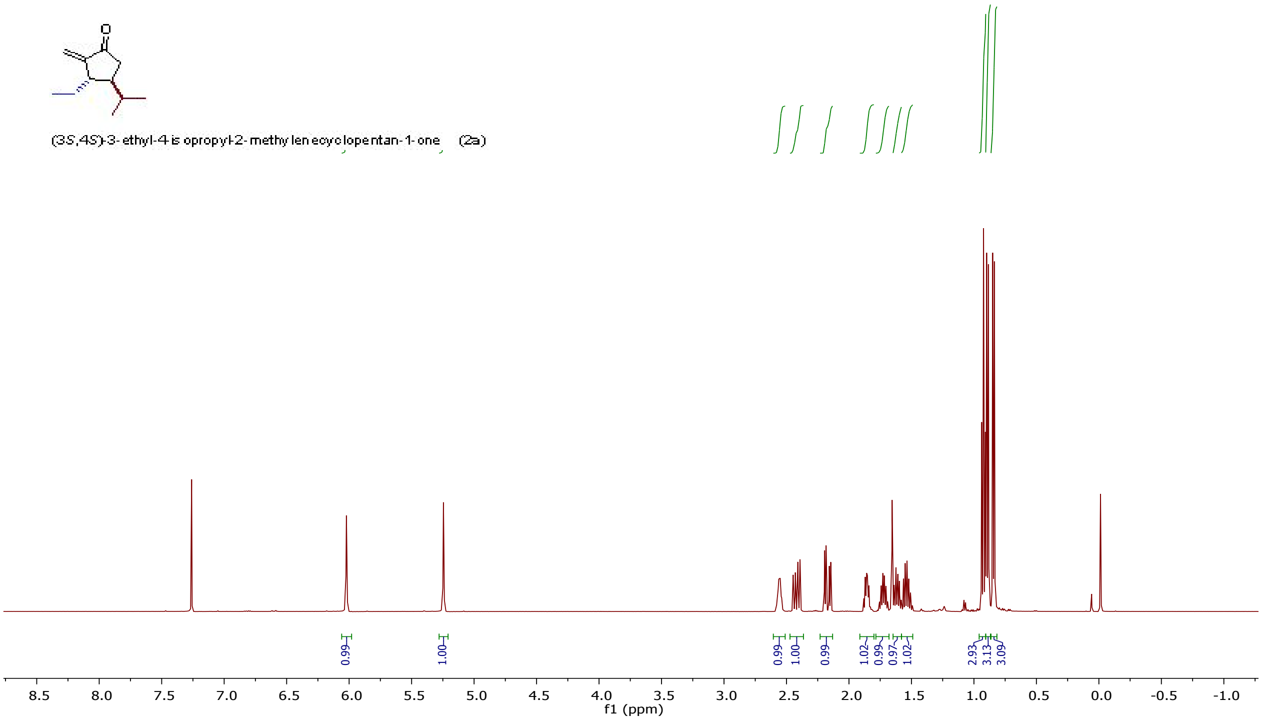


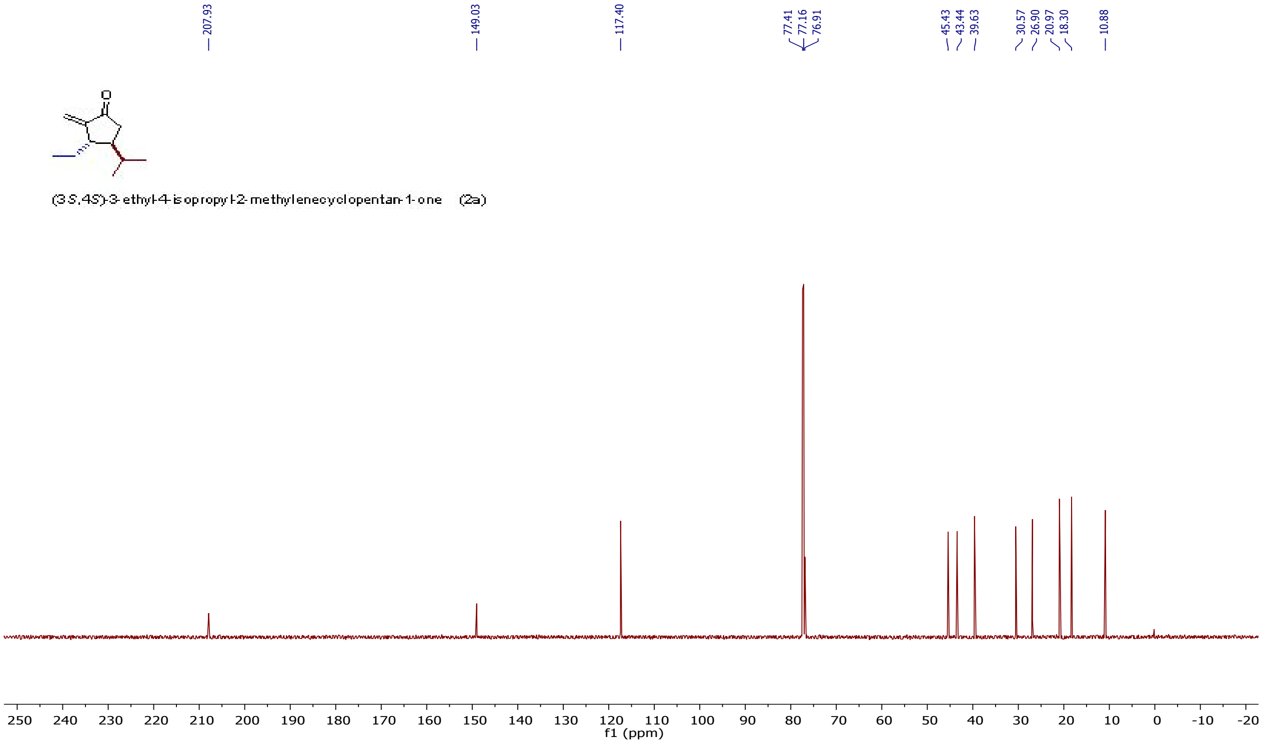
^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **1n**



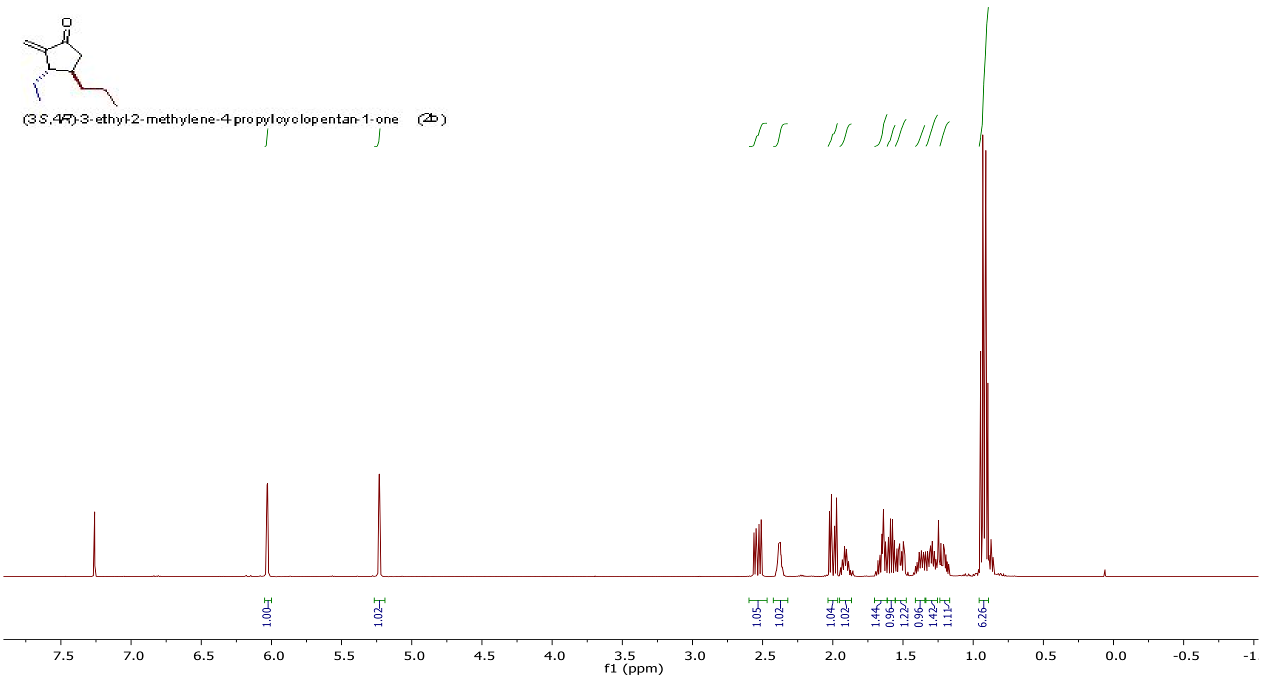


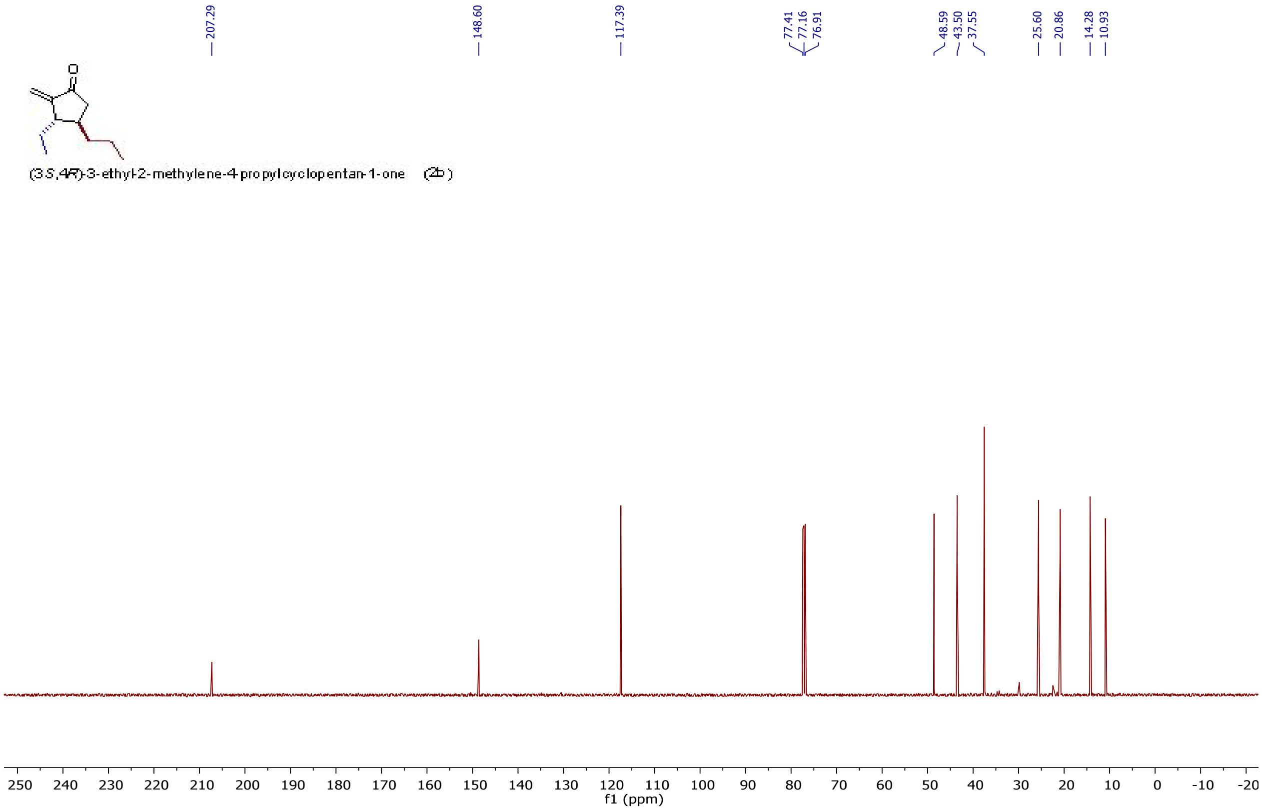
^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **2a**



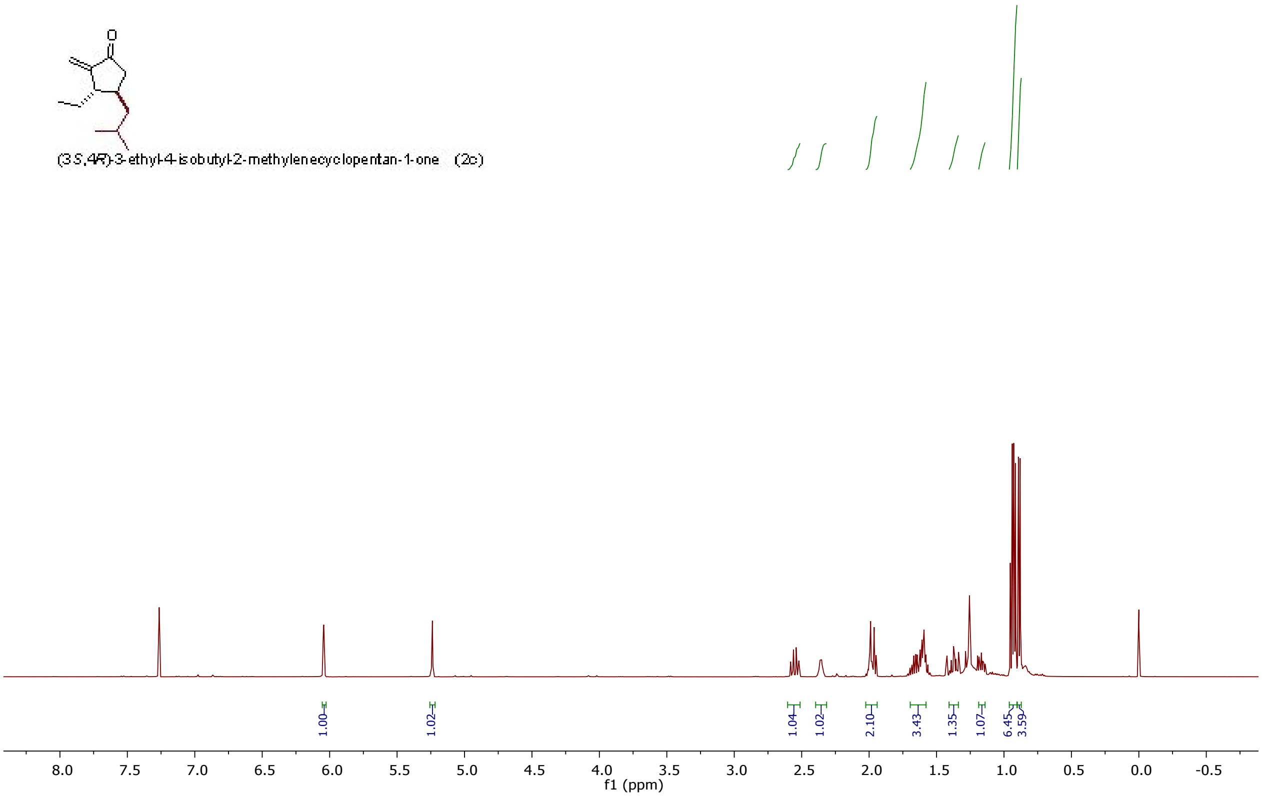


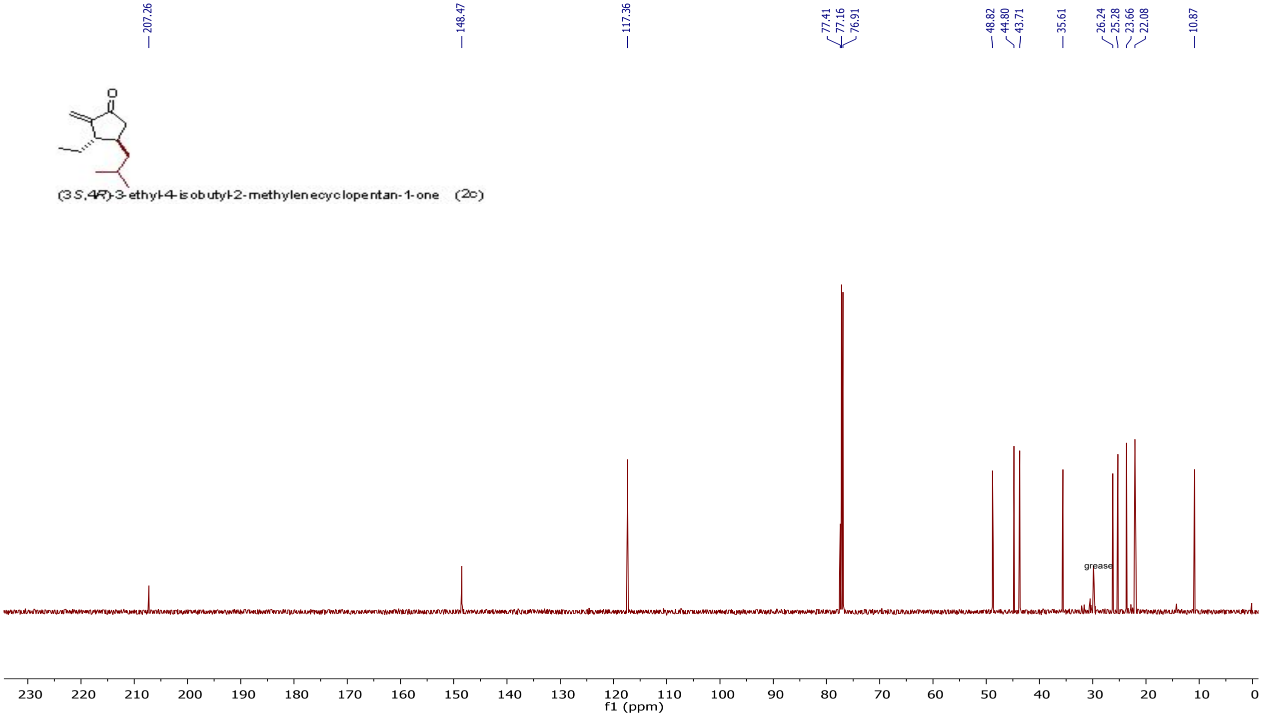
^{1}H NMR (500 MHz, CDCl$_3$) and **^{13}C NMR** (125 MHz, CDCl$_3$) of **2b**





^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **2c**





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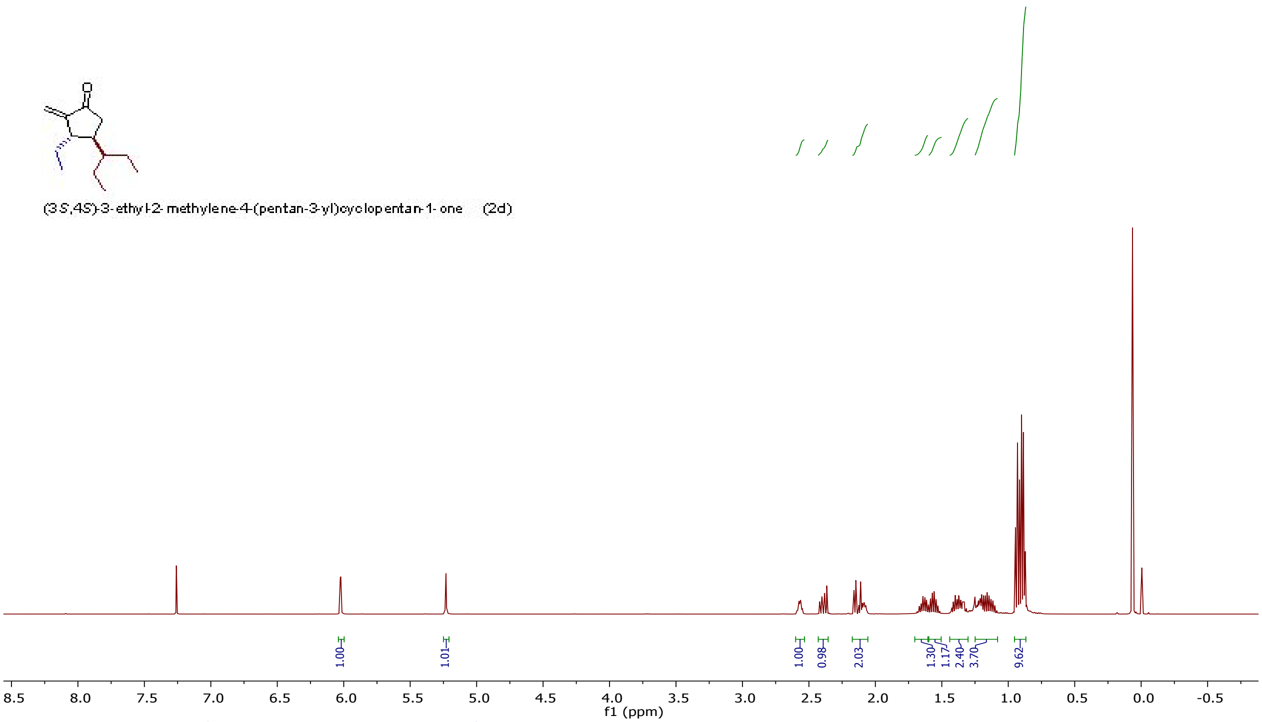
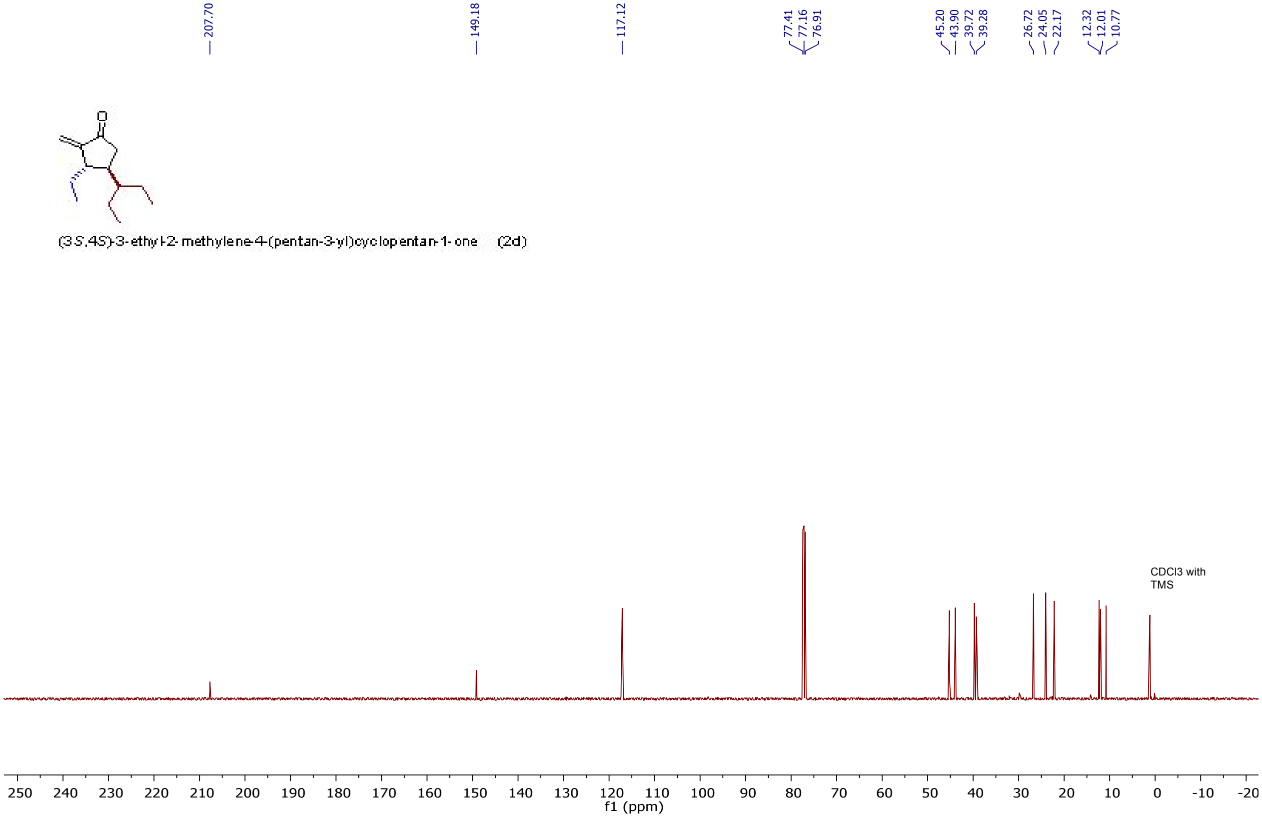
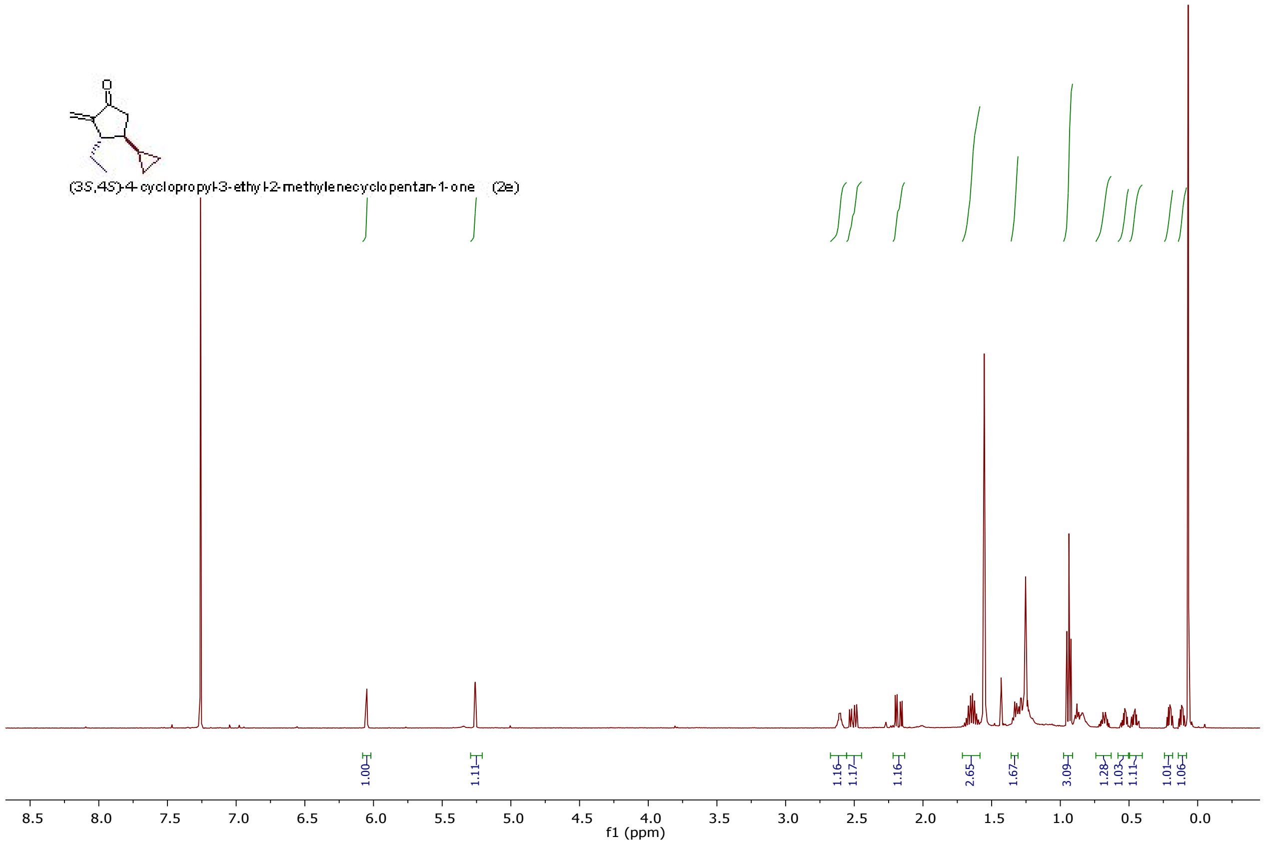
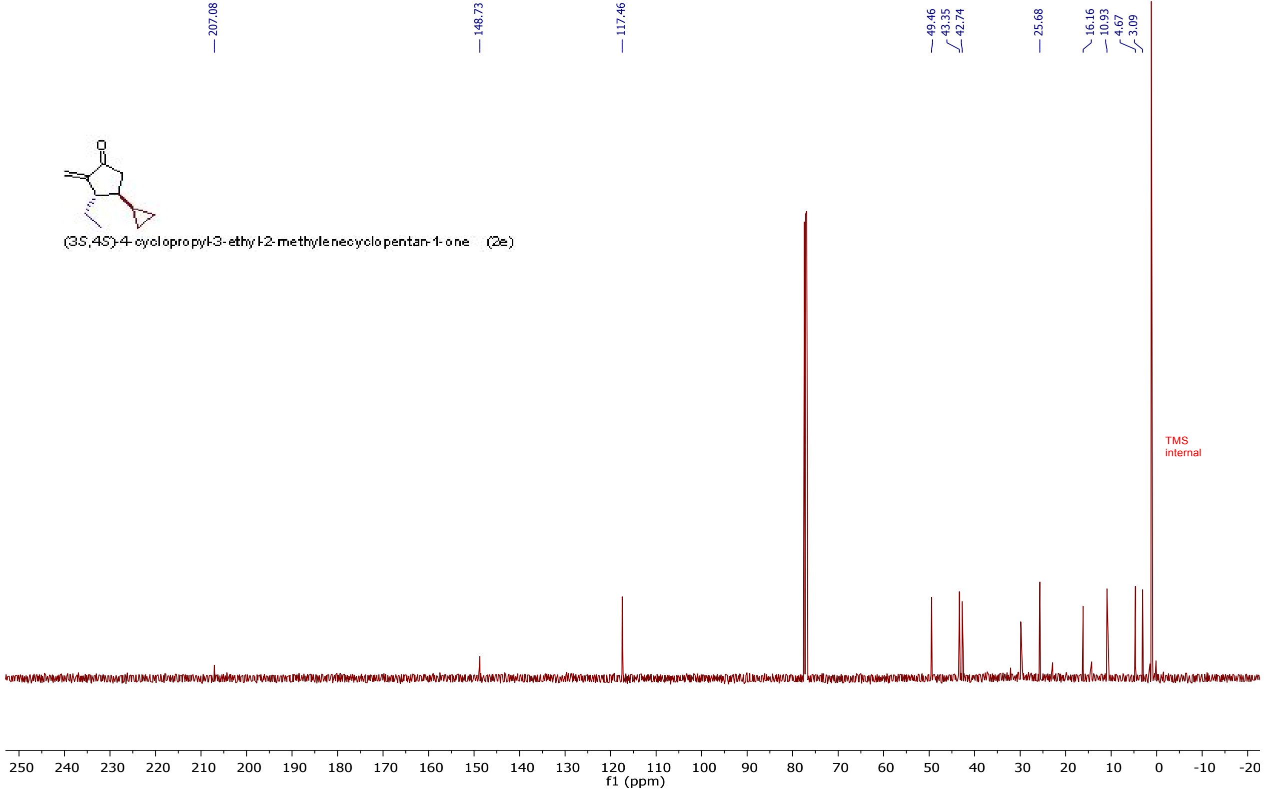


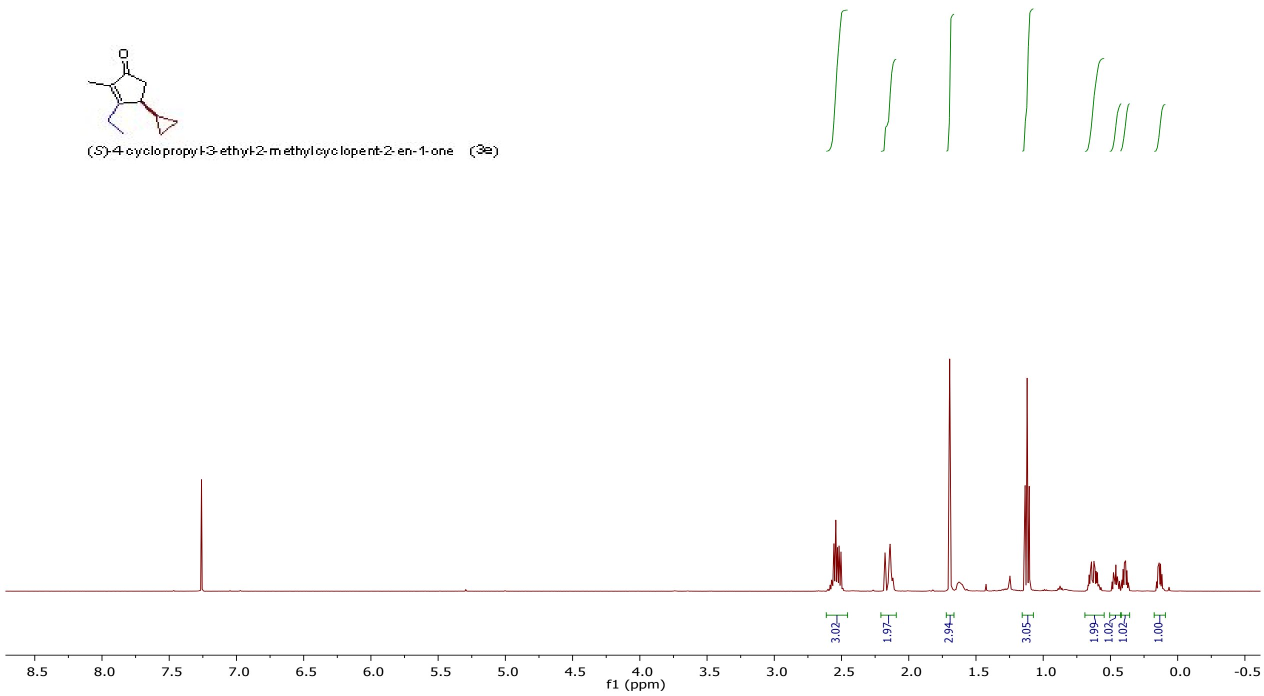


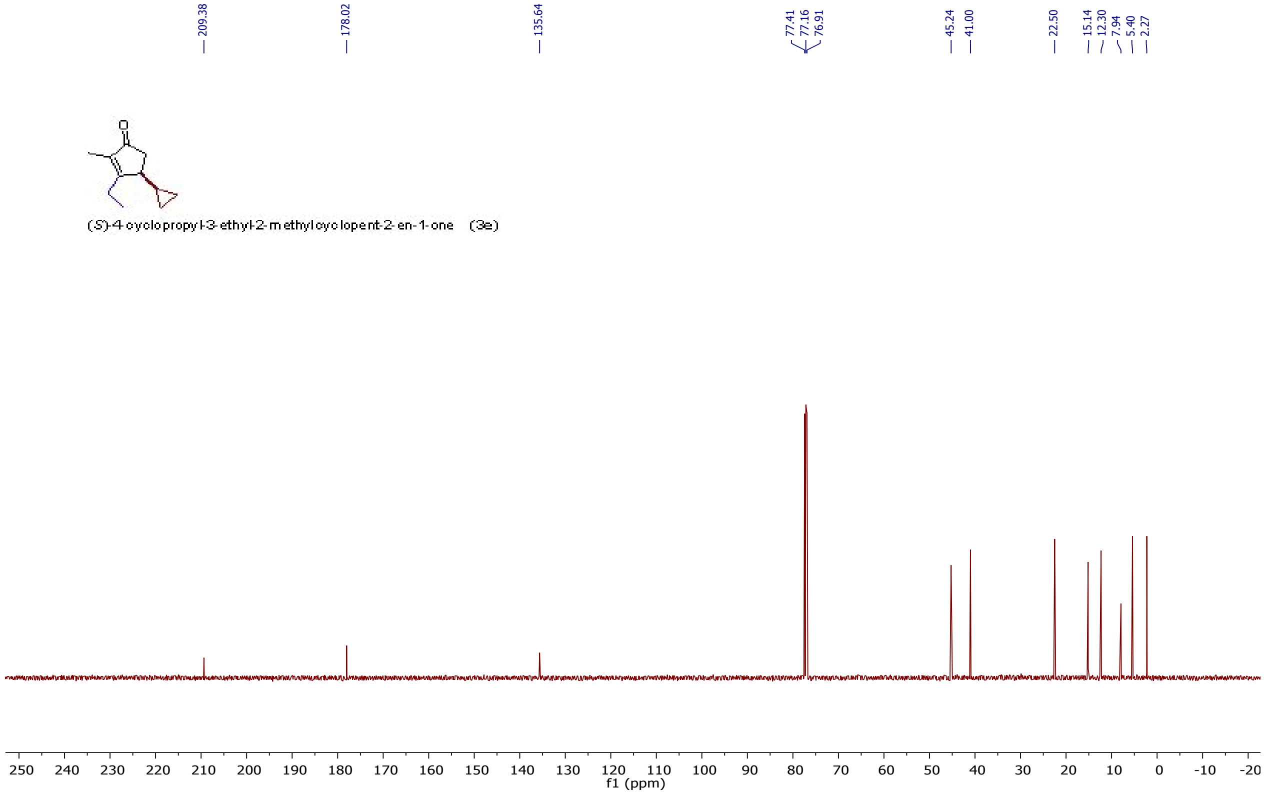
^{1}H NMR (500 MHz, CDCl$_3$) and **^{13}C NMR** (125 MHz, CDCl$_3$) of **2e**



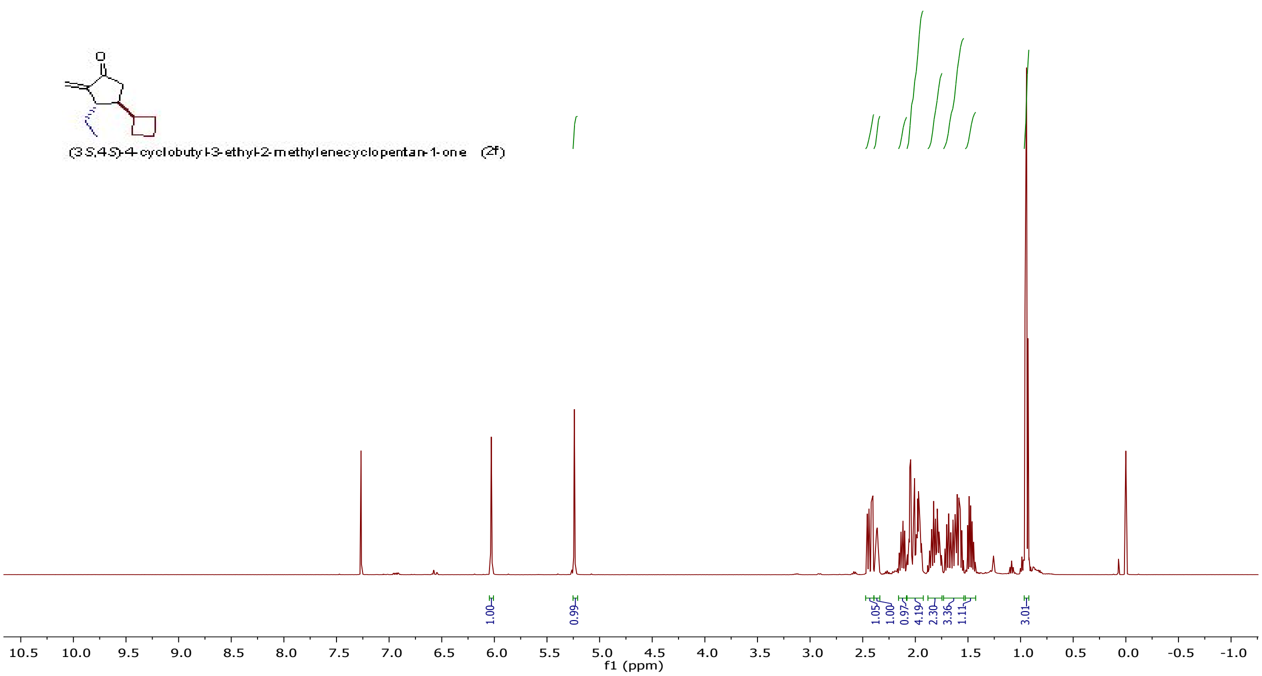


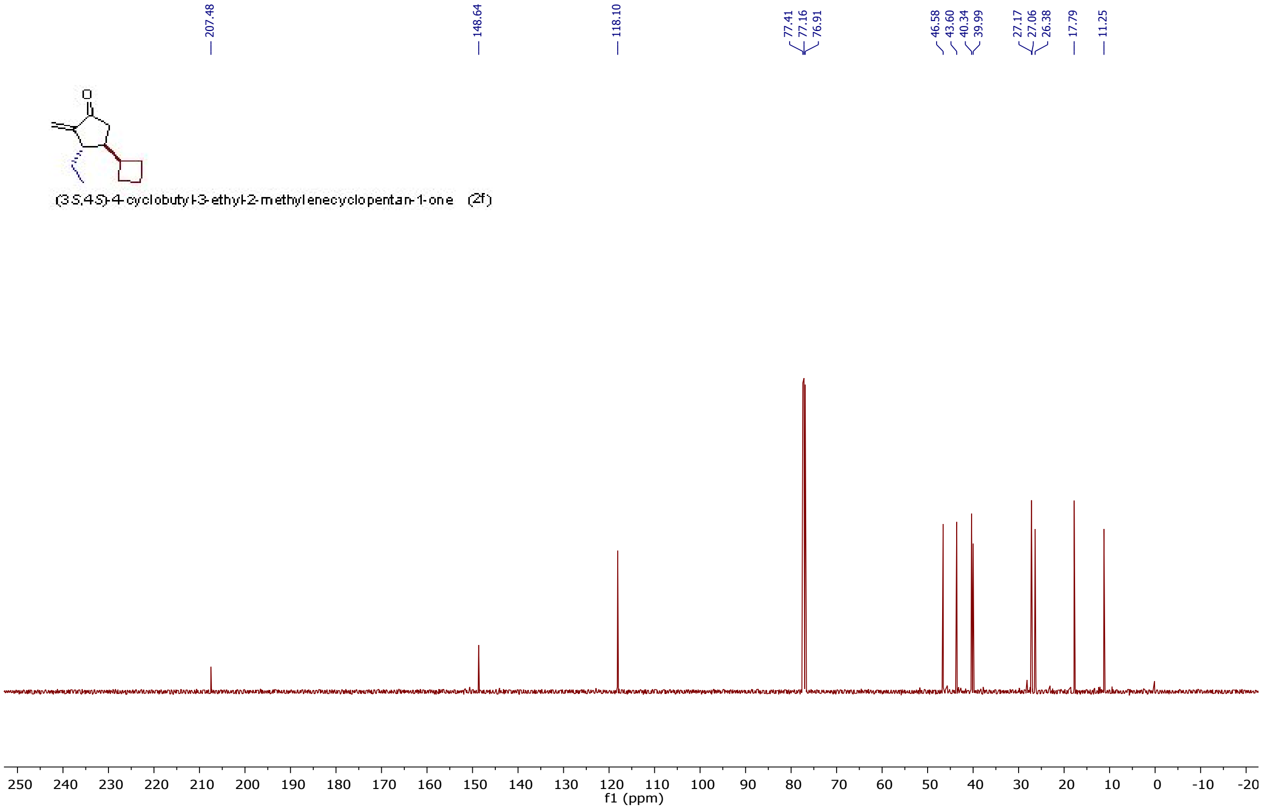
^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **3e**



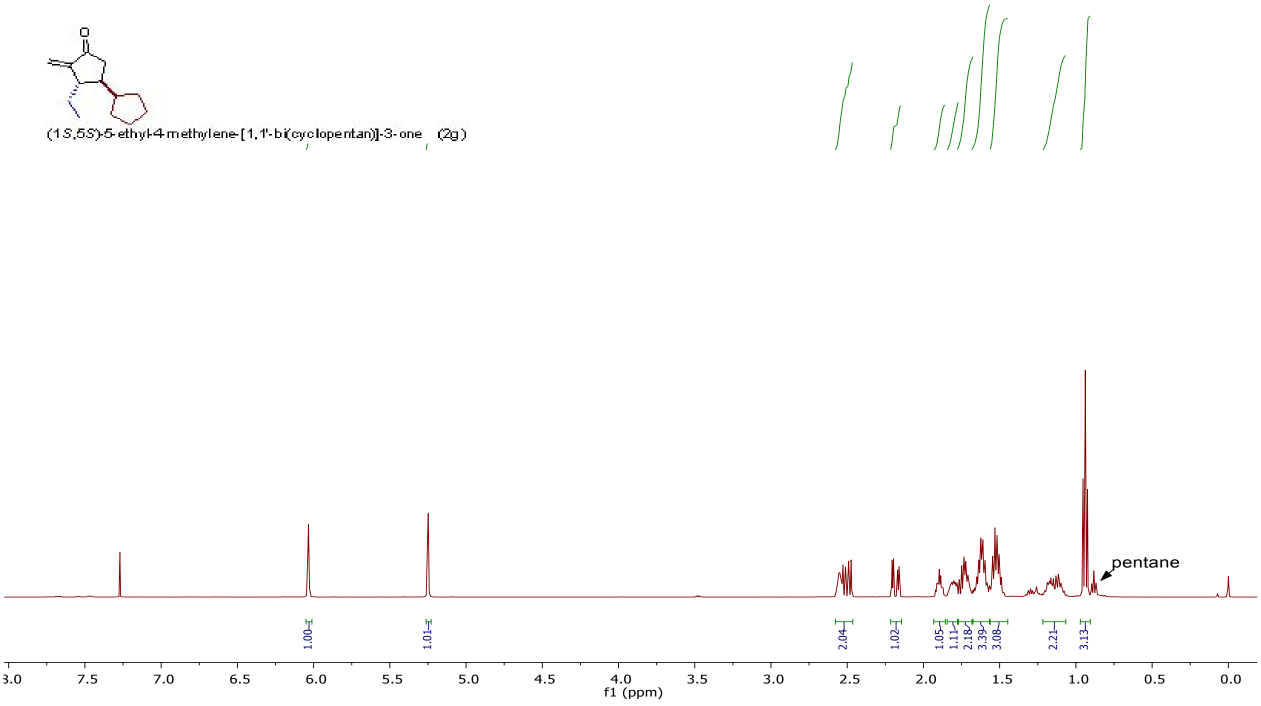


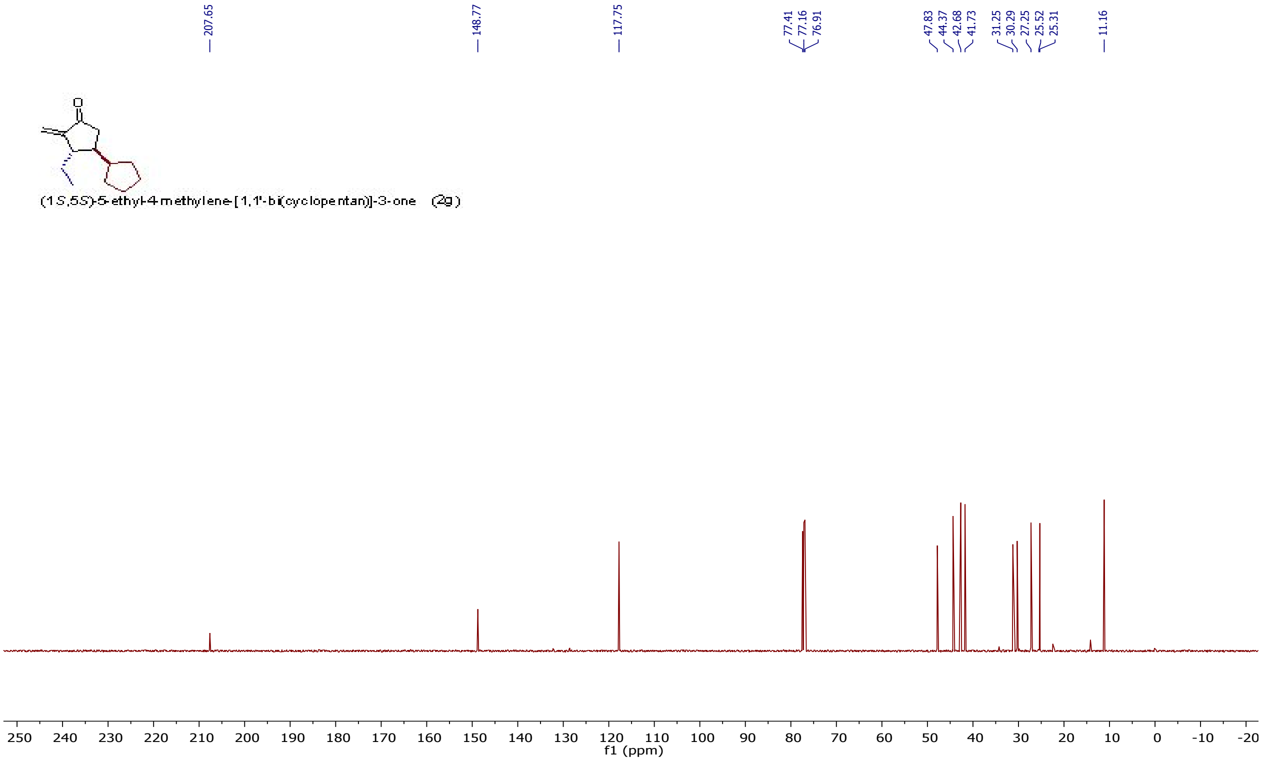
^{1}H NMR (500 MHz, $CDCl_3$) and **^{13}C NMR** (125 MHz, $CDCl_3$) of **2f**



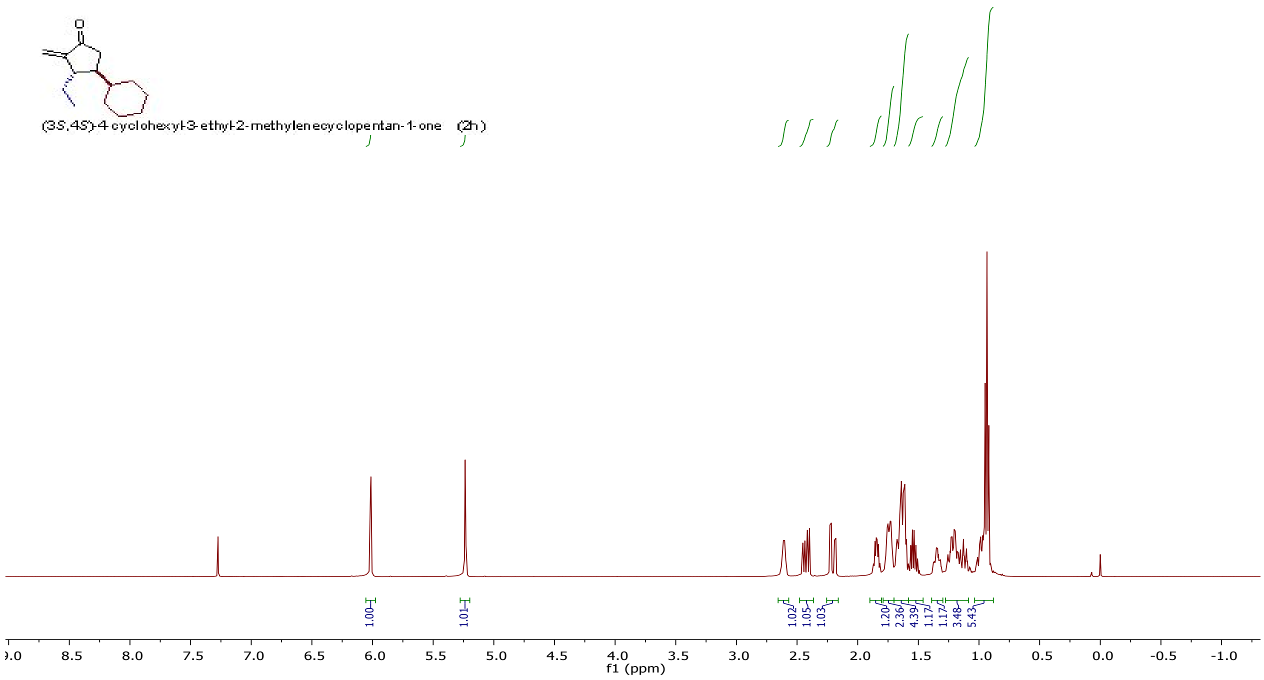


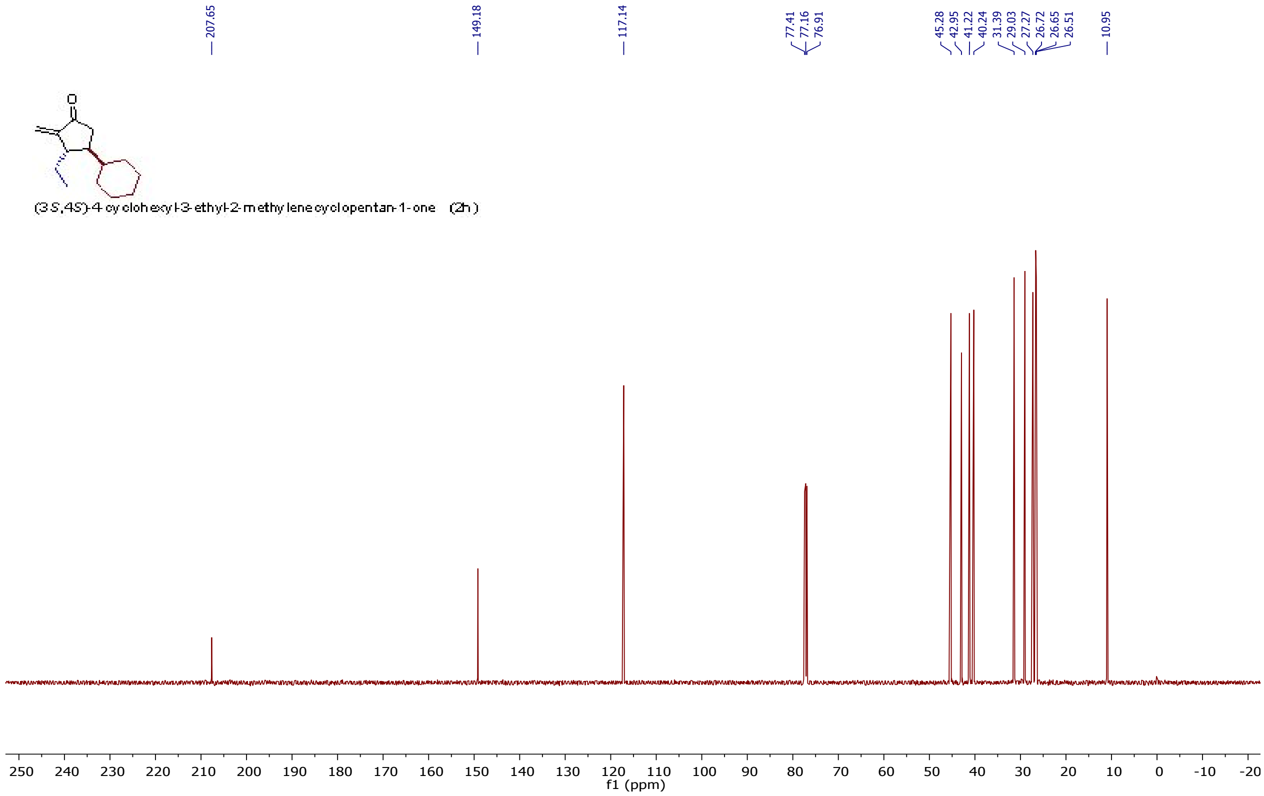
^{1}H NMR (500 MHz, $CDCl_3$) and **^{13}C NMR** (125 MHz, $CDCl_3$) of **2g**



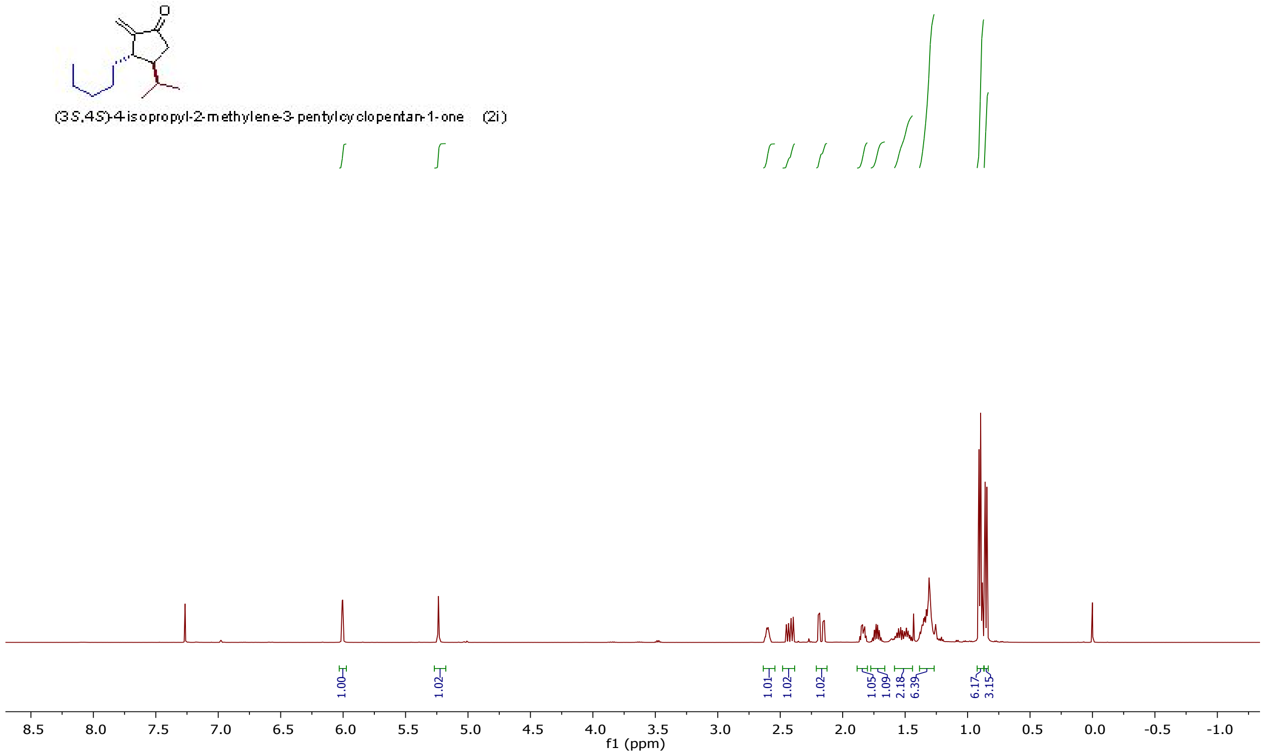


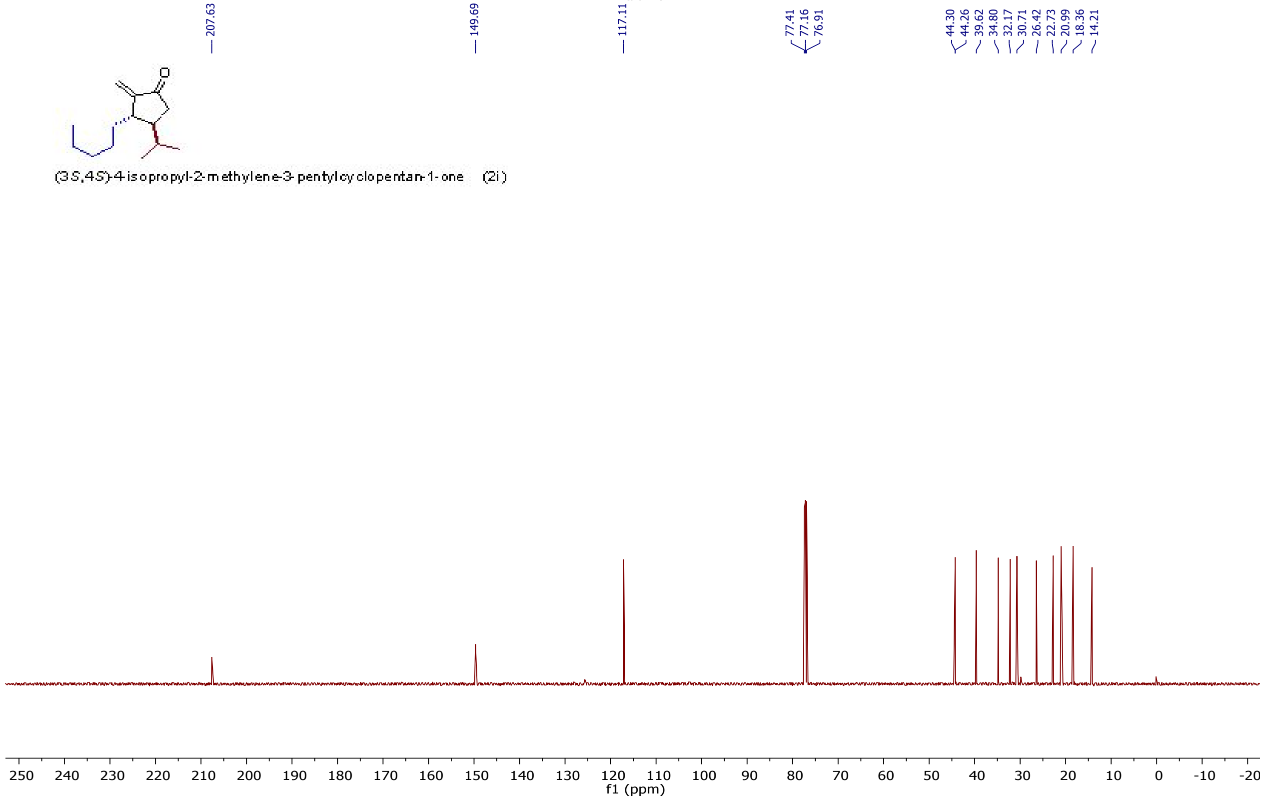
^{1}H NMR (500 MHz, CDCl$_3$) and **^{13}C NMR** (125 MHz, CDCl$_3$) of **2h**



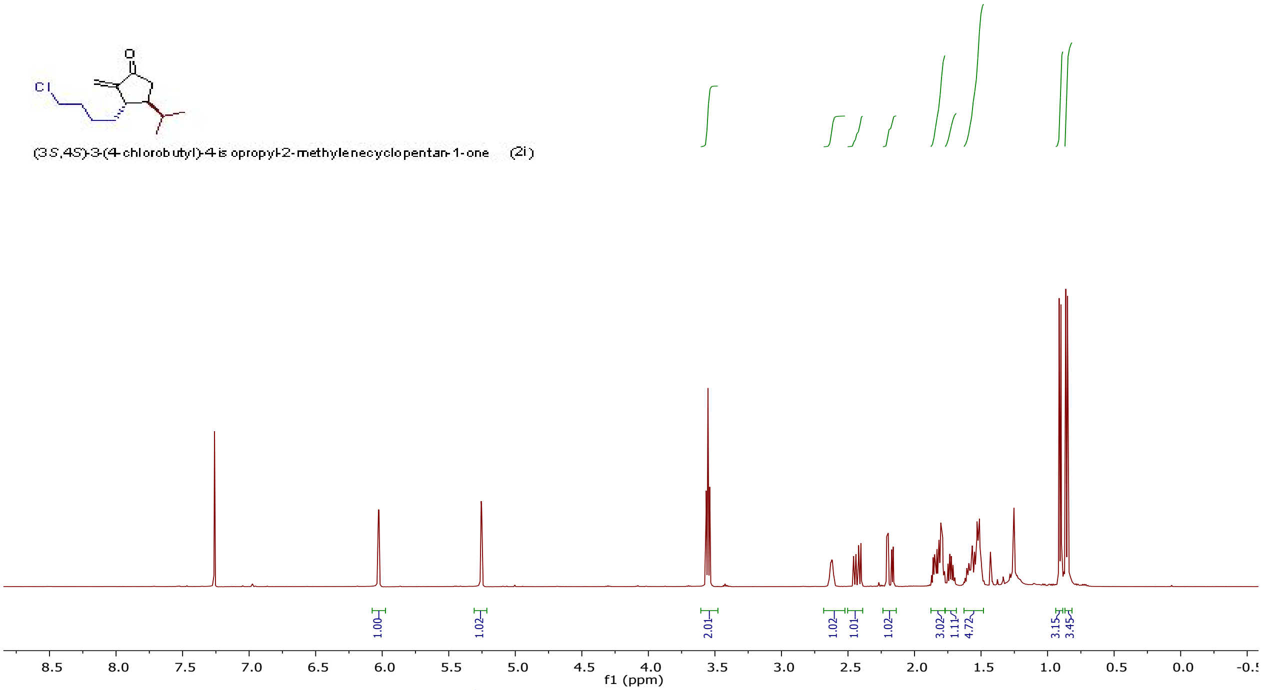


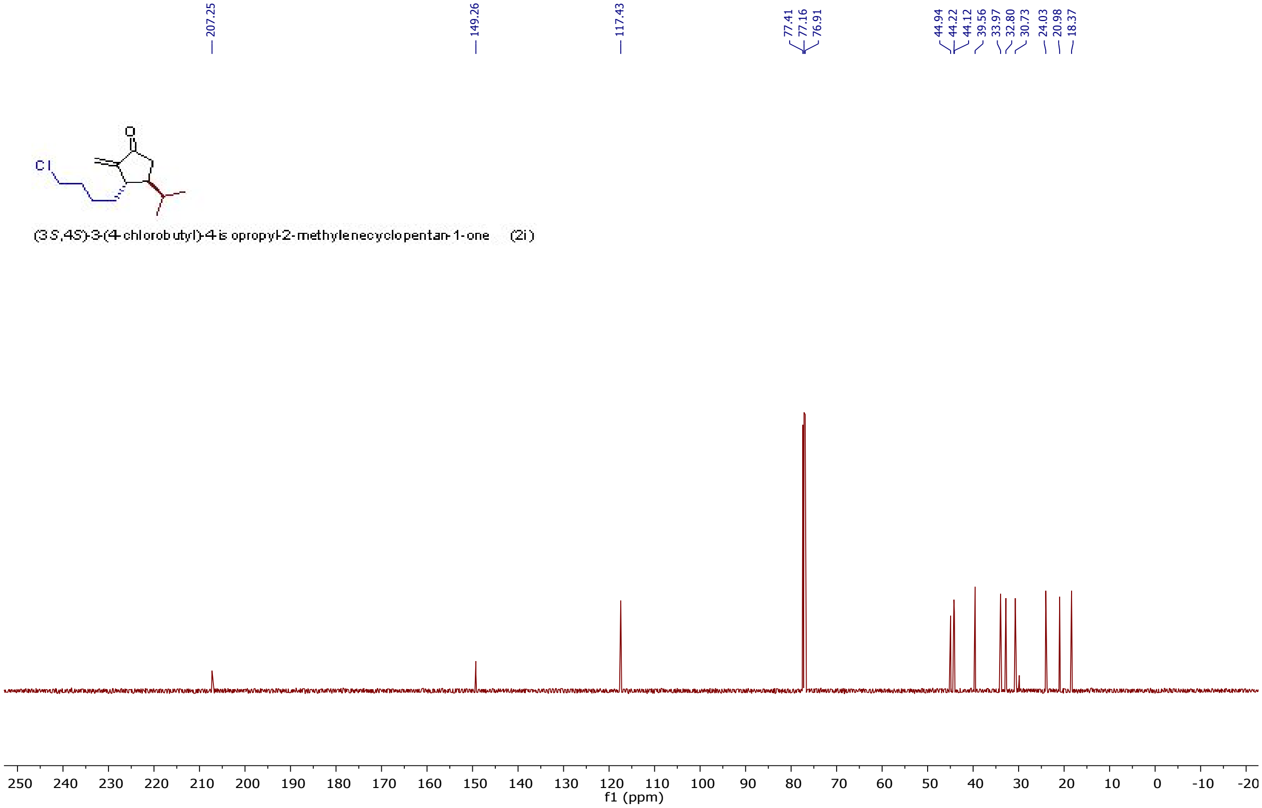
^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **2i**



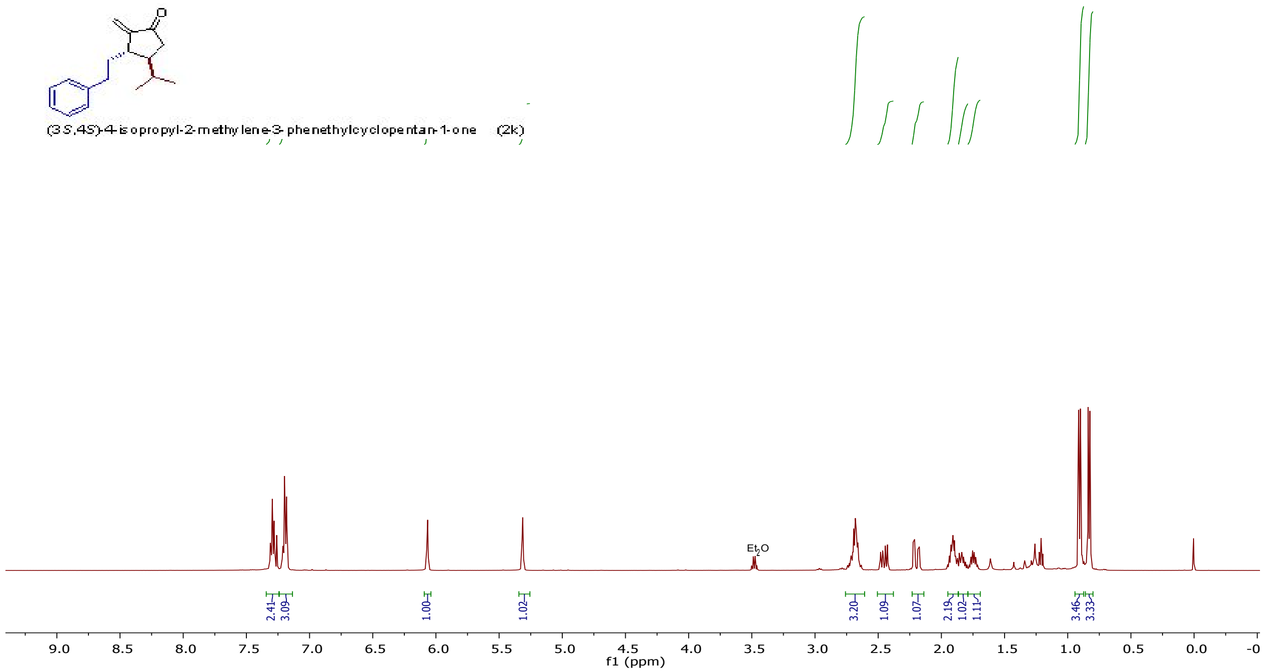


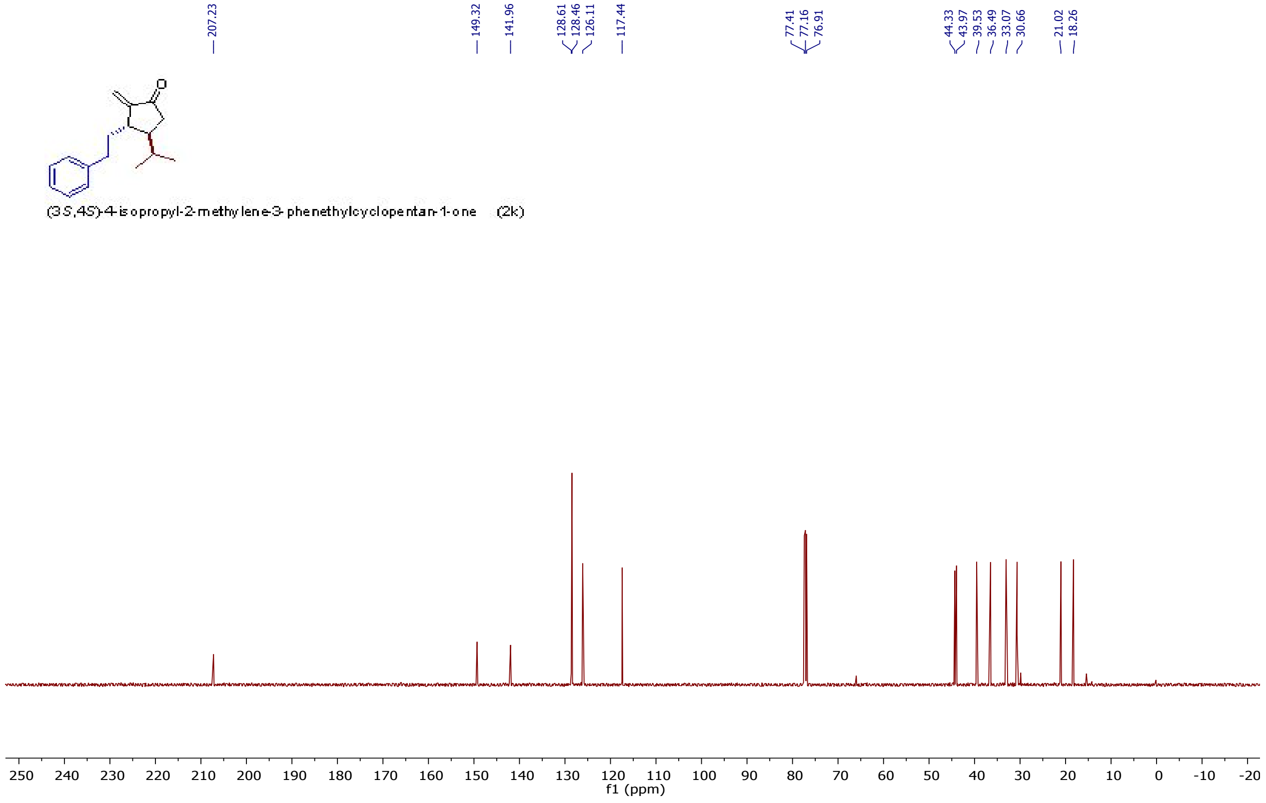
^{1}H NMR (500 MHz, CDCl$_3$) and **^{13}C NMR** (125 MHz, CDCl$_3$) of **2j**



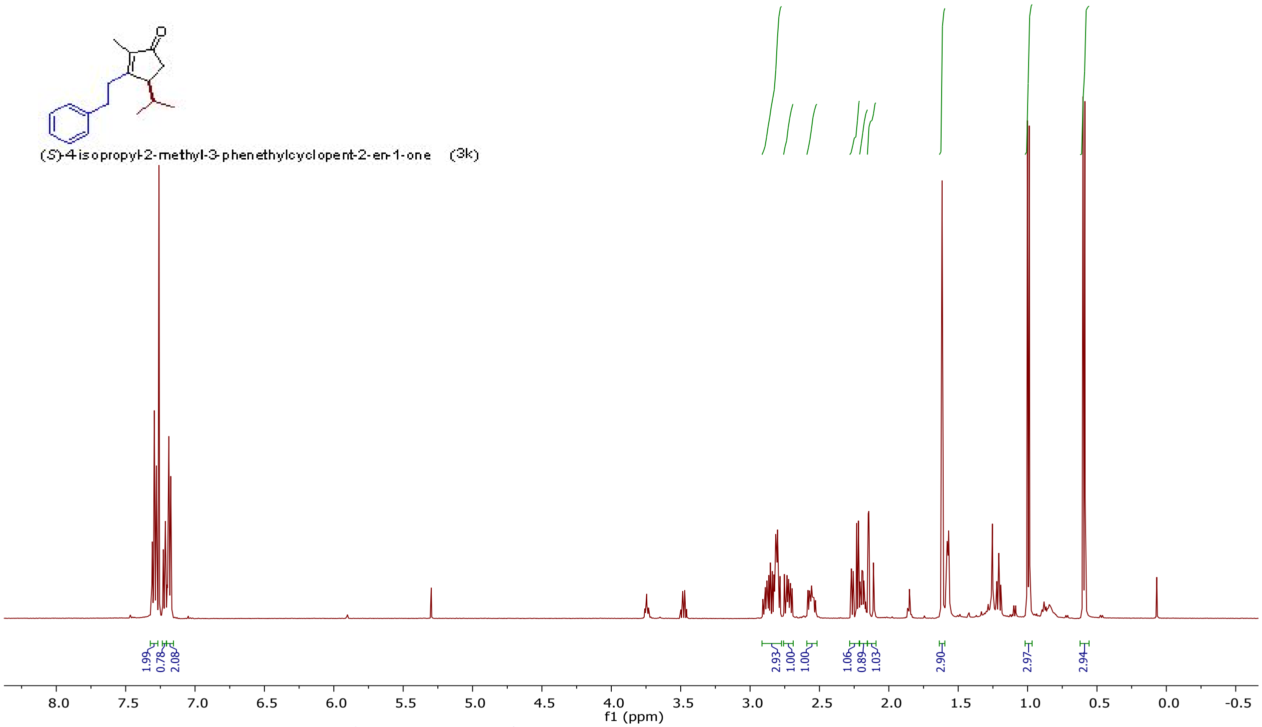


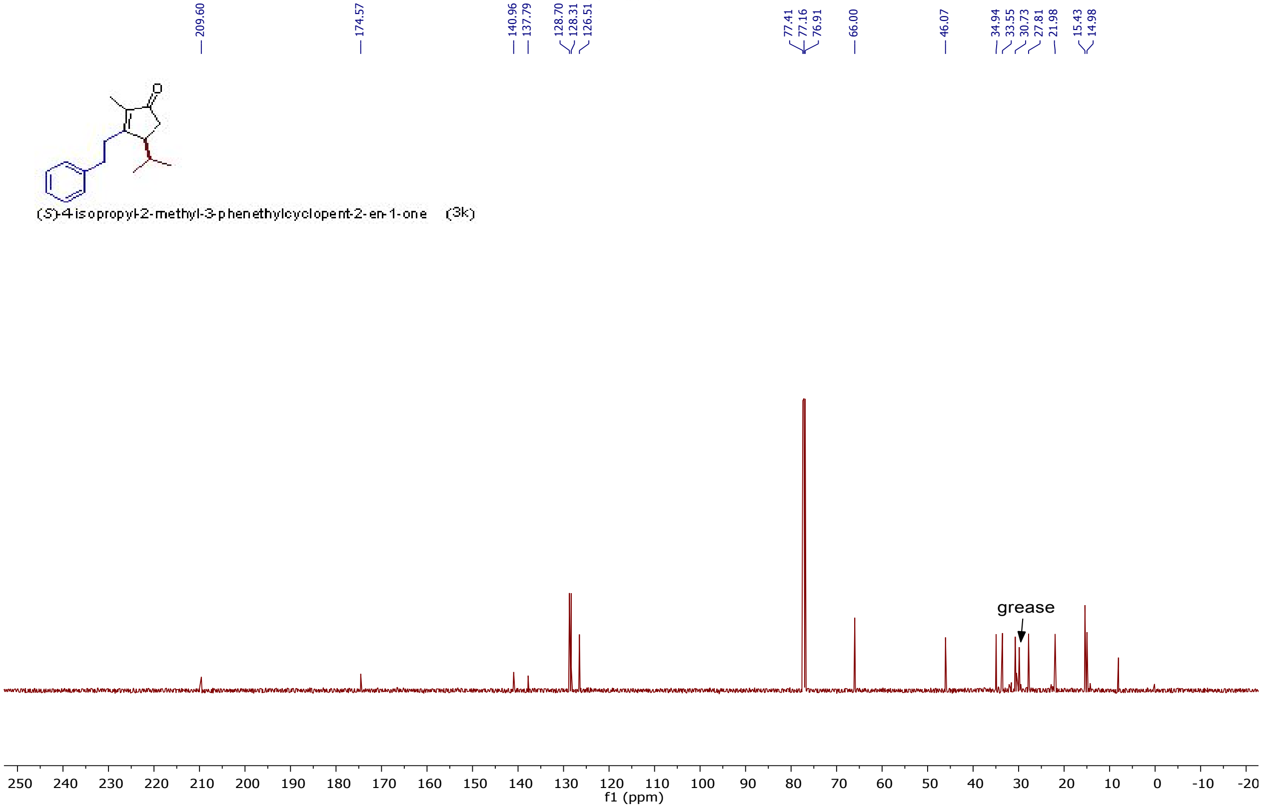
^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **2k**



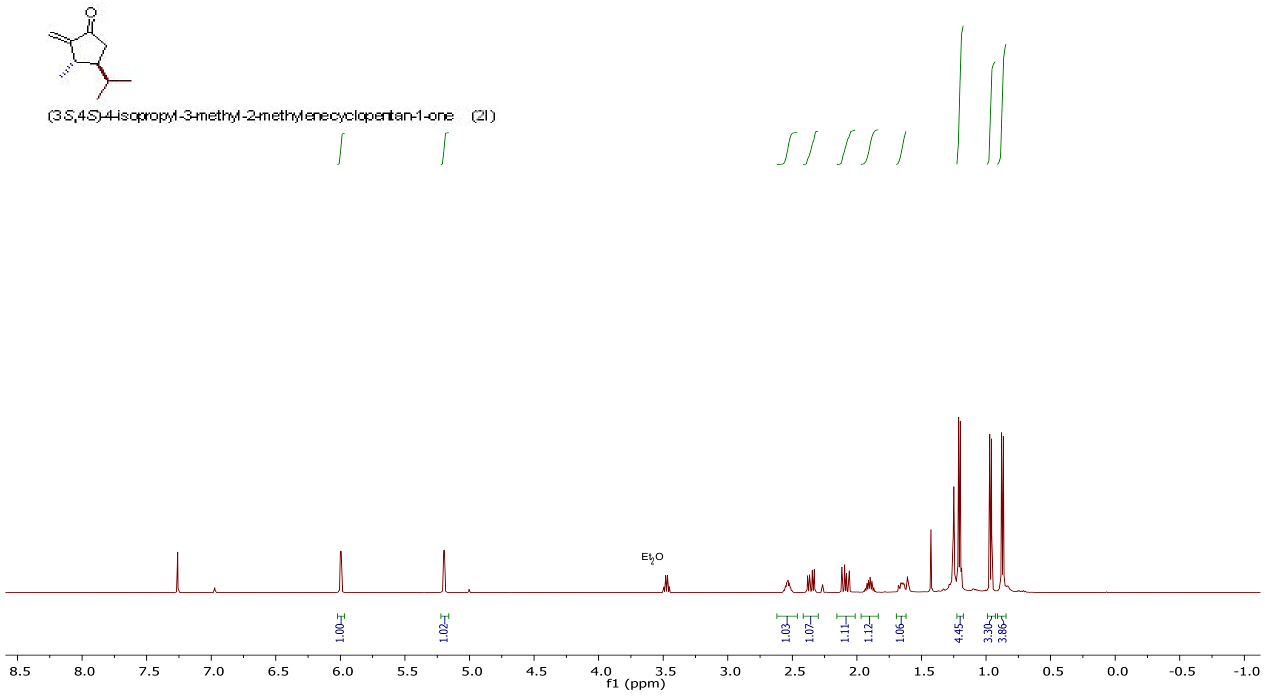


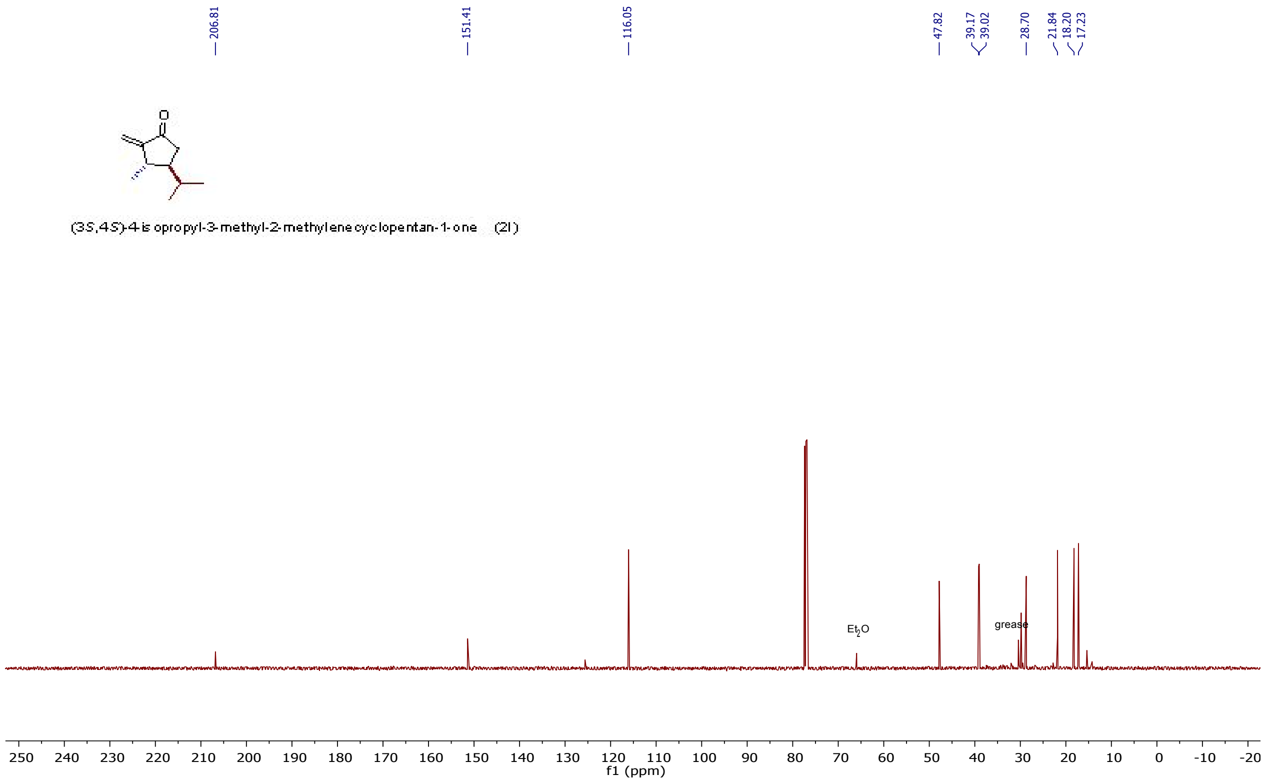
^{1}H NMR (500 MHz, CDCl$_3$) and **^{13}C NMR** (125 MHz, CDCl$_3$) of **3k**



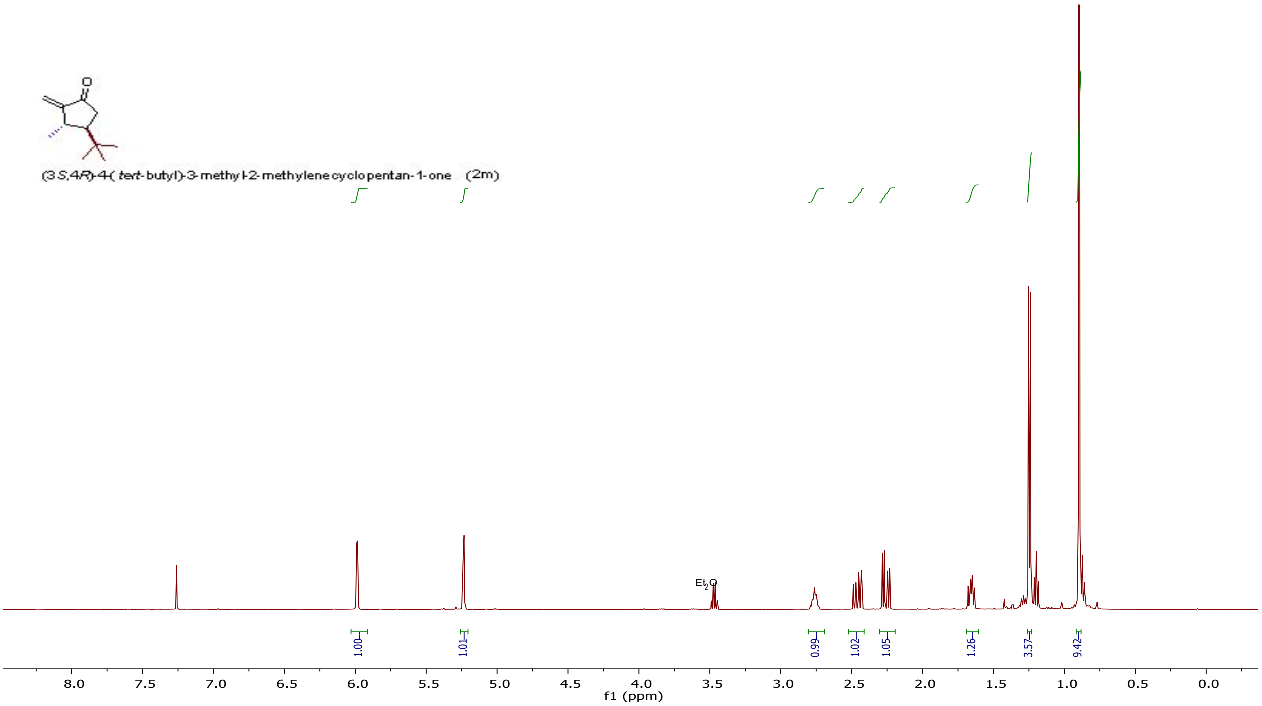


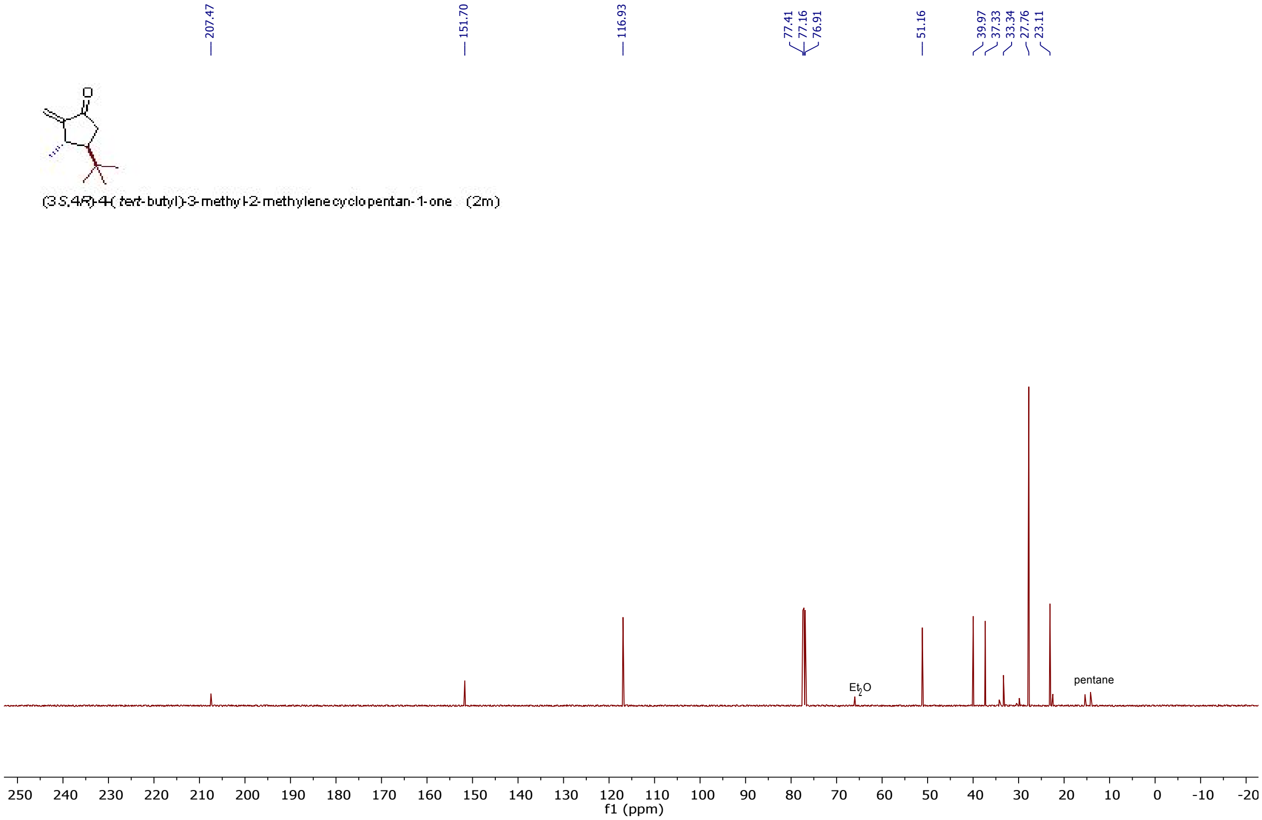
^{1}**H NMR (500 MHz, CDCl$_3$)** and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **2l**





^{1}H NMR (500 MHz, CDCl$_3$) and **^{13}C NMR** (125 MHz, CDCl$_3$) of **2m**





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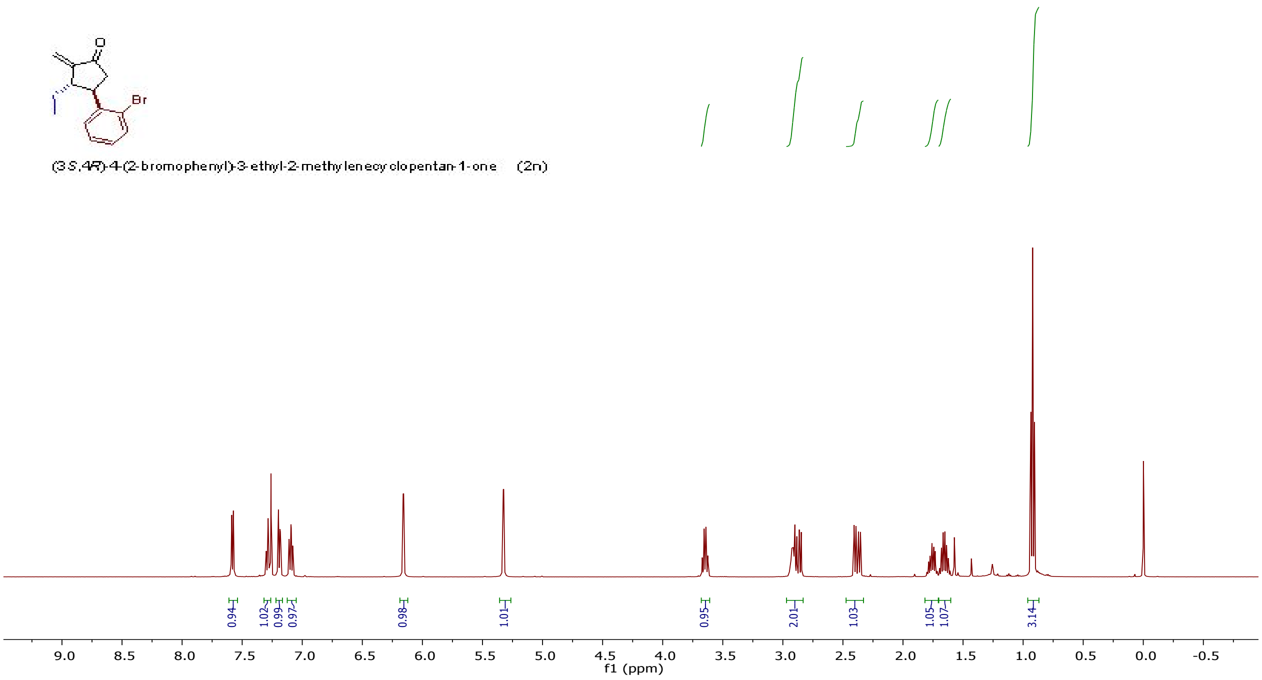

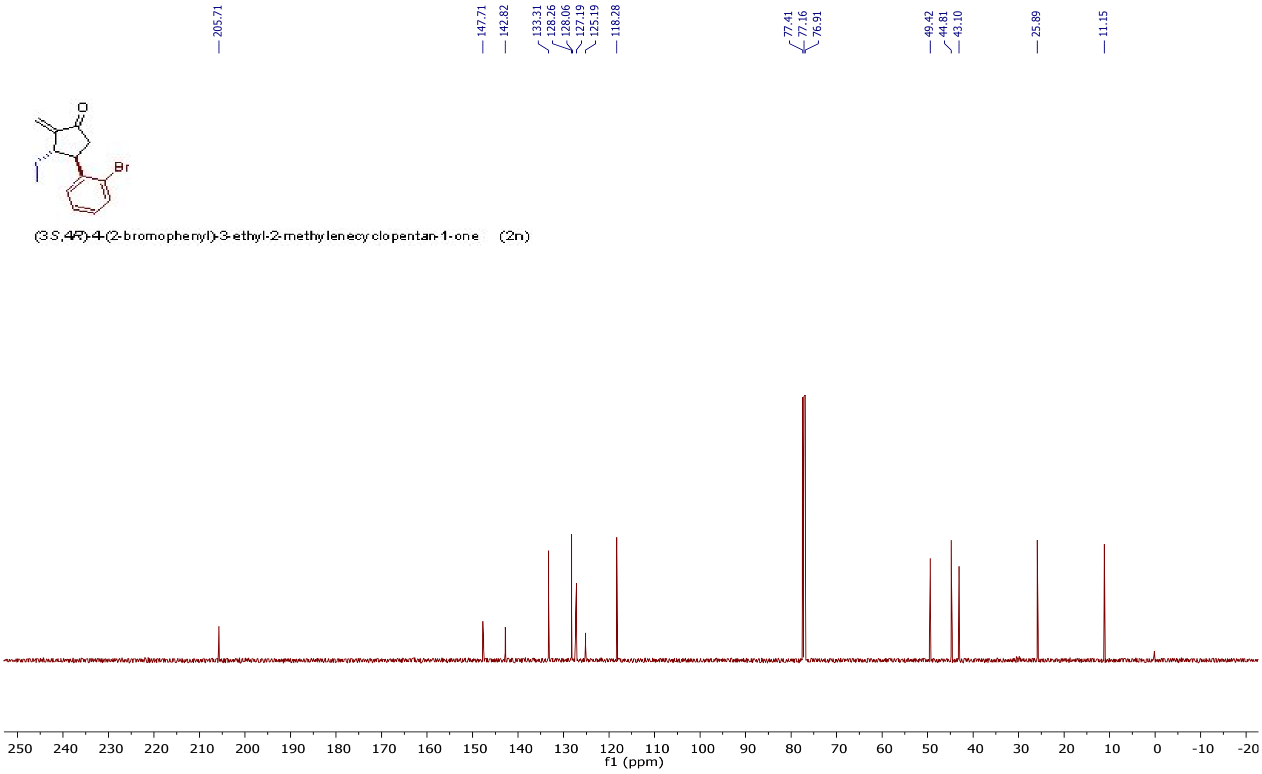

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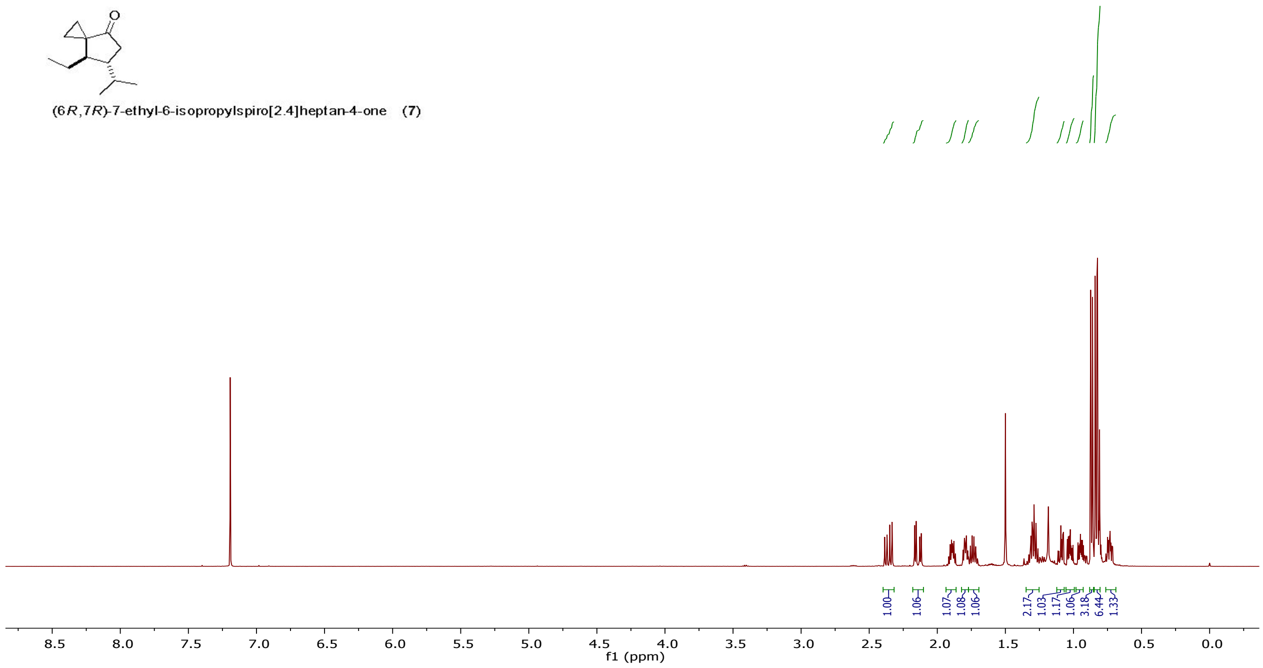

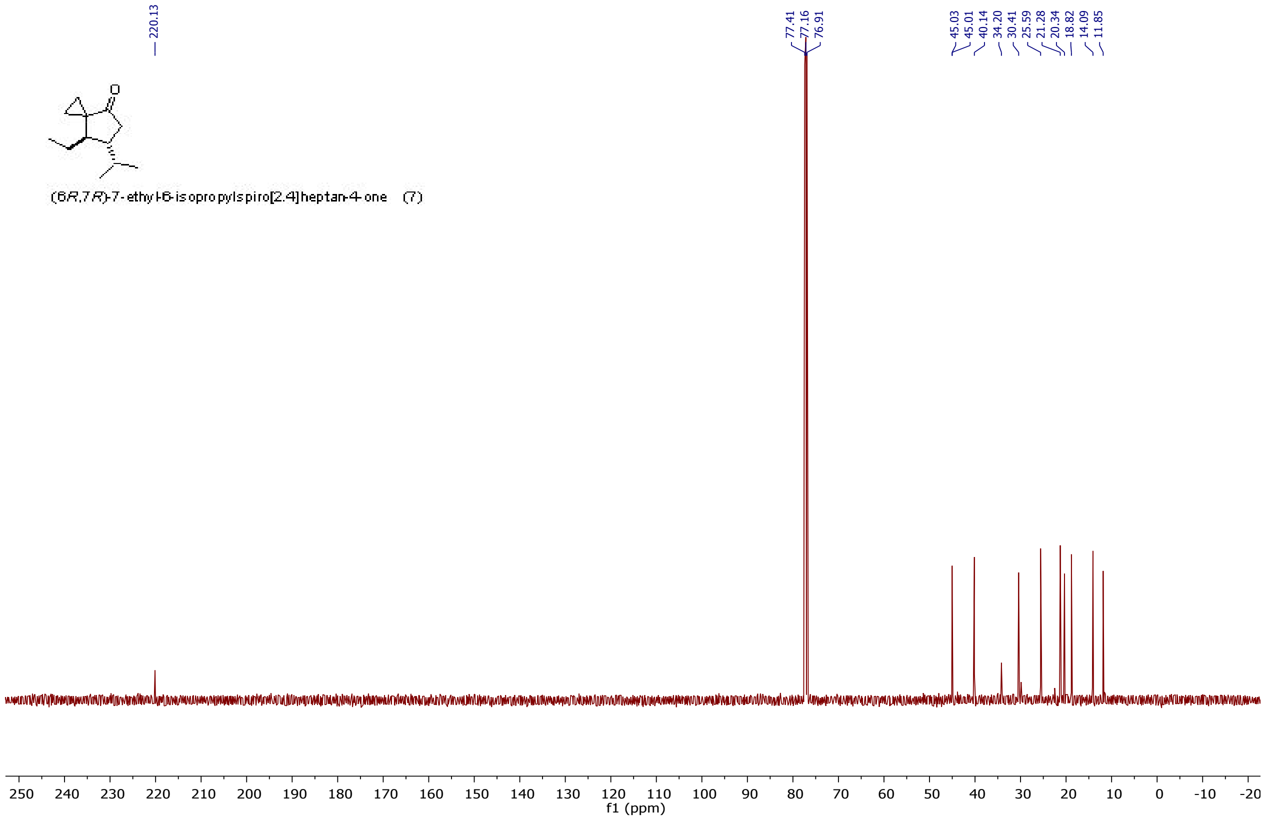

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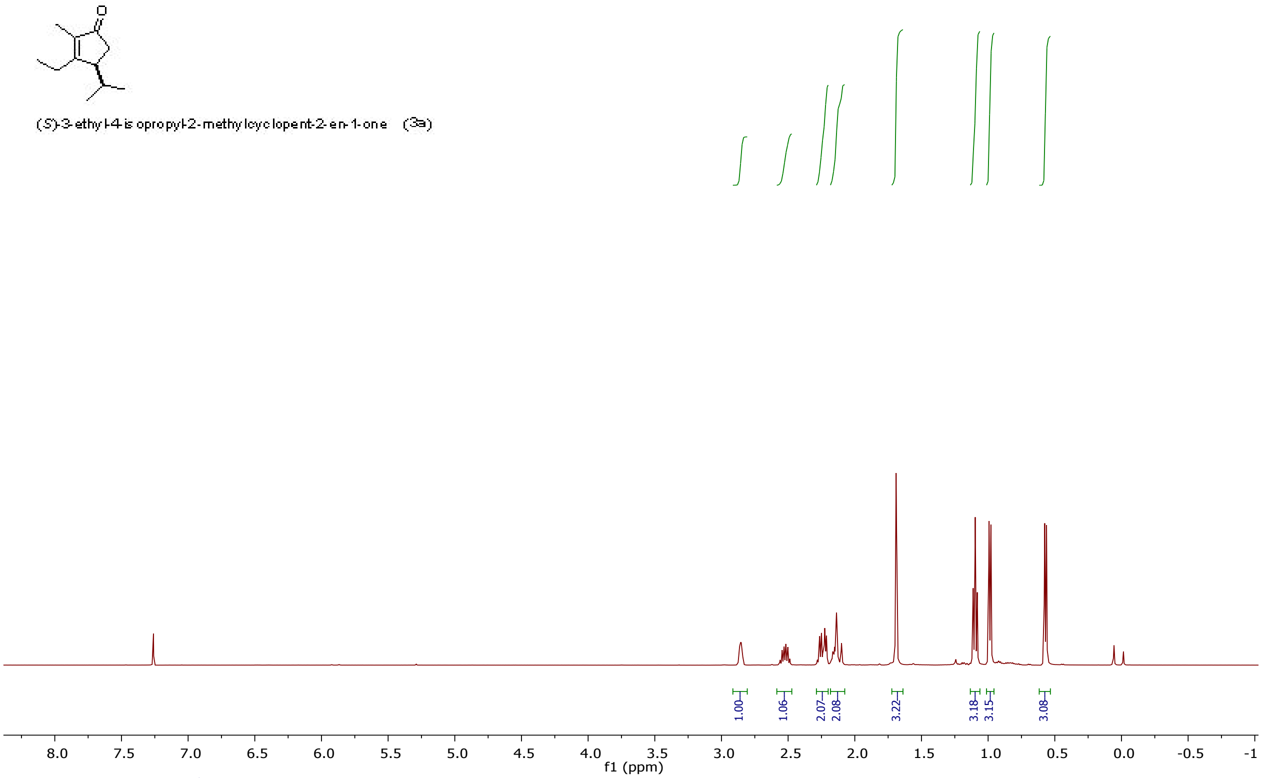
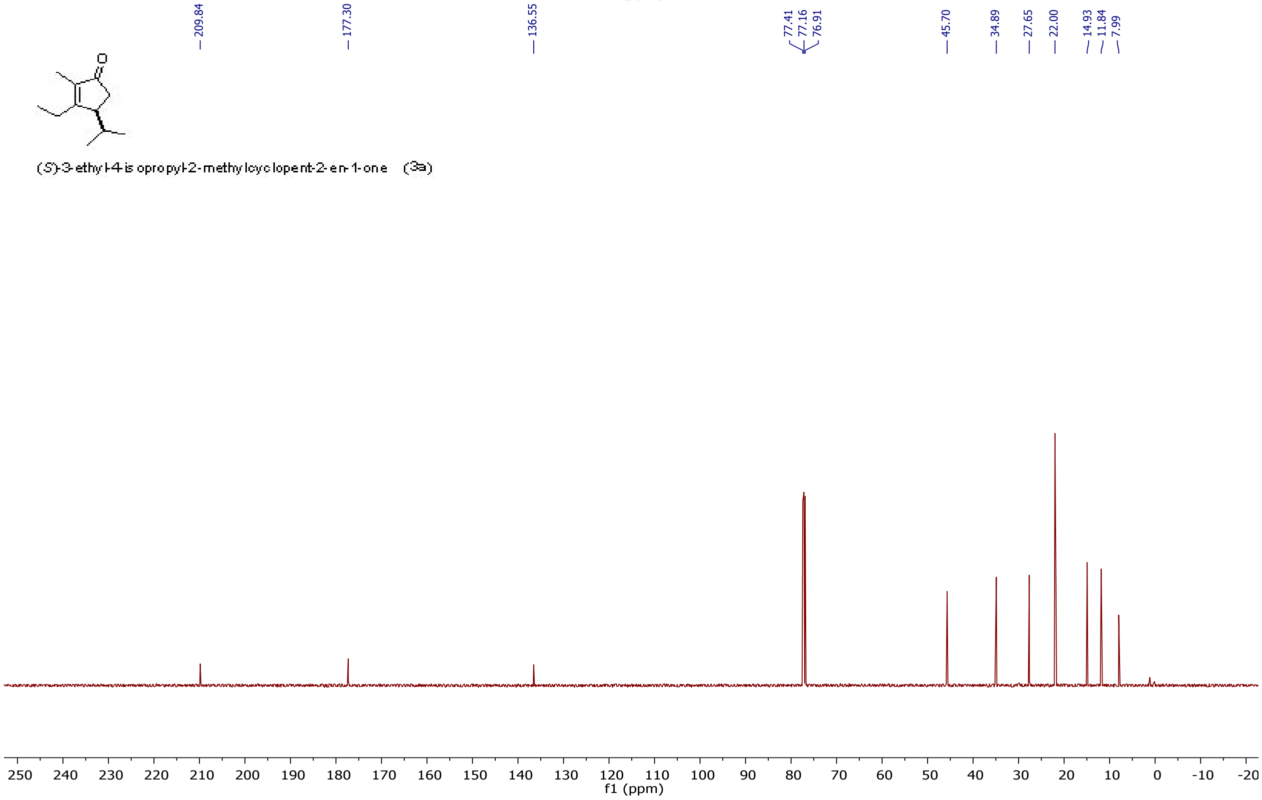
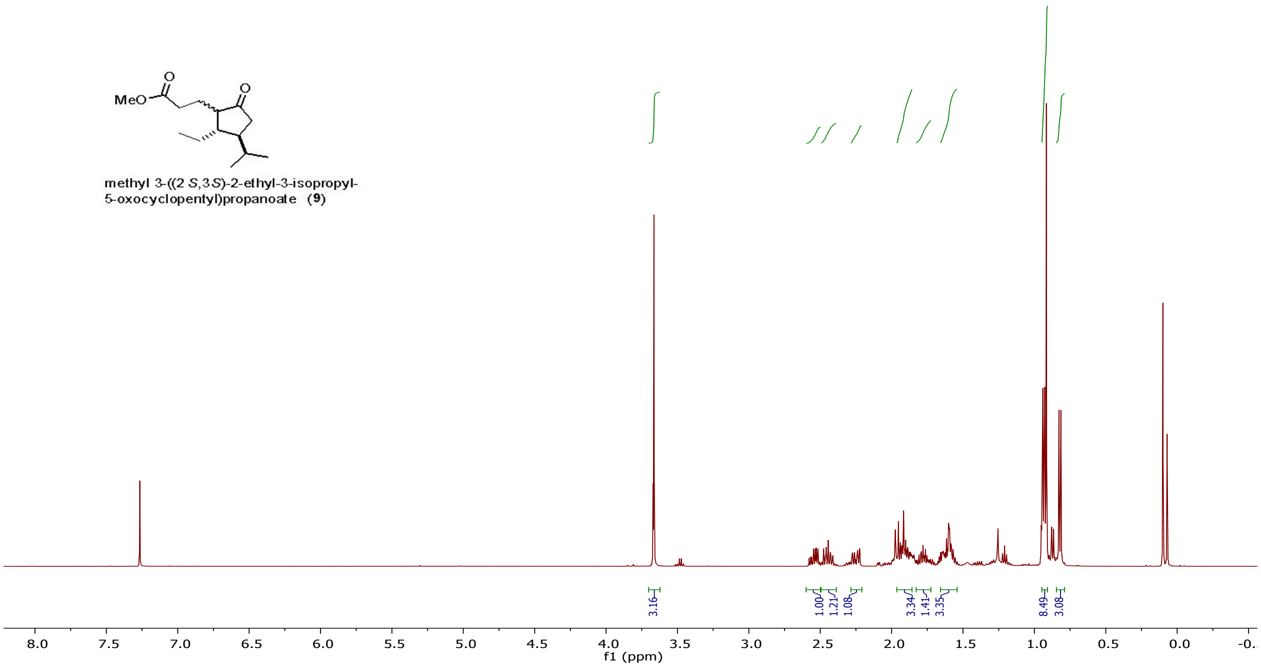
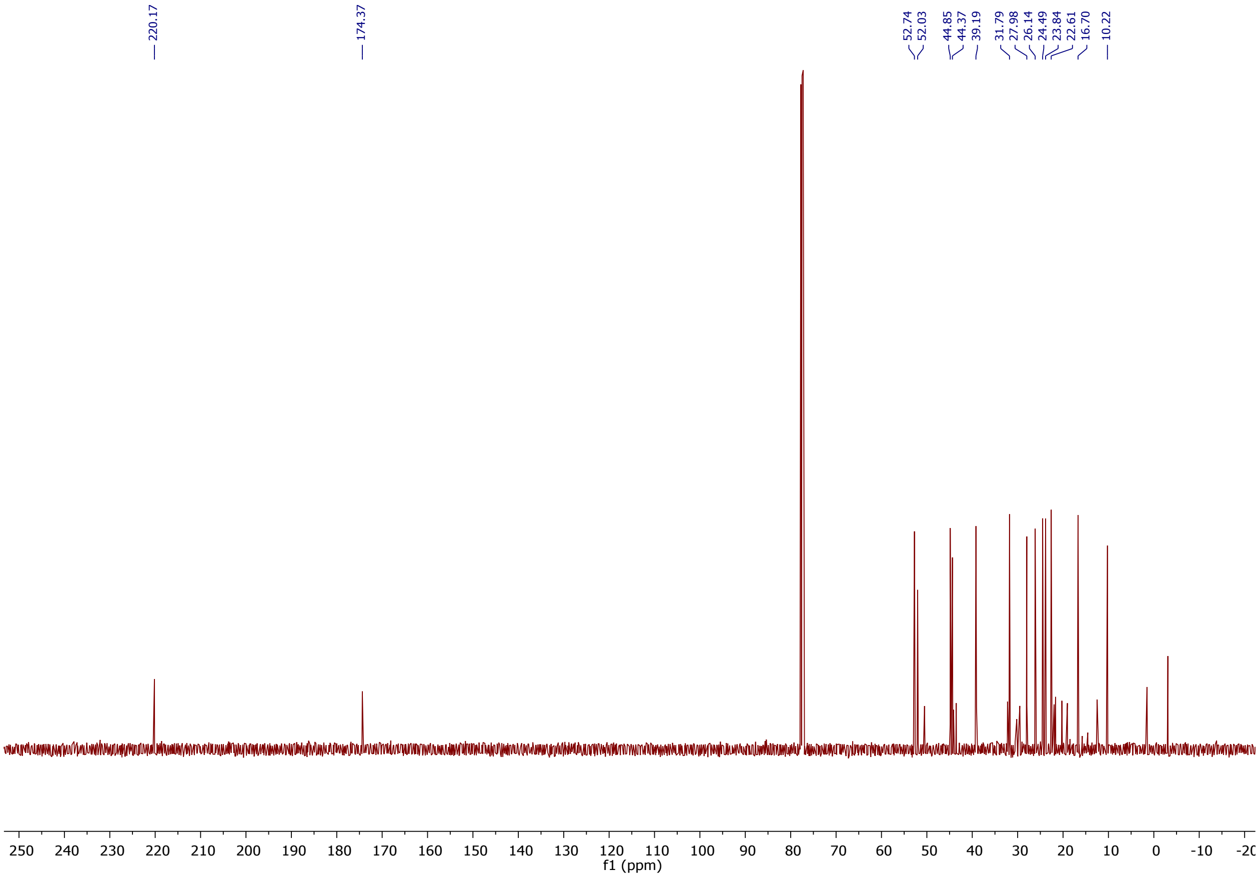


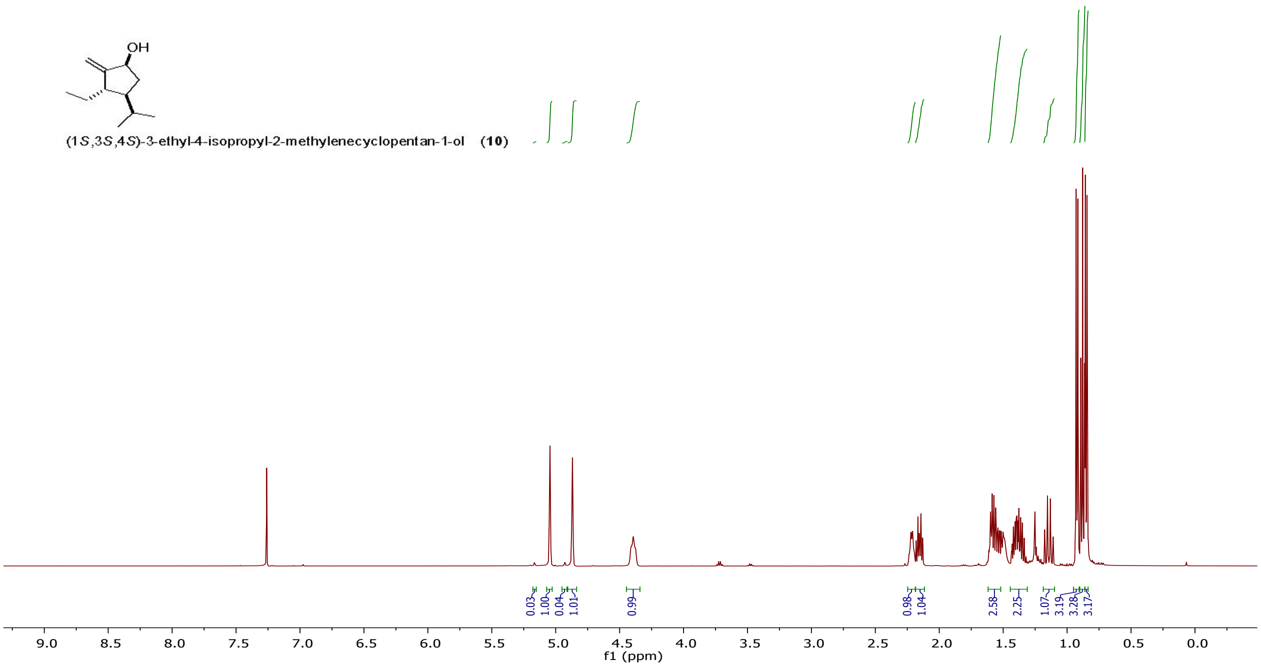


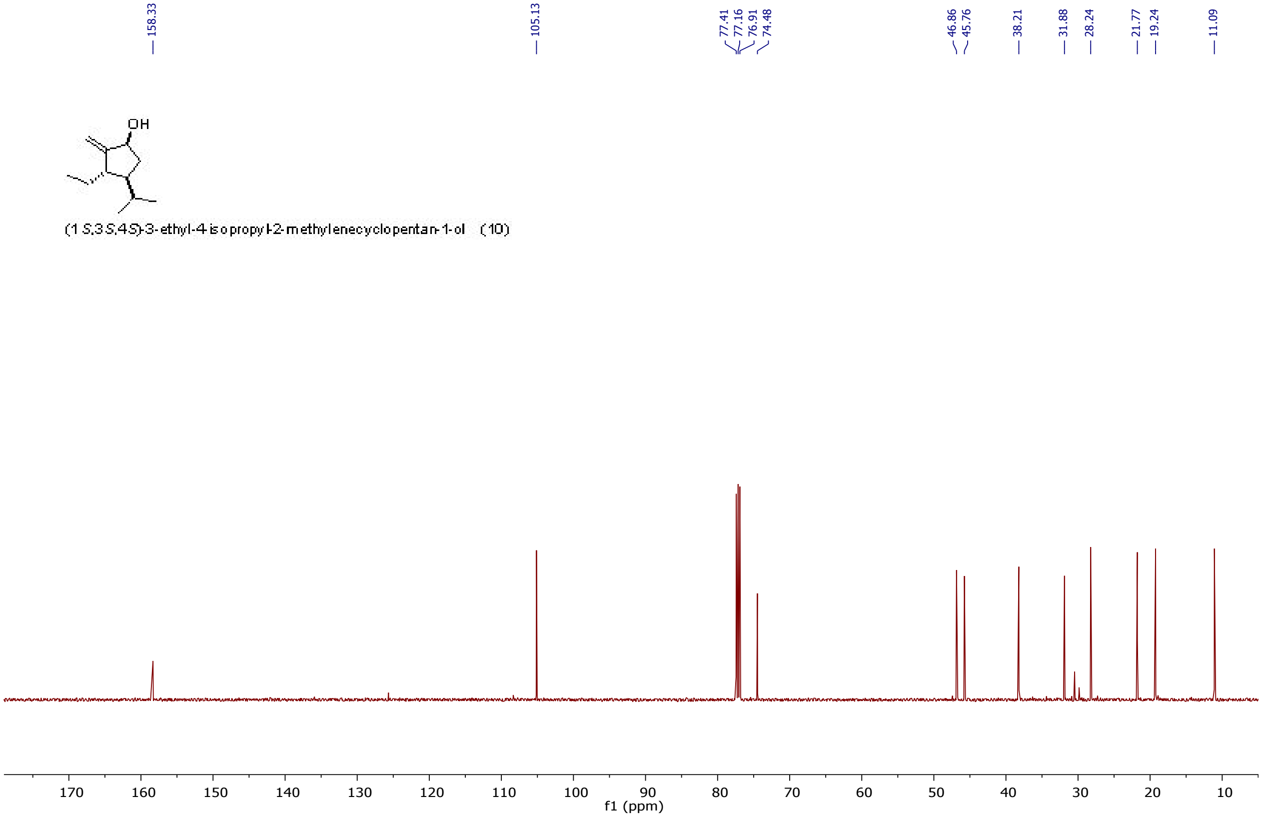
^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **9**



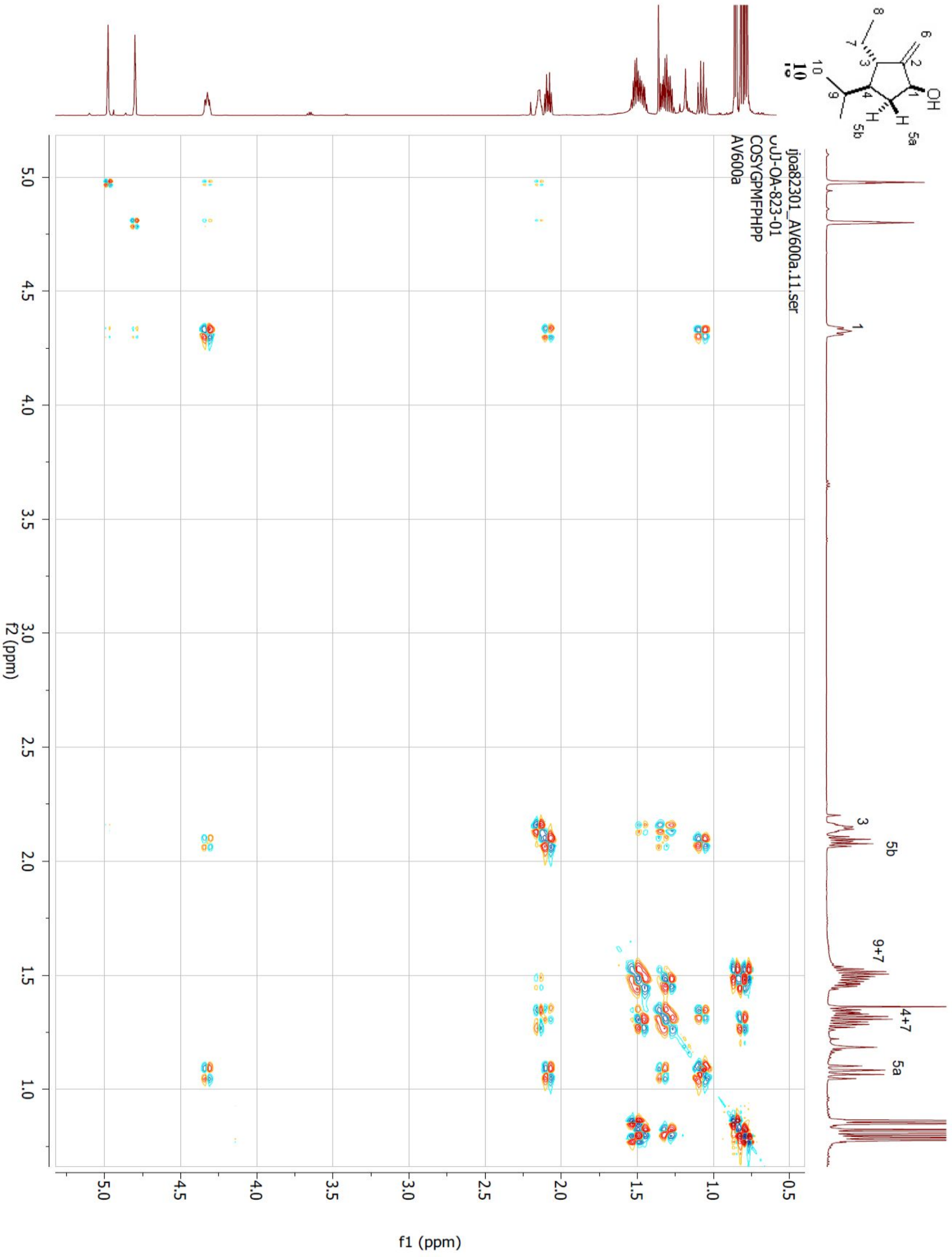


^{1}**H NMR** (500 MHz, CDCl$_3$) and ^{13}**C NMR** (125 MHz, CDCl$_3$) of **10**





H-H COSY of **10**



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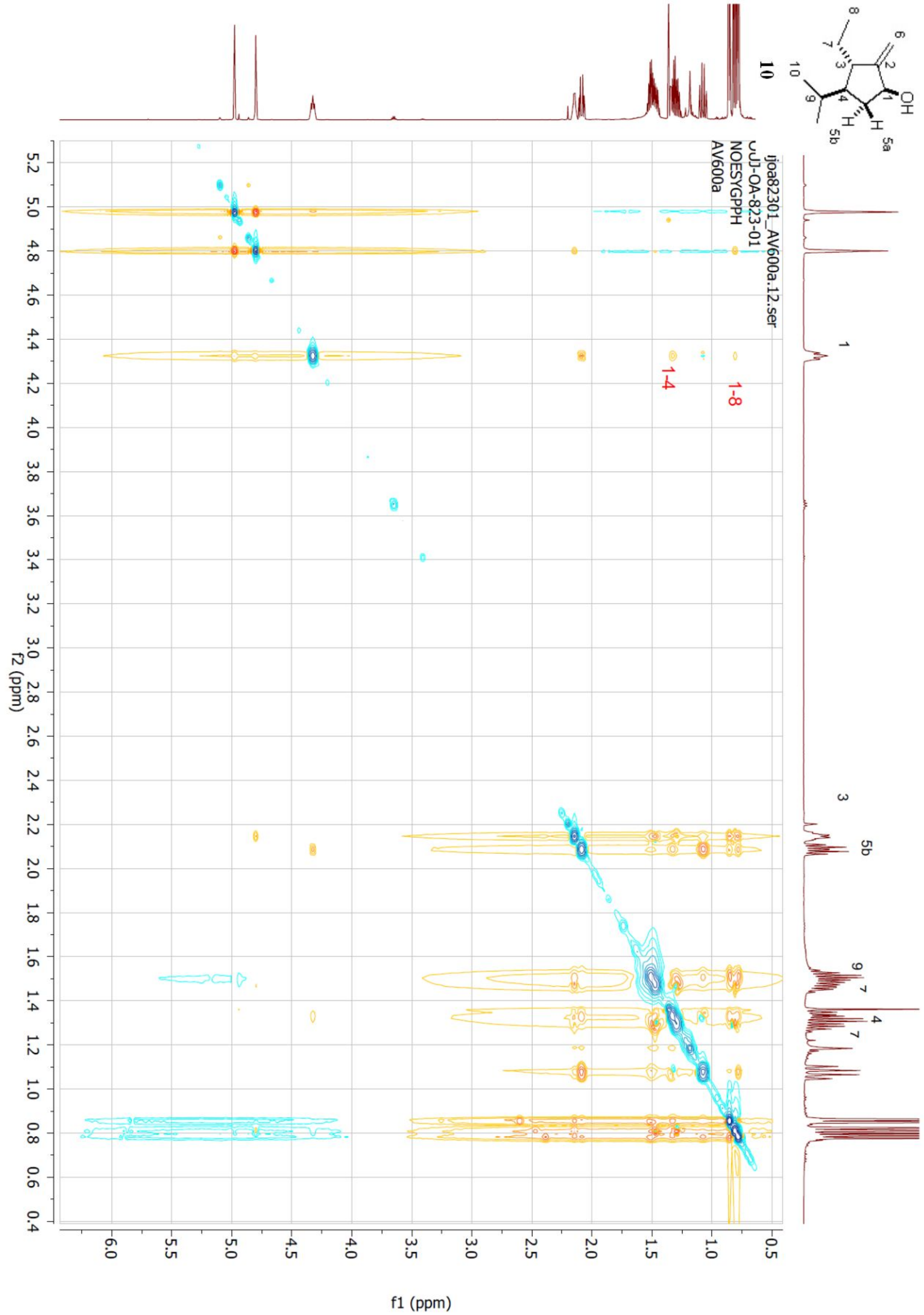
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OH
H
5a
5b
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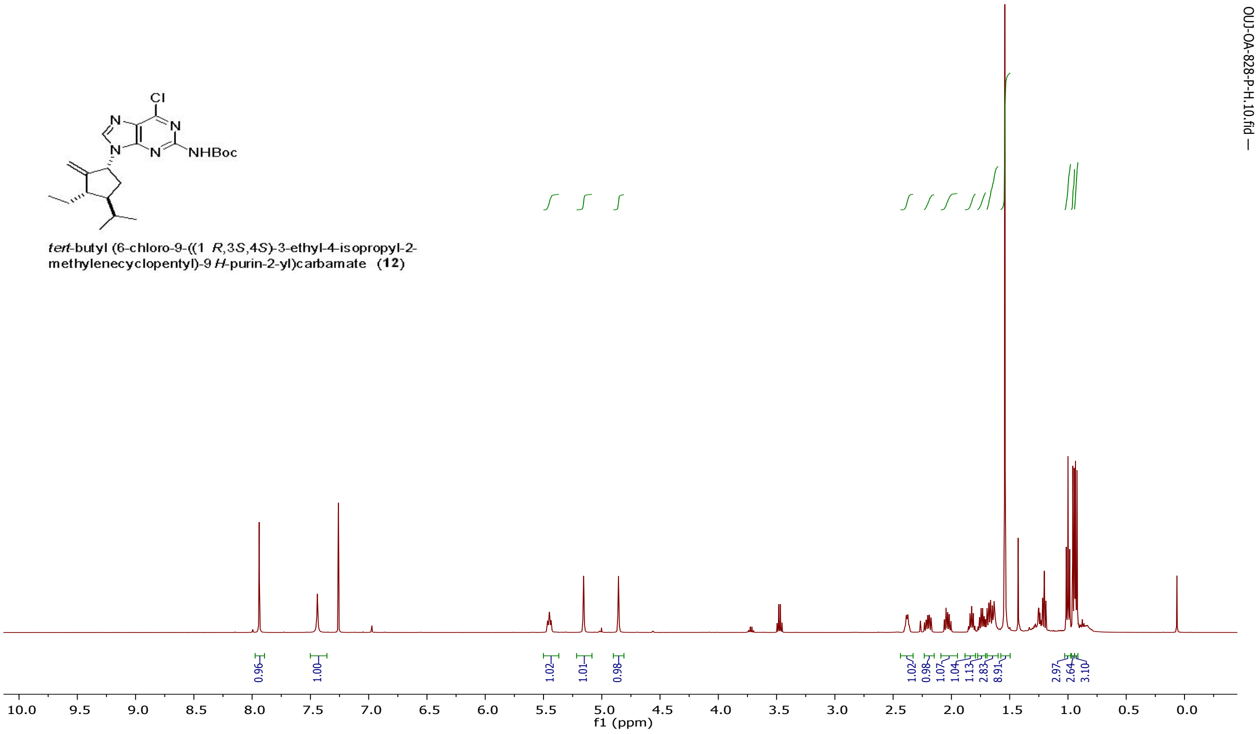
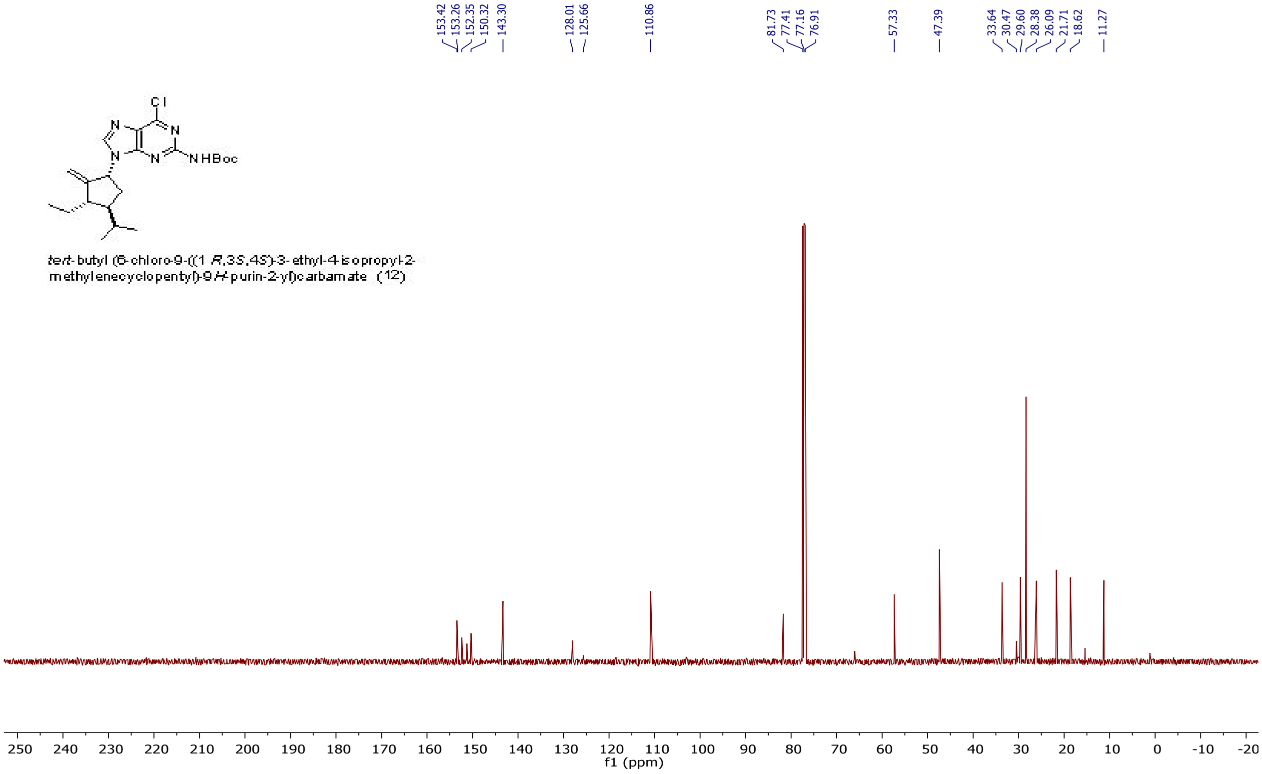
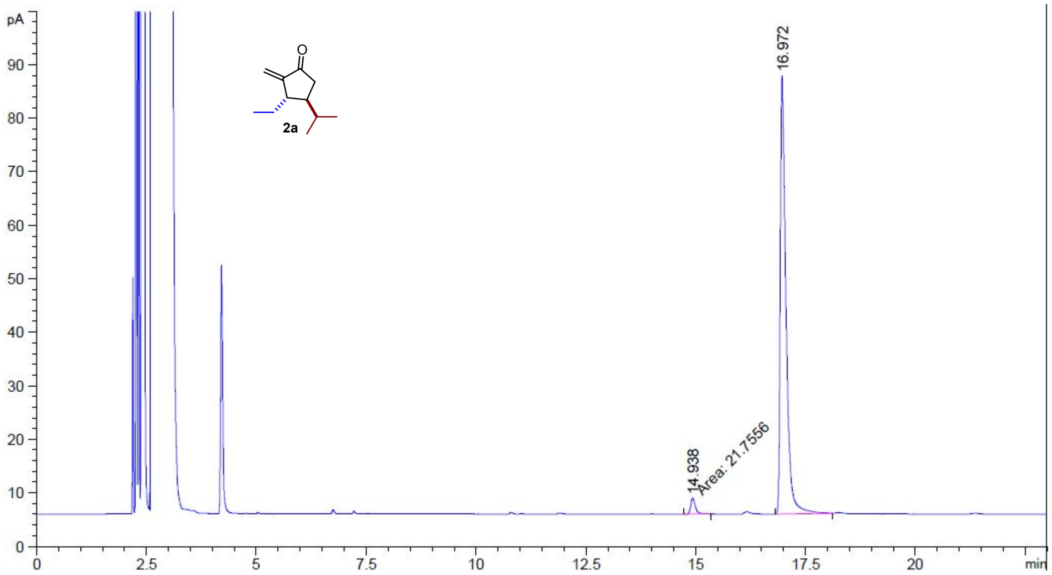
f2 (ppm)
f1 (ppm)

^{1}H NMR (500 MHz, CDCl$_3$) and ^{13}C NMR (125 MHz, CDCl$_3$) of **12**

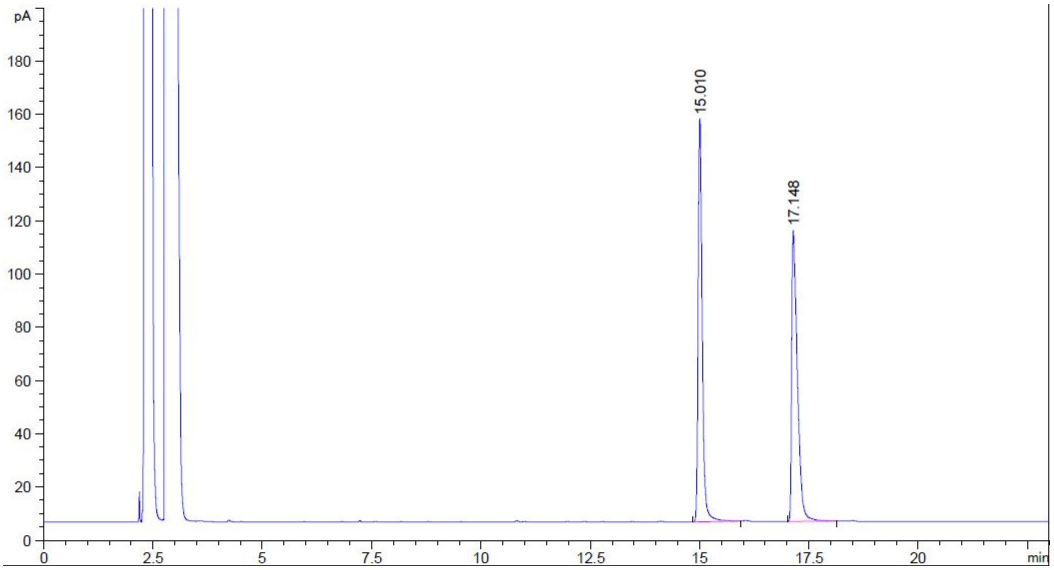




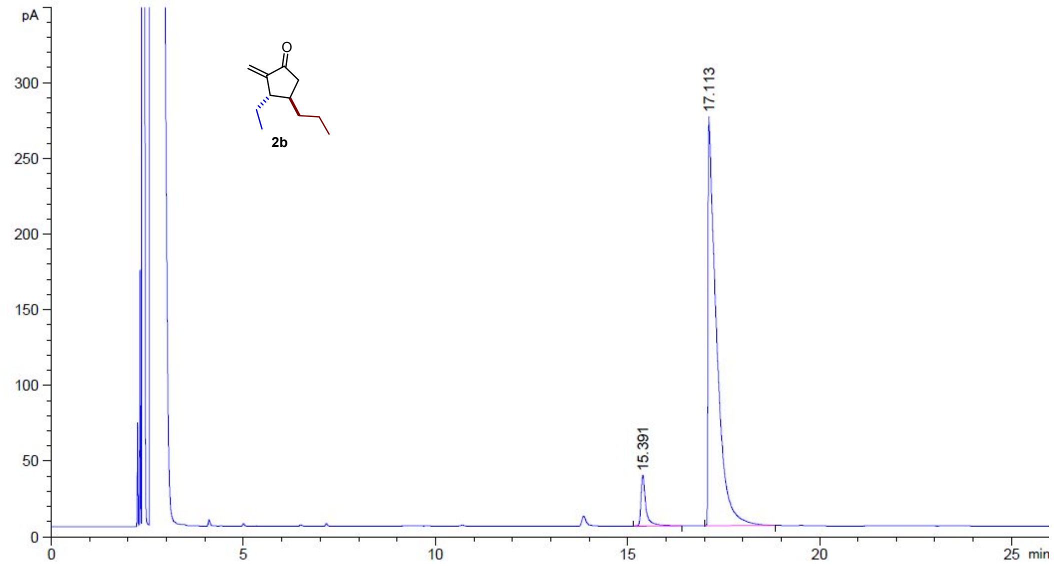
HPLC and GC Traces



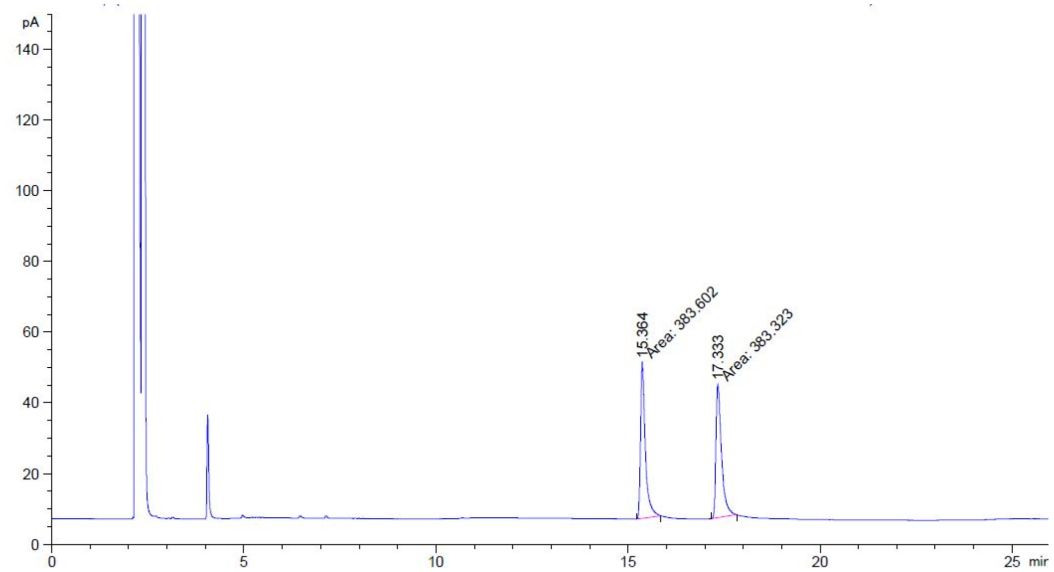
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  14.938 MM    0.1218   21.75561    2.97726  2.86123
   2  16.972 BB    0.1251  738.60394   81.97423 97.13877
```



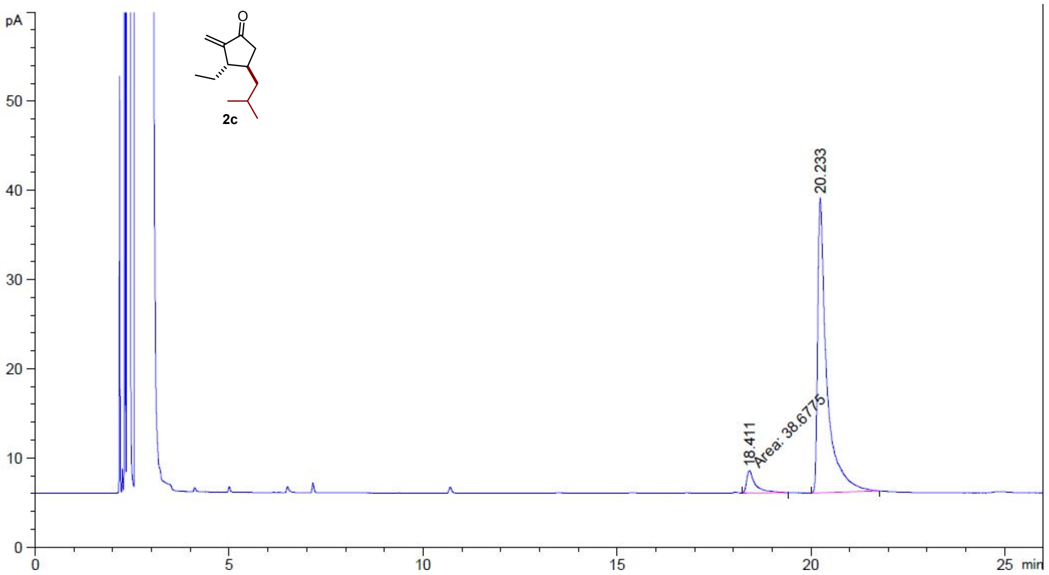
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  15.010 BB    0.0931  988.31958  151.60349 49.96575
   2  17.148 BB    0.1203  989.67438  109.61007 50.03425
```



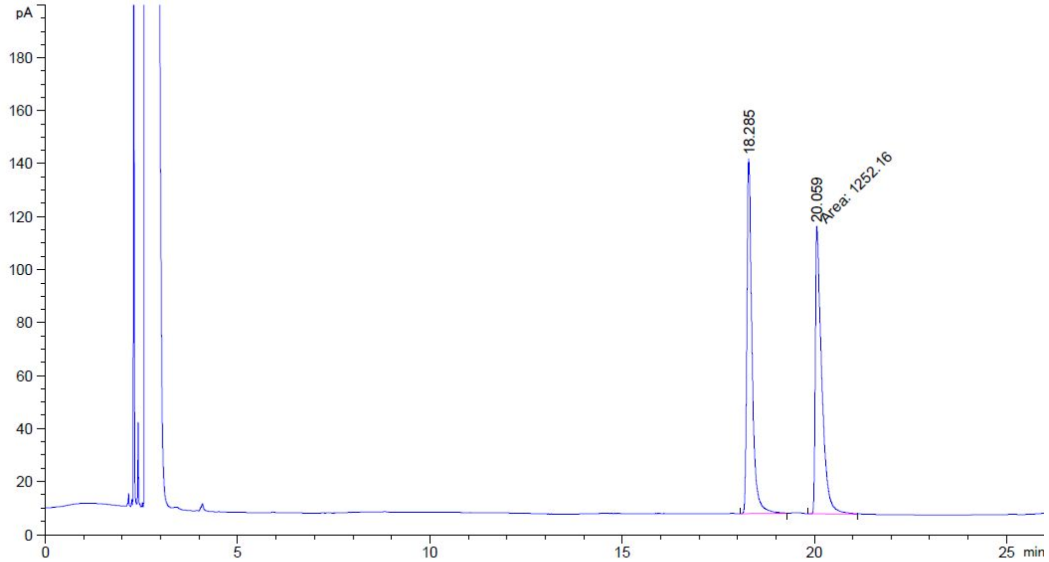
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  15.391 BB    0.1258  299.71332   33.69463  6.78301
   2  17.113 BB    0.1865 4118.87402  270.67563 93.21699
```



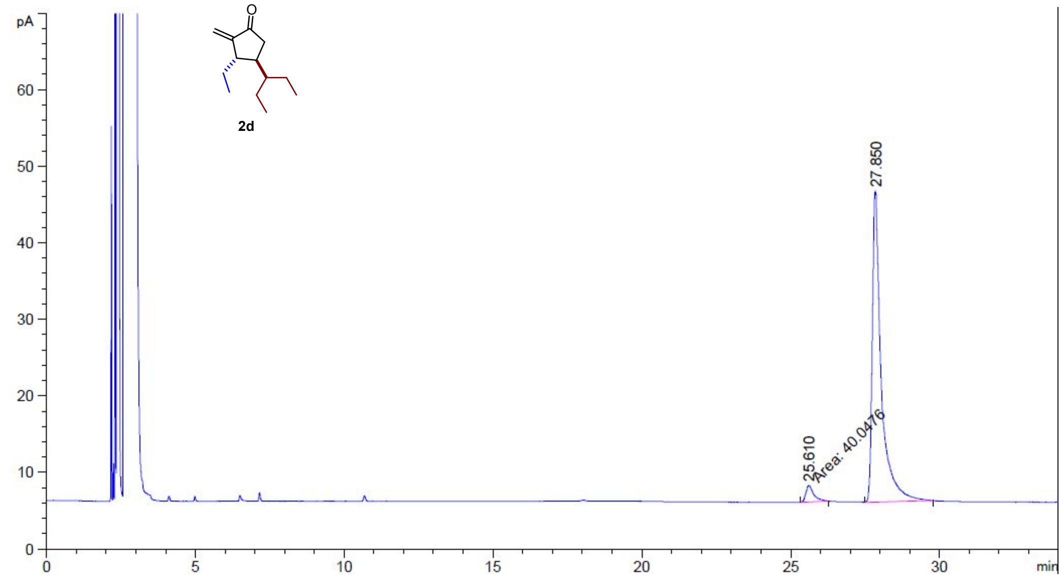
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  15.364 MM    0.1442  383.60187   44.33823 50.01818
   2  17.333 MM    0.1690  383.32297   37.79705 49.98182
```


2c

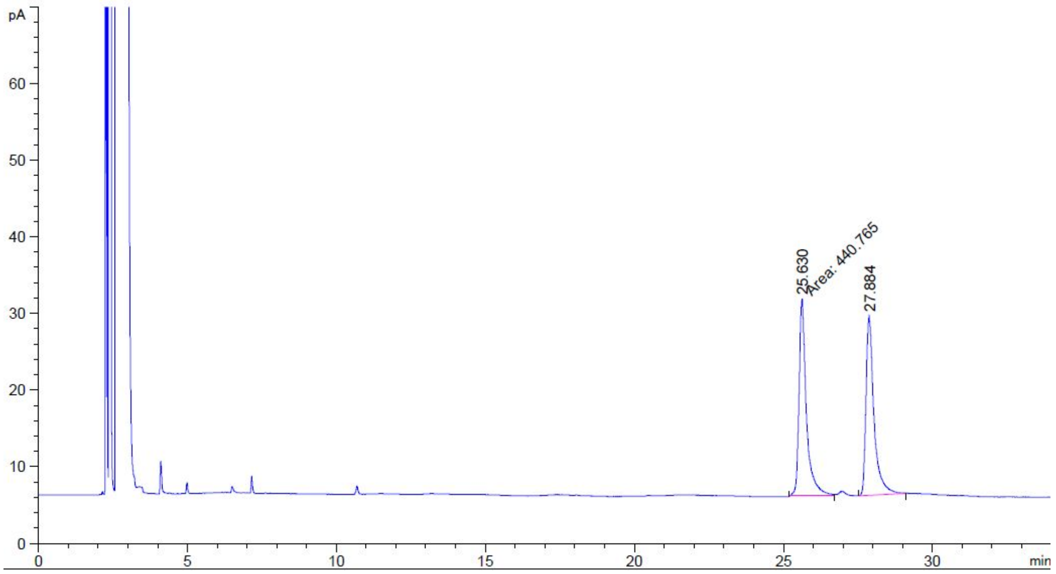
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  18.411 MM    0.2572   38.67746    2.50663  6.64012
   2  20.233 BB    0.2007  543.80408   33.09599 93.35988
```



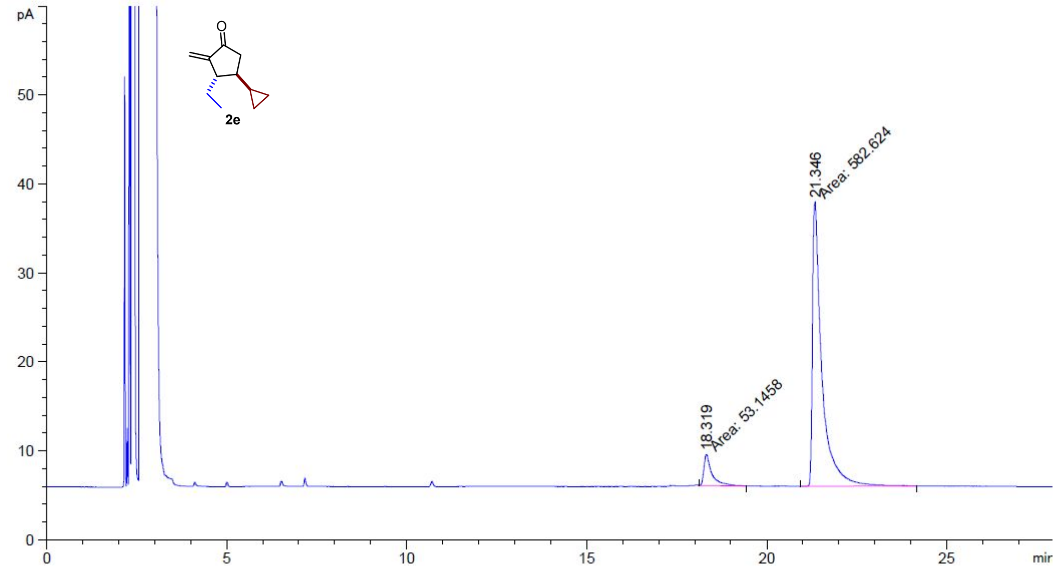
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  18.285 BB    0.1281 1252.32813  133.89185 50.00331
   2  20.059 MM    0.1923 1252.16248  108.53397 49.99669
```



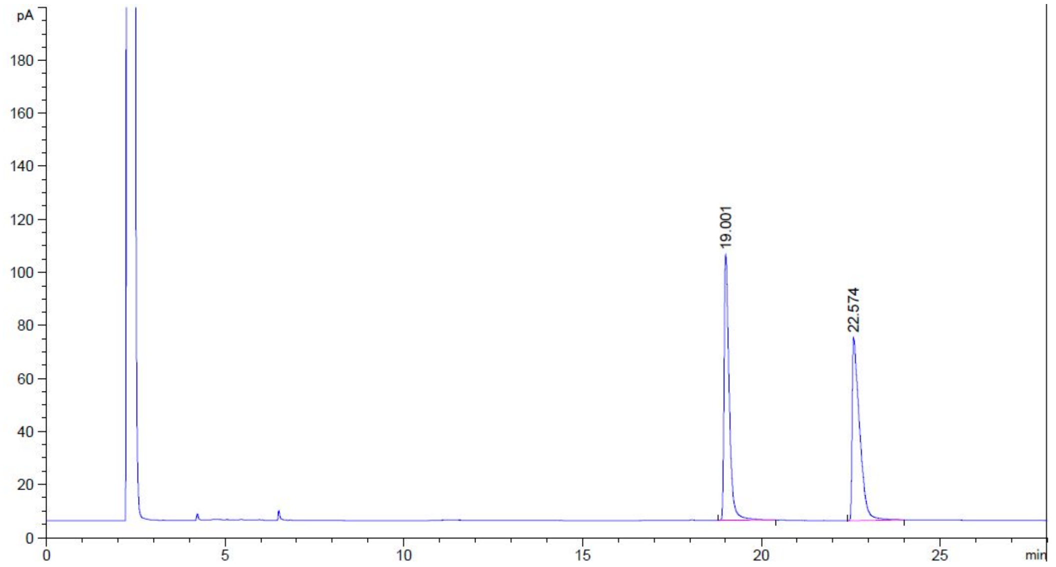
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [pA*s]      [pA]          %
----|-------|----|-------|----------|----------|--------|
   1  25.610 MM    0.3072   40.04757    2.17250  4.50807
   2  27.850 BB    0.2493  848.30621   40.67644 95.49193
```



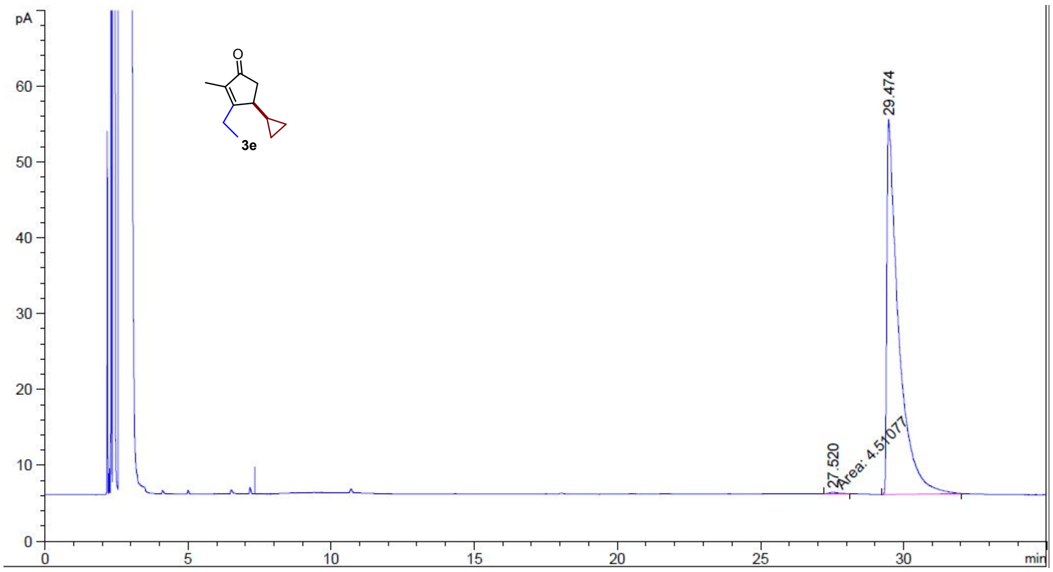
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [pA*s]      [pA]          %
----|-------|----|-------|----------|----------|--------|
   1  25.630 MM    0.2859  440.76489   25.69806 50.36864
   2  27.884 BB    0.2258  434.31311   23.48179 49.63136
```



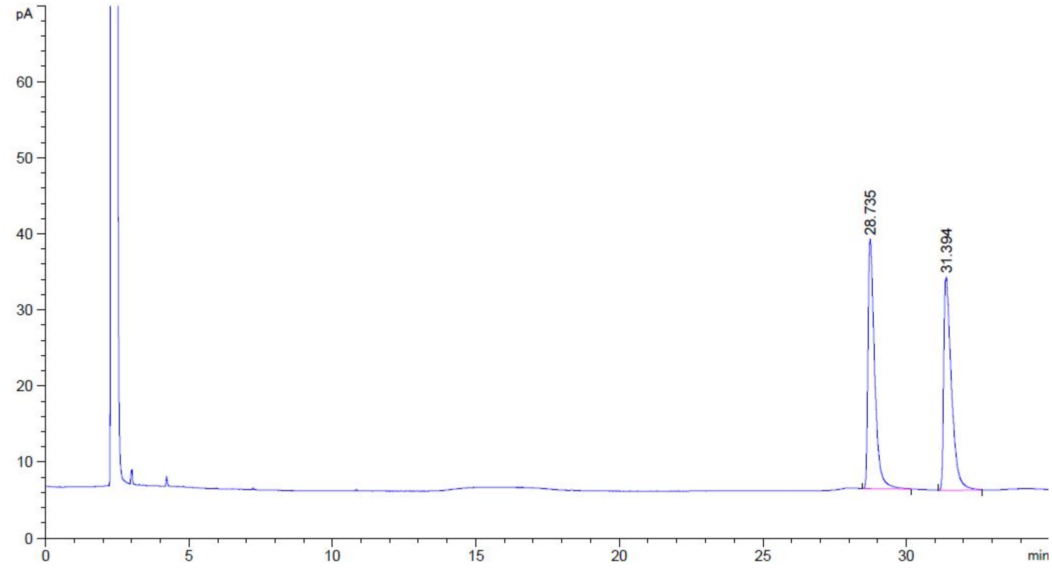
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  18.319 MM    0.2559   53.14576    3.46135  8.35928
   2  21.346 MM    0.3036  582.62354   31.98459 91.64072
```



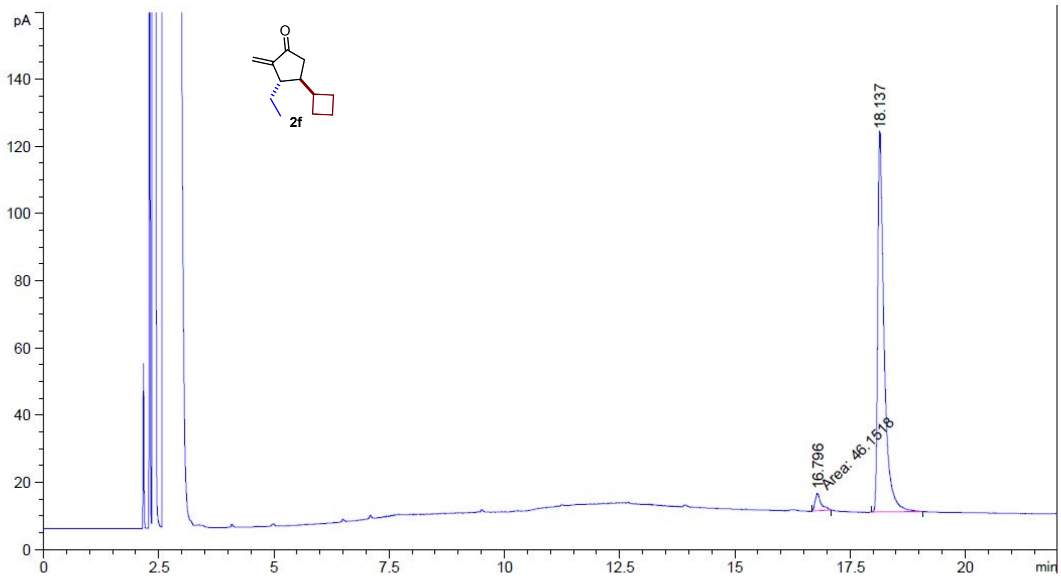
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  19.001 BB    0.1280  998.87085  100.42361 50.03397
   2  22.574 BB    0.1809  997.51465   69.30116 49.96603
```



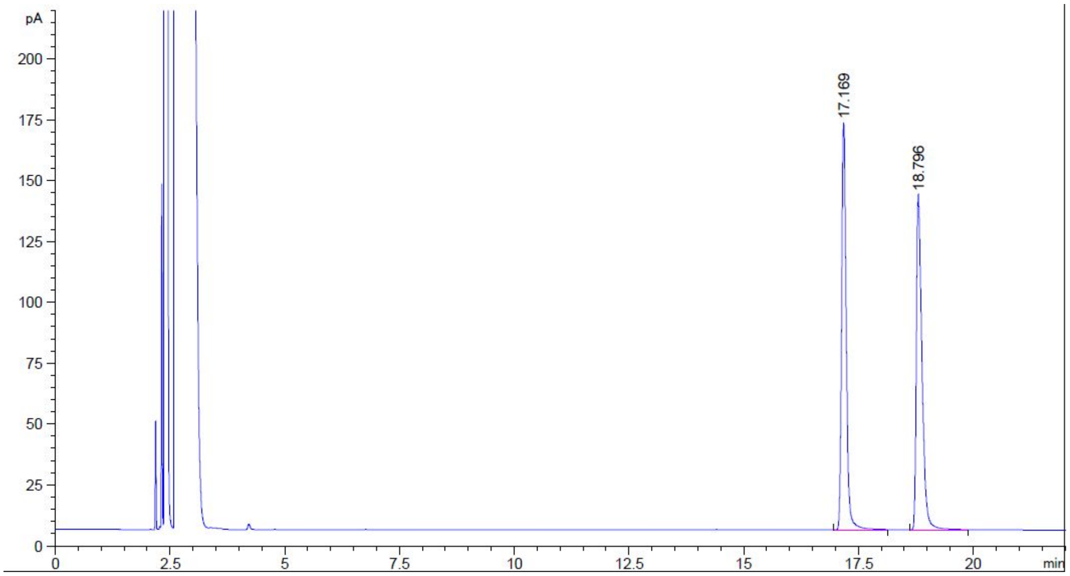
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  27.520 MM    0.3770    4.51077 1.99437e-1  0.31824
   2  29.474 BB    0.3424 1412.91113   49.44844 99.68176
```



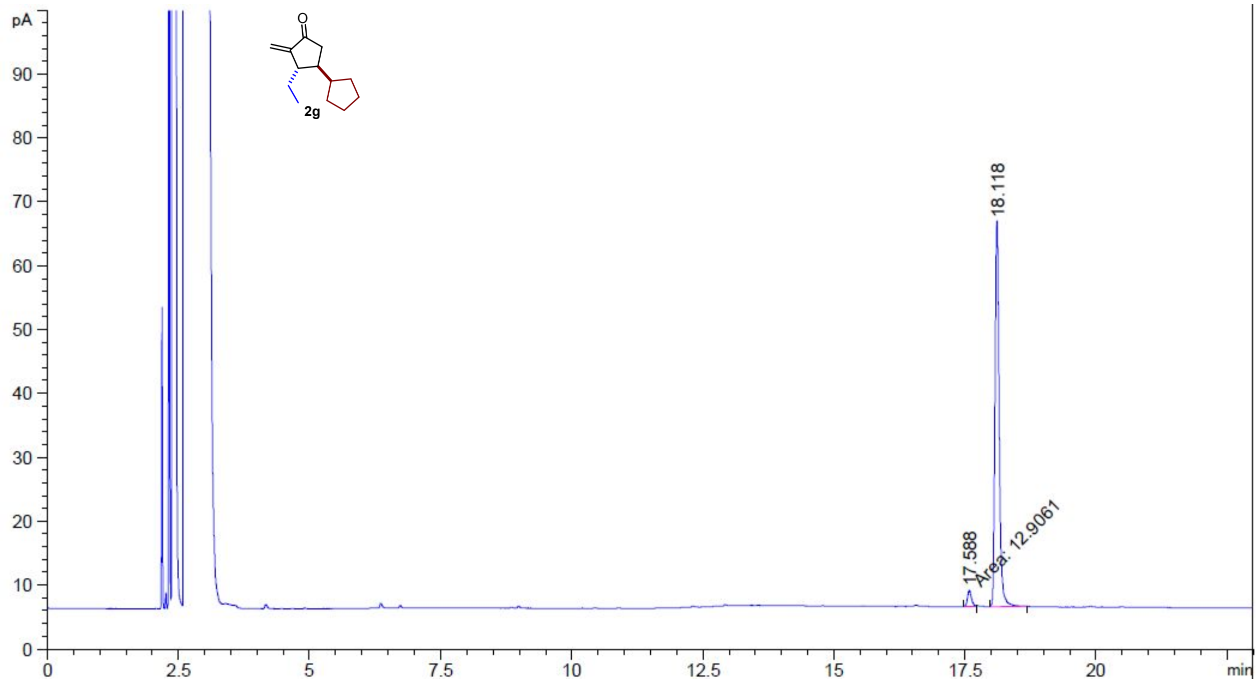
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  28.735 BB    0.1918  527.47125   32.76172 50.21322
   2  31.394 BB    0.2279  522.99170   27.99739 49.78678
```



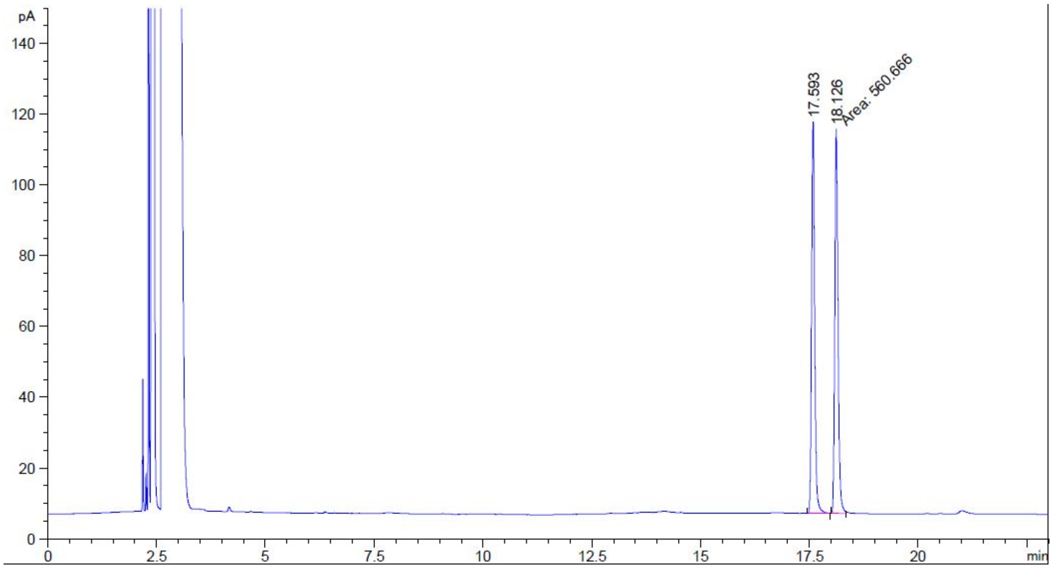
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [pA*s]       [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  16.796 MM    0.1482   46.15181    5.18965  4.06006
   2  18.137 BB    0.1307 1090.57629  112.85995 95.93994
```



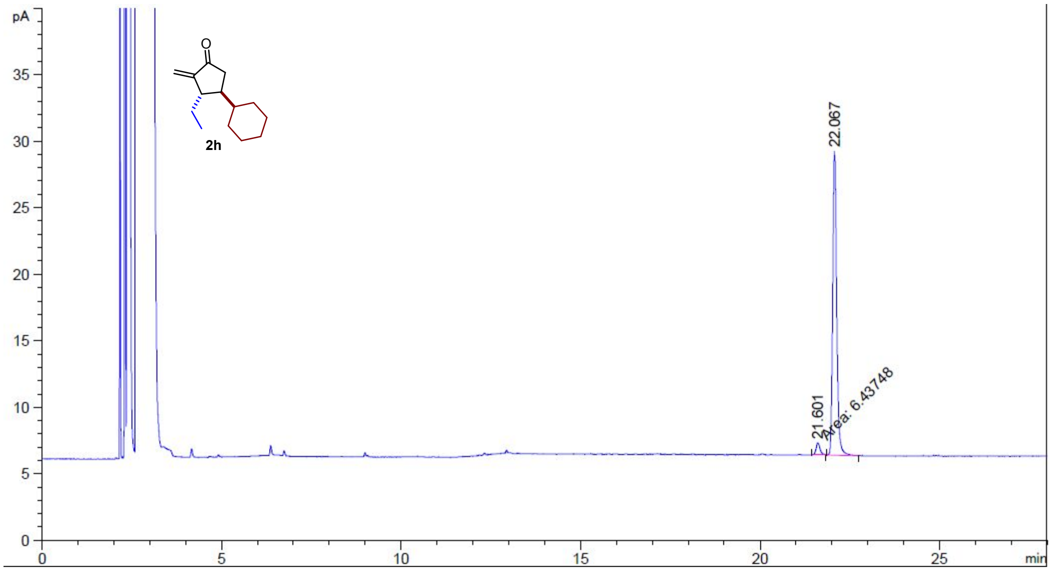
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [pA*s]       [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  17.169 BB    0.1078 1172.30774  167.19647 49.93501
   2  18.796 BB    0.1116 1175.35925  137.72757 50.06499
```



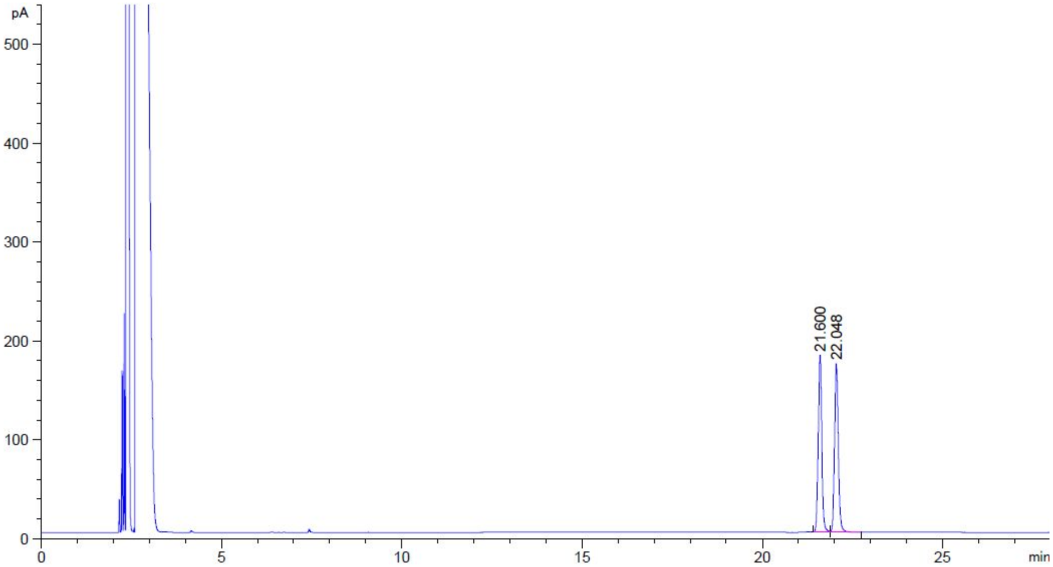
```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [pA*s]      [pA]          %
----|-------|----|-------|----------|----------|--------|
   1  17.588 MM    0.0859   12.90606    2.50445  3.69280
   2  18.118 BB    0.0842  336.58618   60.19957 96.30720
```



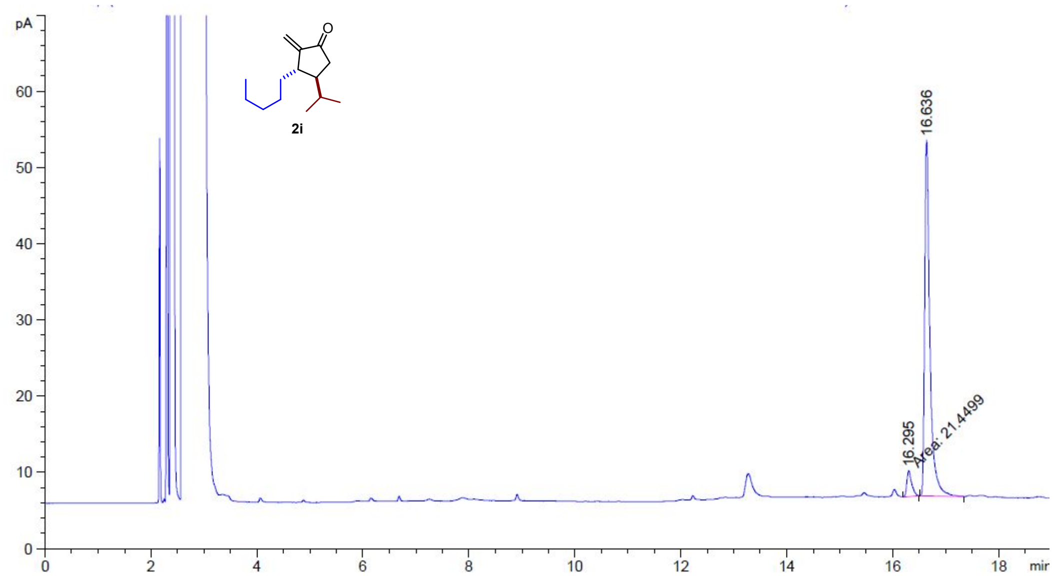
```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [pA*s]      [pA]          %
----|-------|----|-------|----------|----------|--------|
   1  17.593 BB    0.0755  555.85999  110.87234 49.78477
   2  18.126 MF    0.0859  560.66620  108.73307 50.21523
```



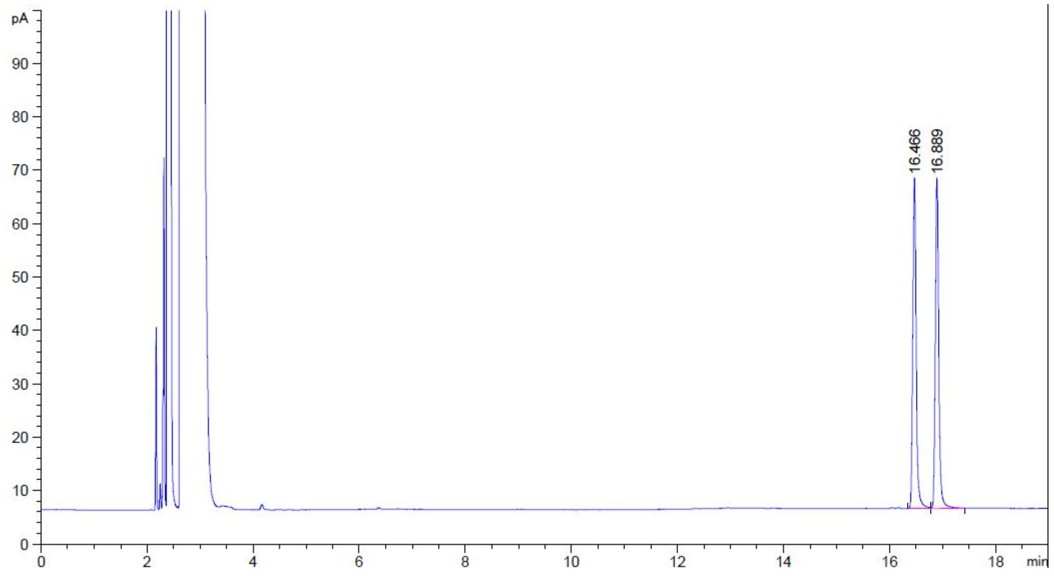
```
Peak RetTime Type  Width     Area      Height      Area
  #   [min]        [min]   [pA*s]     [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  21.601 MM    0.1230    6.43748 8.71994e-1  3.51846
   2  22.067 BB    0.1033  176.52524   22.81151 96.48154
```



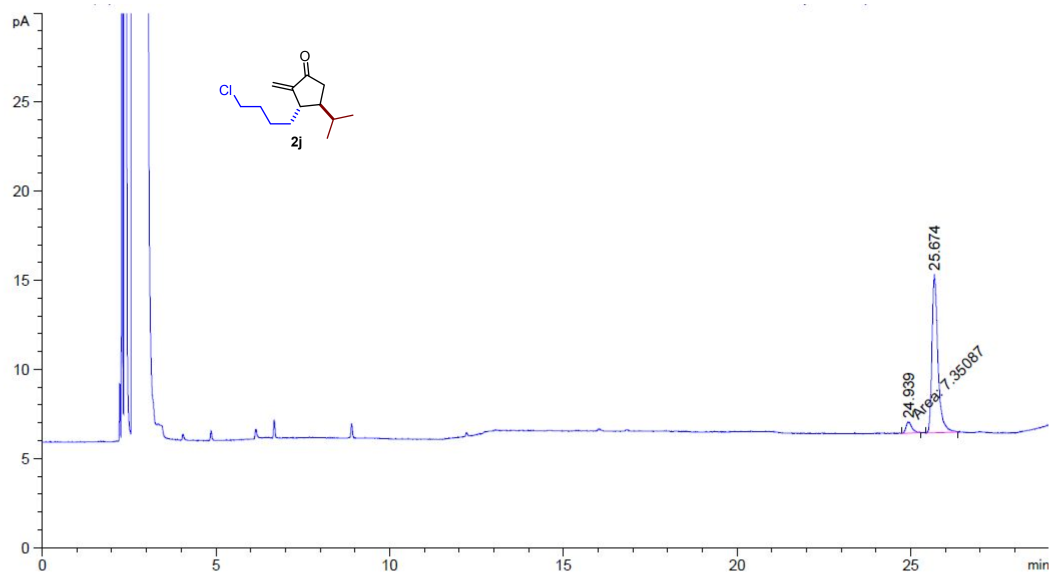
```
Peak RetTime Type  Width     Area      Height      Area
  #   [min]        [min]   [pA*s]     [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  21.600 BV    0.0990 1221.09631  178.15886 49.67081
   2  22.048 VB    0.1049 1237.28174  169.92409 50.32919
```



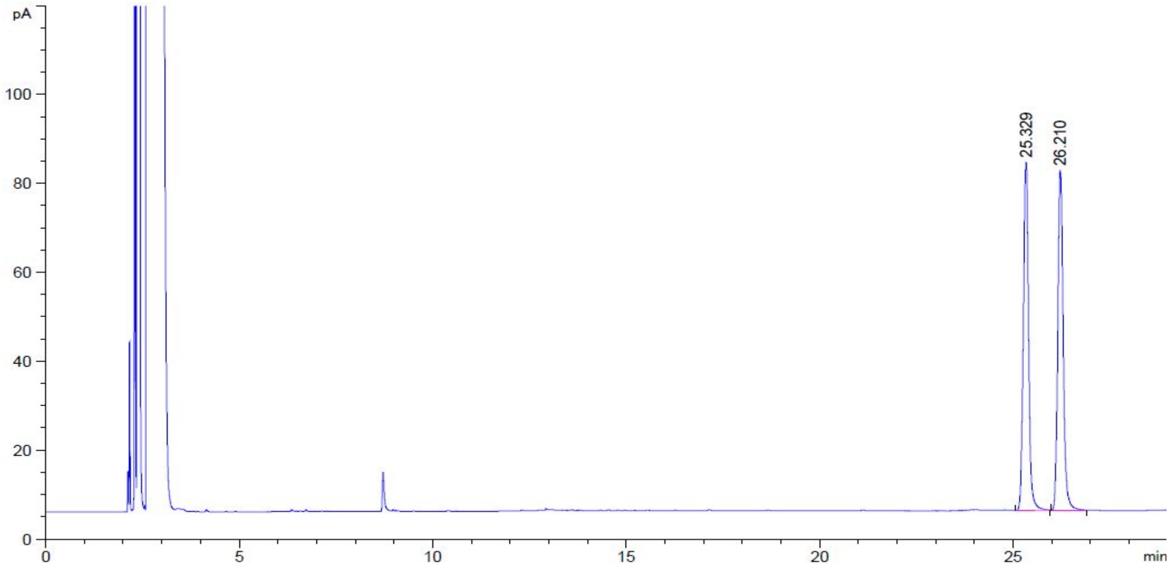
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  16.295 MM    0.1046   21.44985    3.41878  6.24202
   2  16.636 BB    0.0943  322.18643   46.80595 93.75798
```



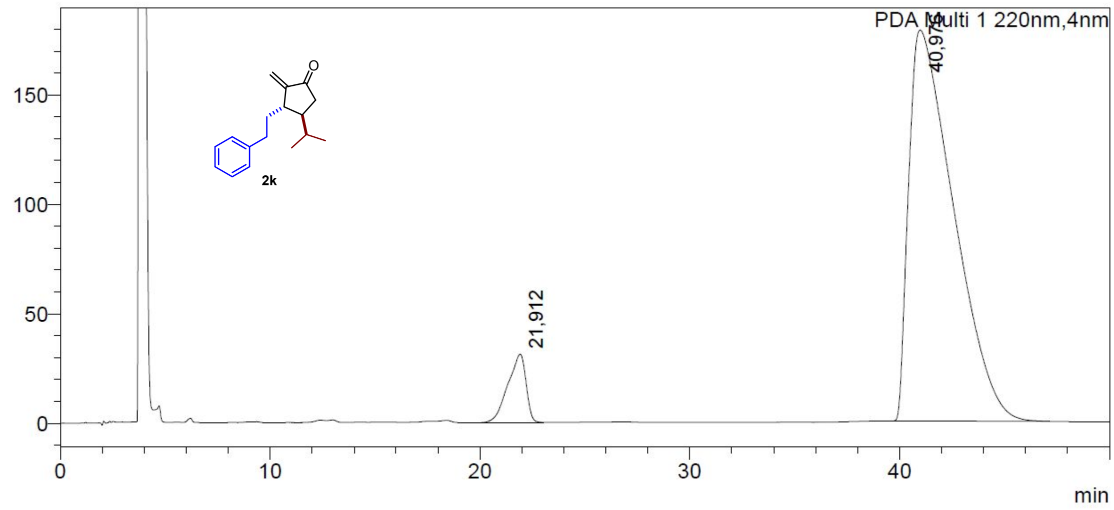
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  16.466 BV    0.0693  277.65585   61.96900 49.80191
   2  16.889 VB    0.0678  279.86459   61.80460 50.19809
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  24.939 MM    0.1944    7.35087 6.30127e-1  6.49196
   2  25.674 BB    0.1551  105.87947    8.87846 93.50804
```



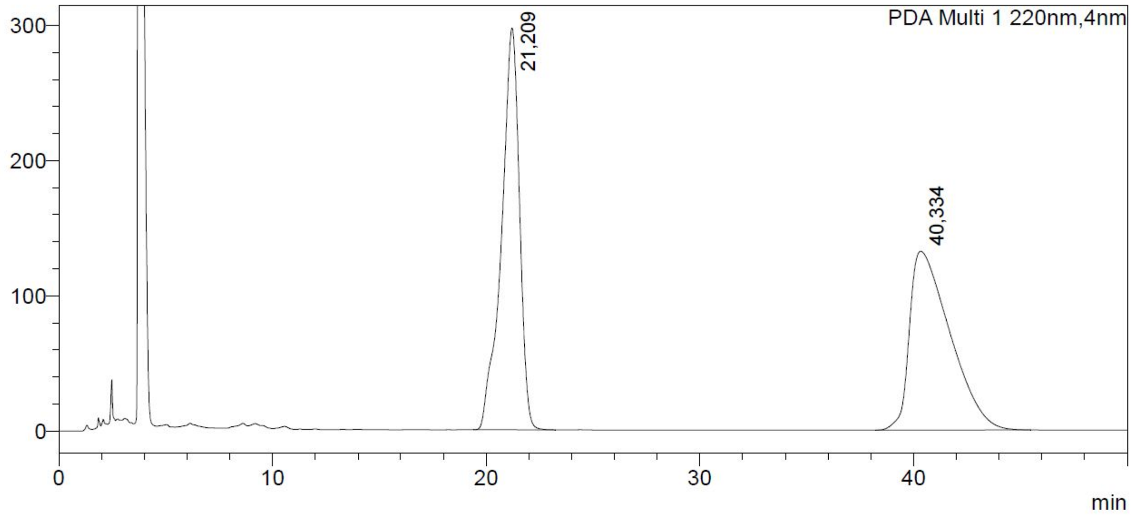
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  25.329 BB    0.1142  741.61896   78.51183 50.01438
   2  26.210 BB    0.1209  741.19244   76.59077 49.98562
```



<Peak Table>

PDA Ch1 220nm

Peak#	Ret. Time	Area%	Area	Height
1	21,912	6,566	1868415	31213
2	40,976	93,434	26585879	178743
Total		100,000	28454294	209955

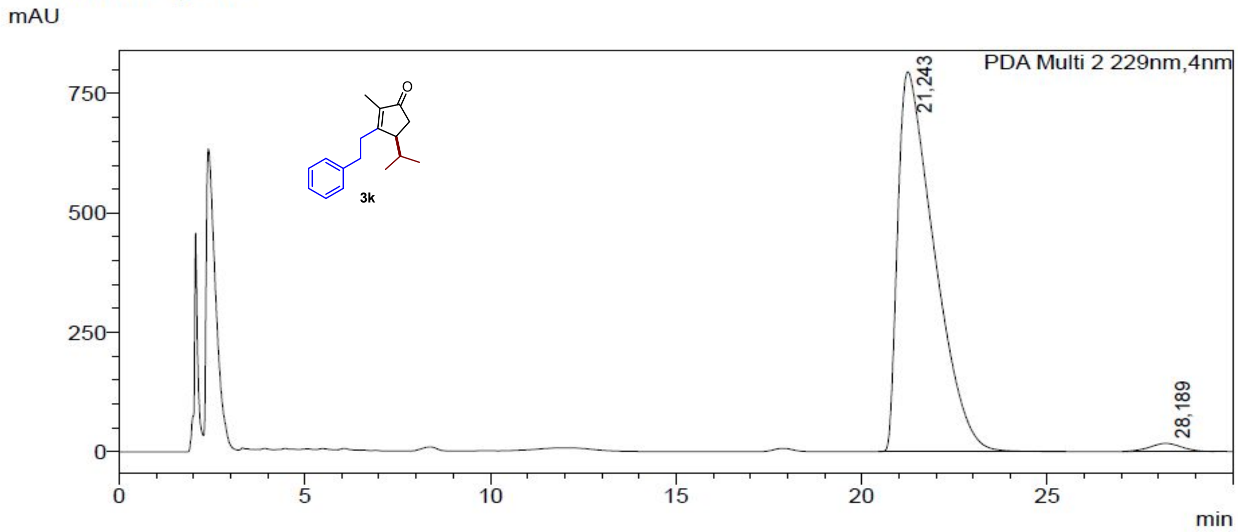


<Peak Table>

PDA Ch1 220nm

Peak#	Ret. Time	Area%	Area	Height
1	21,209	50,088	17511313	297218
2	40,334	49,912	17449862	132362
Total		100,000	34961176	429580

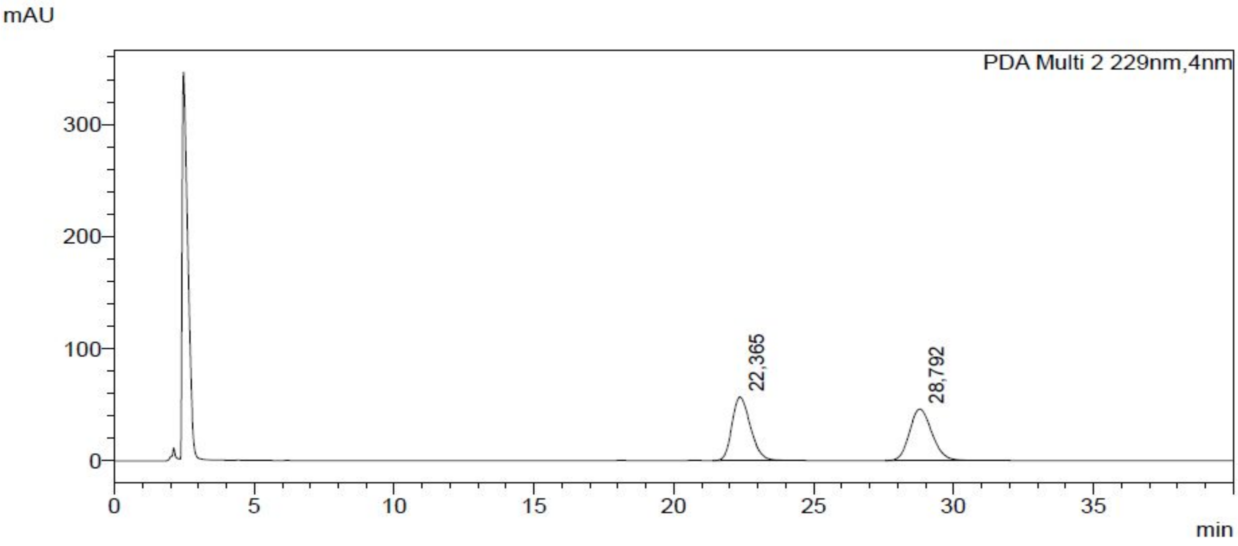
<Chromatogram>



<Peak Table>

PDA Ch2 229nm

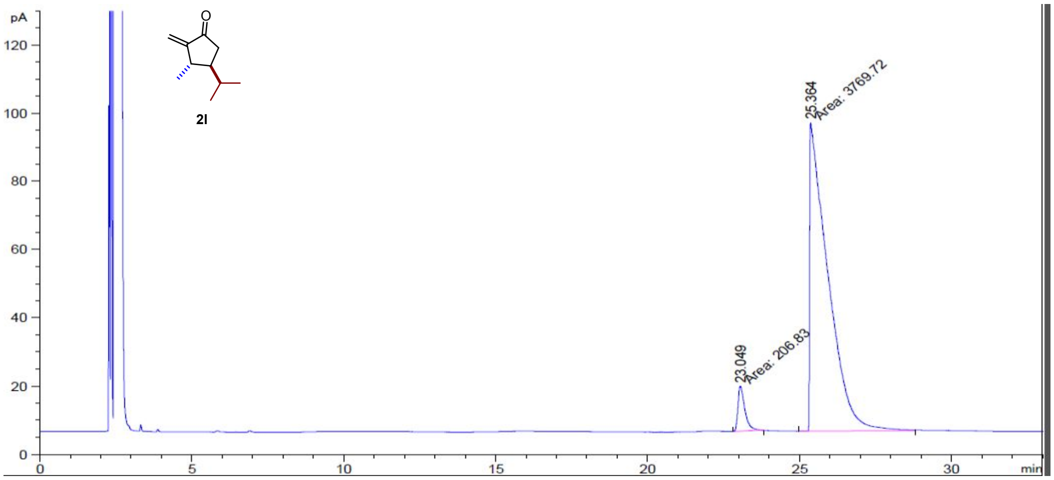
Peak#	Ret. Time	Area%	Area	Height
1	21,243	98,234	54117165	795109
2	28,189	1,766	973114	16672
Total		100,000	55090279	811781



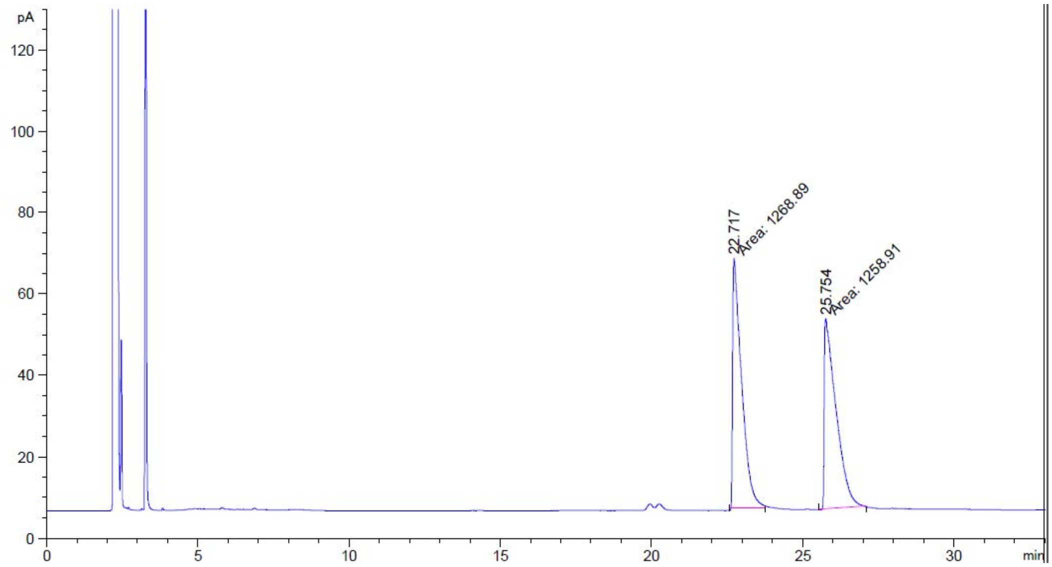
<Peak Table>

PDA Ch2 229nm

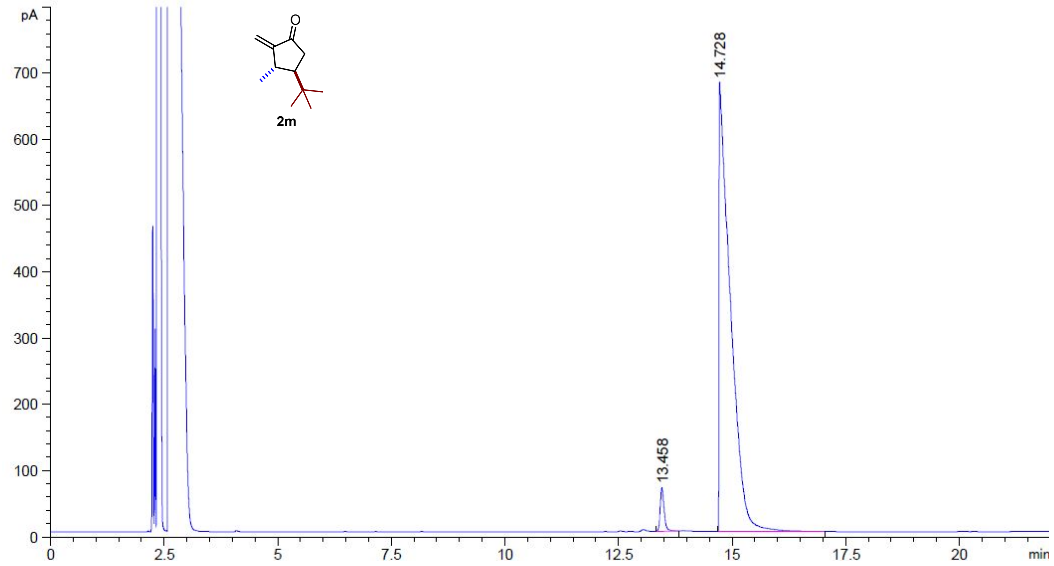
Peak#	Ret. Time	Area%	Area	Height
1	22,365	50,373	2565962	56478
2	28,792	49,627	2528008	45799
Total		100,000	5093971	102277



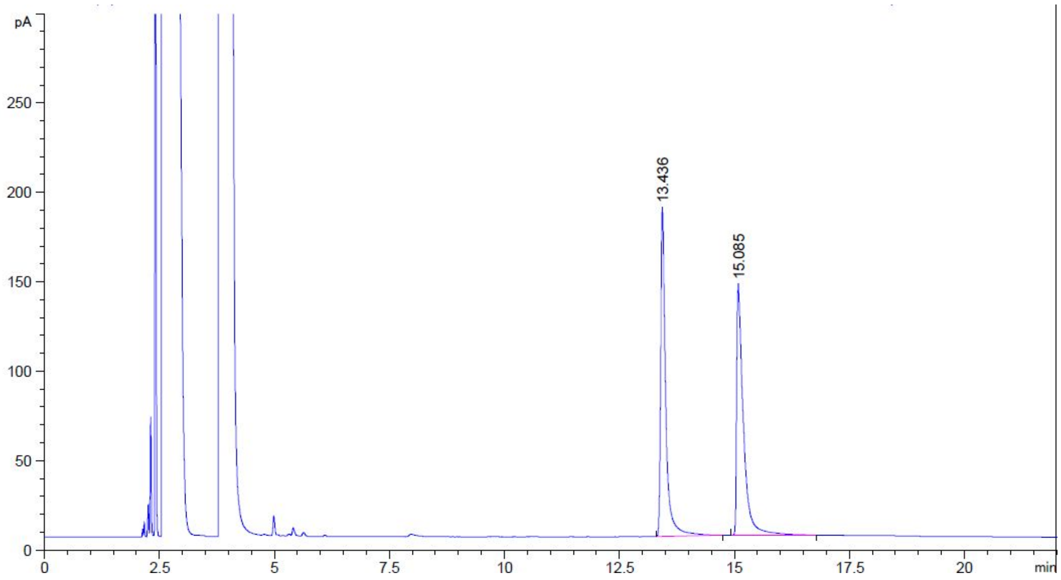
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  23.049 MM    0.2622  206.82990   13.14680  5.20124
   2  25.364 MM    0.6941 3769.71973   90.52276 94.79876
```



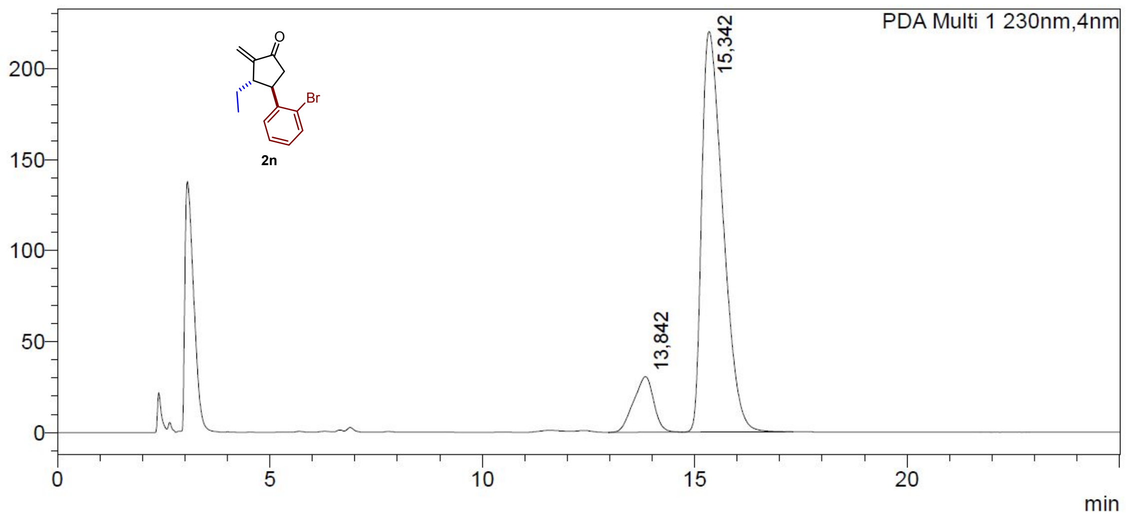
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  22.717 MM    0.3442 1268.89136   61.44370 50.19740
   2  25.754 MM    0.4495 1258.91138   46.68020 49.80260
```



```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]         [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  13.458 BB    0.0878  395.29996   66.06901  3.26760
   2  14.728 BB    0.2072 1.17023e4   678.49976 96.73240
```



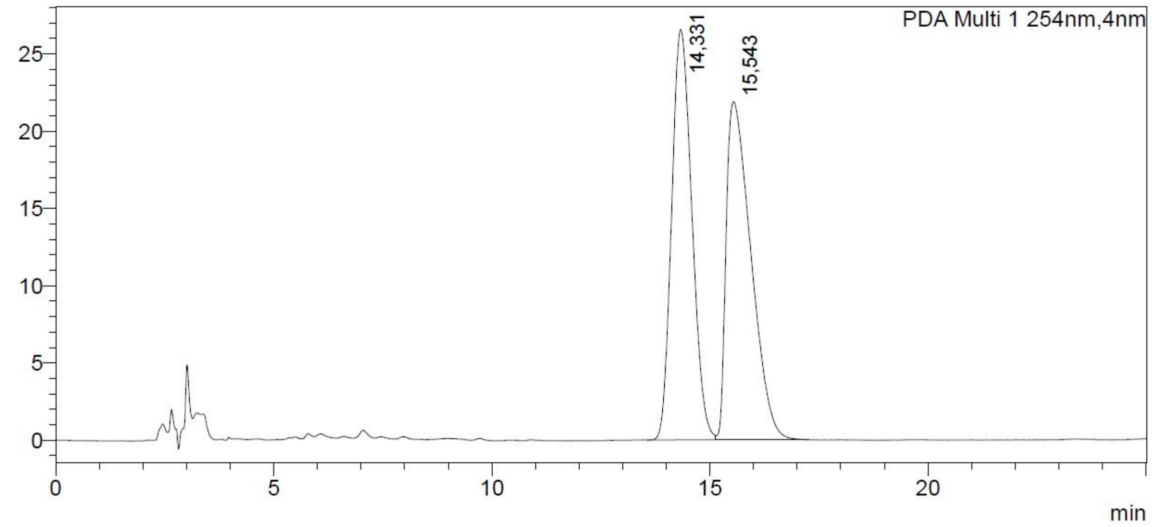
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]         [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  13.436 BB    0.1097 1401.58276  184.29607 49.43769
   2  15.085 BB    0.1328 1433.46655  140.75502 50.56231
```



<Peak Table>

PDA Ch1 230nm

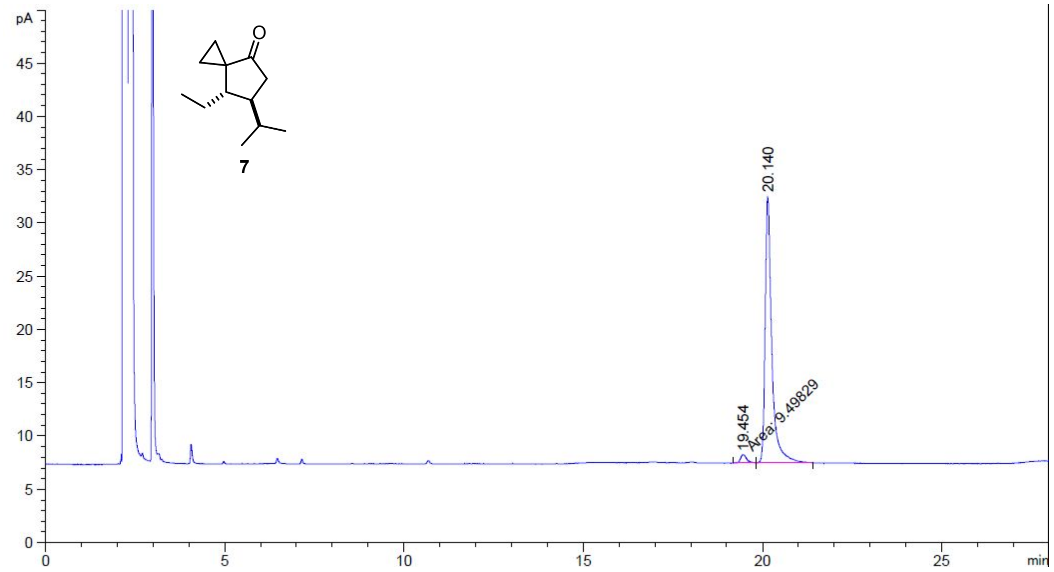
Peak#	Ret. Time	Area	Area%	Height
1	13,842	1005480	11,614	30537
2	15,342	7651714	88,386	219940
Total		8657195	100,000	250477



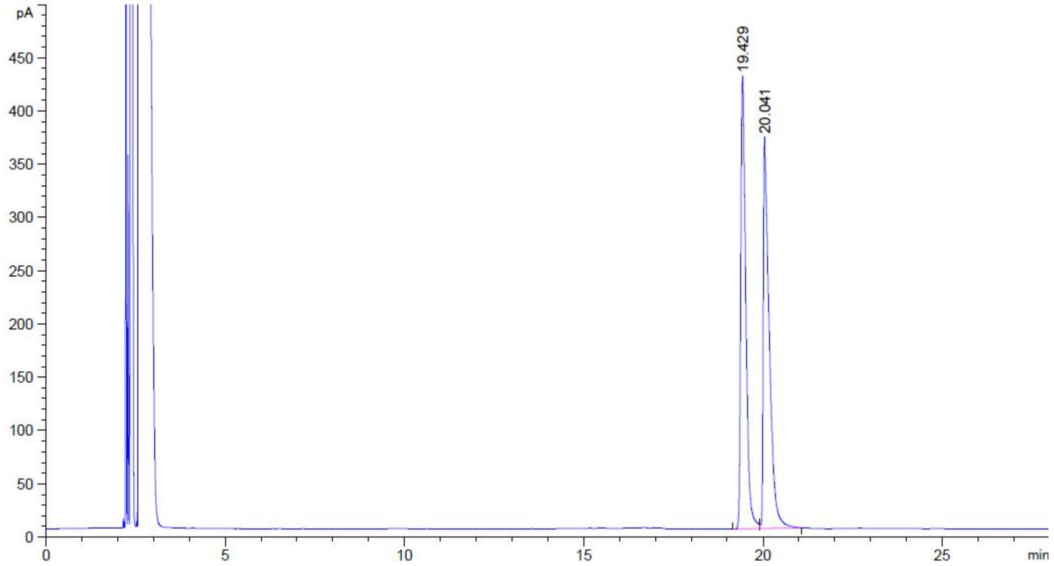
<Peak Table>

PDA Ch1 254nm

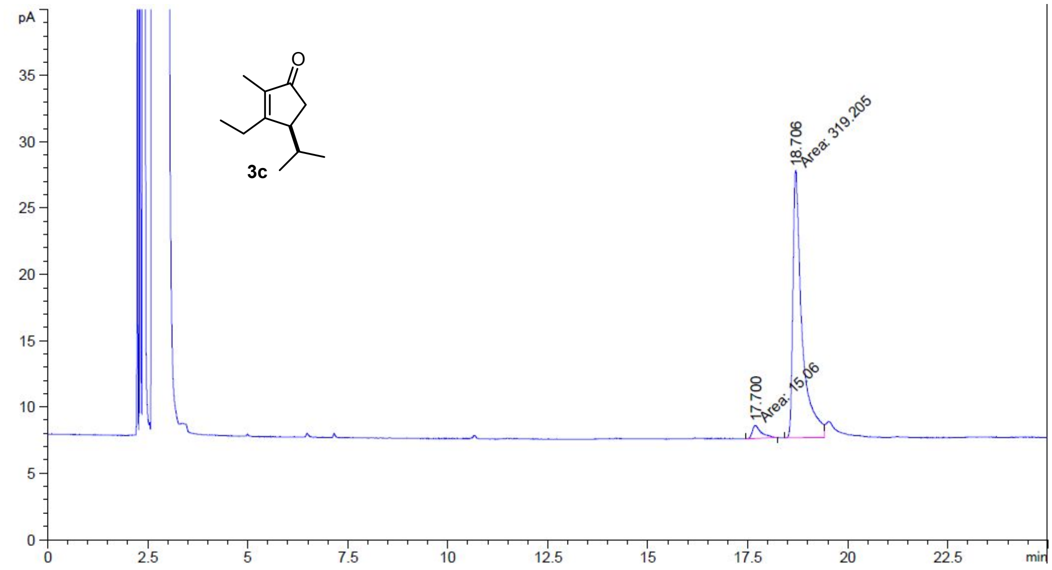
Peak#	Ret. Time	Area%	Area	Height	Conc.
1	14,331	49,777	855845	26544	0,000
2	15,543	50,223	863516	21879	0,000
Total		100,000	1719360	48423	



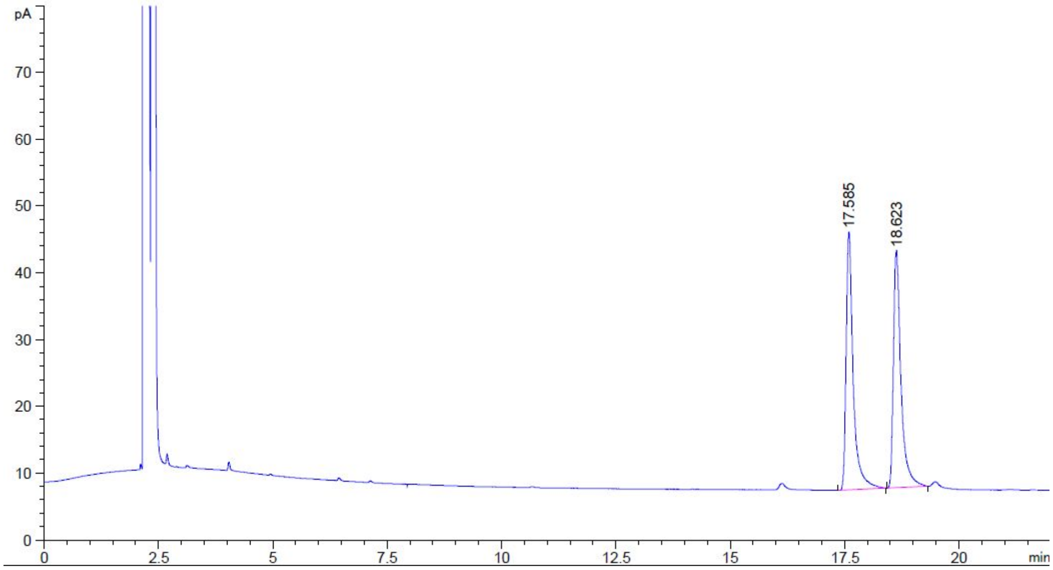
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]          %
----|-------|----|-------|----------|----------|--------|
   1  19.454 MM    0.1971    9.49829 8.03312e-1  2.85426
   2  20.140 BB    0.1587  323.27719   25.03071 97.14574
```



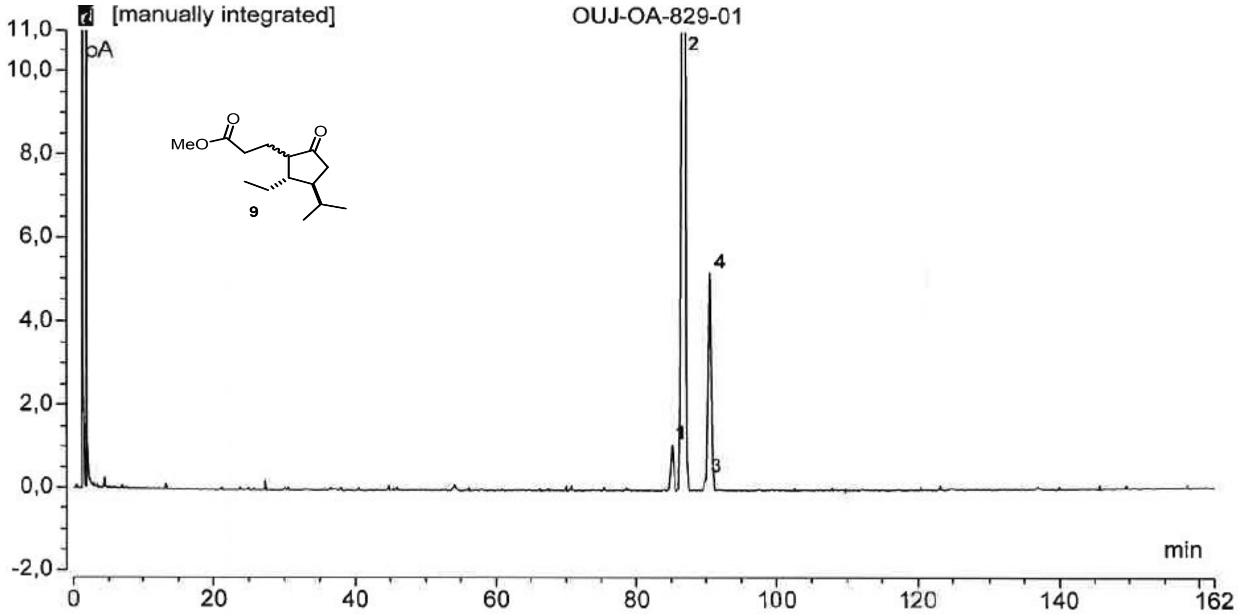
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]     [pA]          %
----|-------|----|-------|----------|----------|--------|
   1  19.429 BV    0.1376 4173.50879  424.91177 49.62860
   2  20.041 VB    0.1496 4235.97461  367.15088 50.37140
```



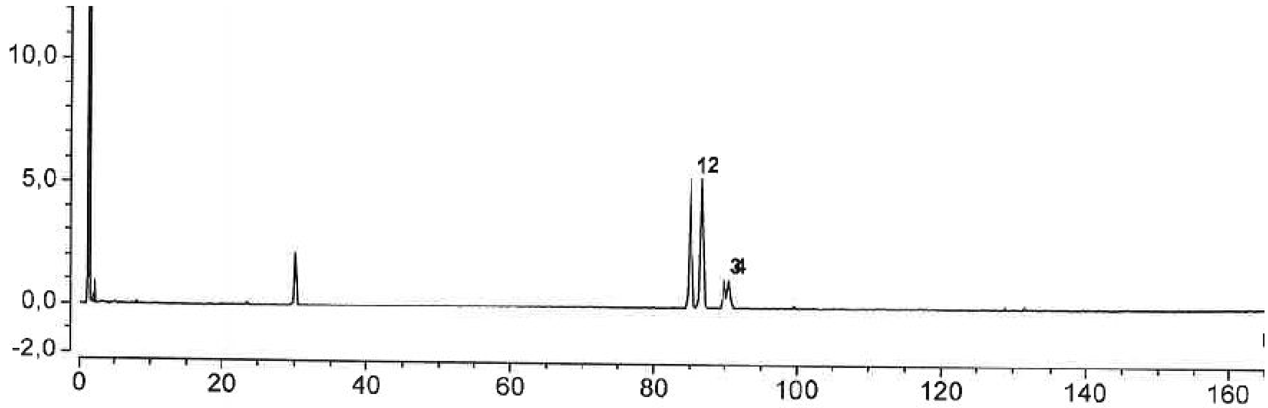
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [pA*s]     [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  17.700 MM    0.2581   15.05998 9.72331e-1  4.50540
   2  18.706 MF    0.2636  319.20517   20.18125 95.49460
```

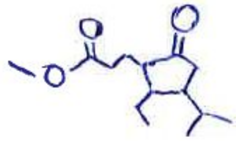


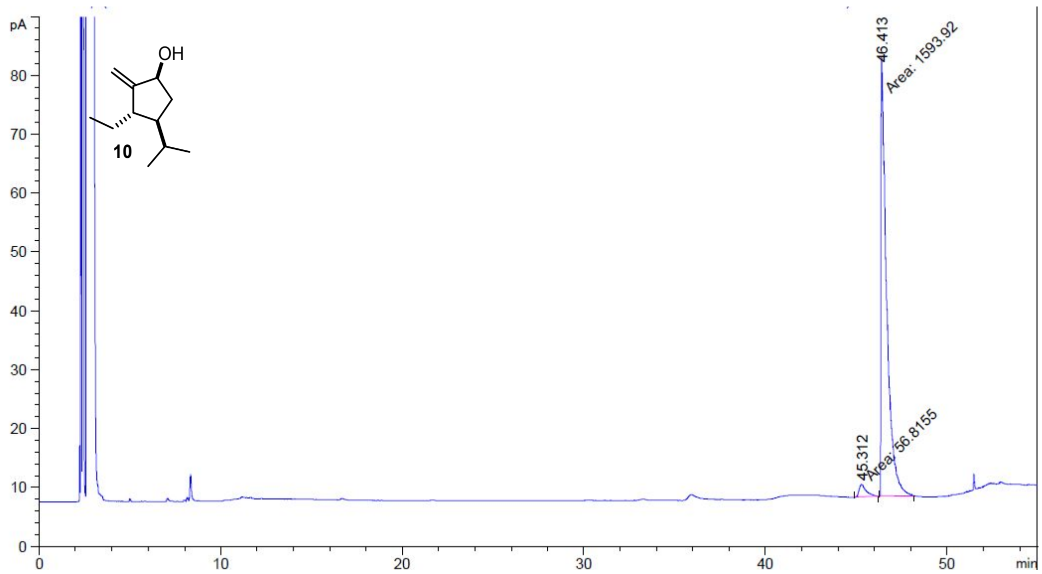
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [pA*s]     [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  17.585 BB    0.1420  416.67603   38.59152 50.53559
   2  18.623 BB    0.1551  407.84387   35.49393 49.46441
```



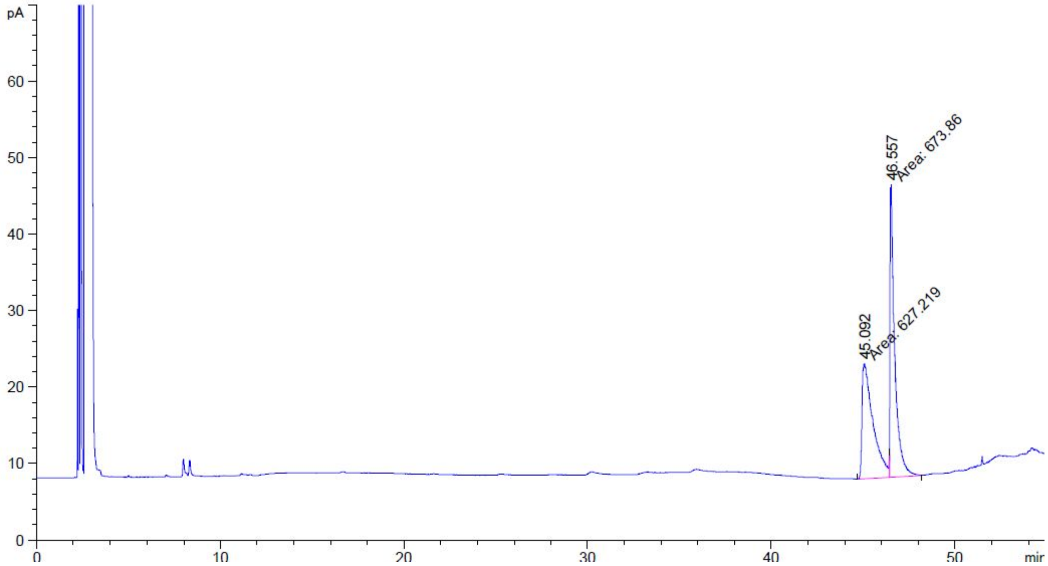
No.	Ret.Time min	area-% %	Peak Name
1	85,13	3,50	
2	86,85	79,00	
3	90,04	0,67	
4	90,54	16,83	



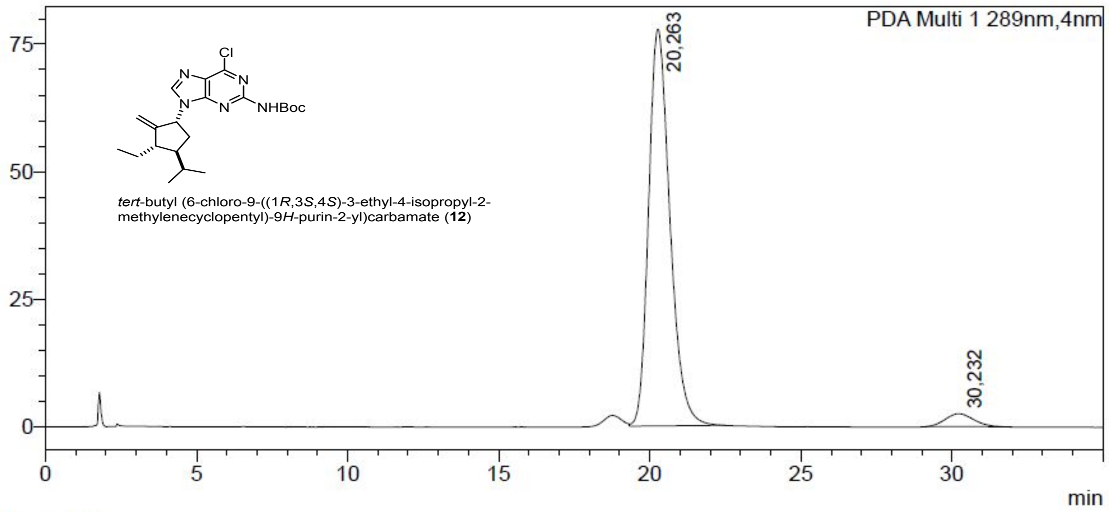
No.	Ret.Time min	area-% %	Peak Name
1	85,16	40,90	
2	86,69	41,20	
3	89,85	8,82	
4	90,50	9,08	



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  45.312 MM    0.4407   56.81547    2.14850  3.44183
   2  46.413 MM    0.3555 1593.91858   74.73600 96.55817
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  45.092 MF    0.6902  627.21881   15.14659 48.20759
   2  46.557 FM    0.2931  673.86011   38.32196 51.79241
```

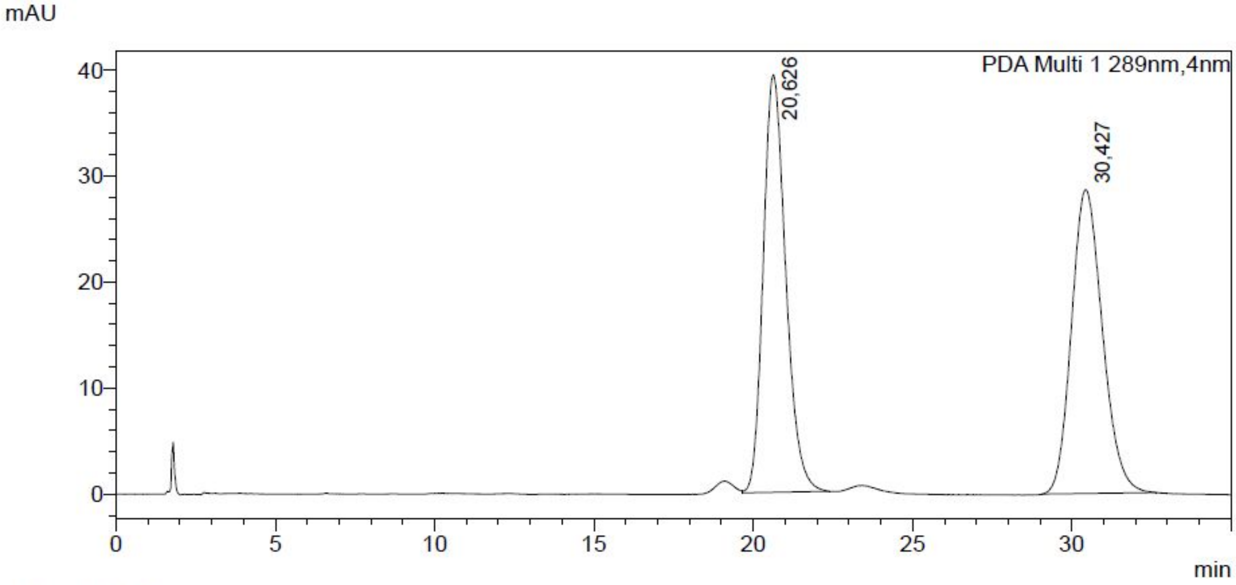


tert-butyl (6-chloro-9-((1*R*,3*S*,4*S*)-3-ethyl-4-isopropyl-2-methylenecyclopentyl)-9*H*-purin-2-yl)carbamate (**12**)

<Peak Table>

PDA Ch1 289nm

Peak#	Ret. Time	Area%	Area	Height
1	20,263	95,909	3817812	77811
2	30,232	4,091	162861	2510
Total		100,000	3980673	80321



<Peak Table>

PDA Ch1 289nm

Peak#	Ret. Time	Area%	Area	Height	Height%
1	20,626	49,910	1930931	39377	57,879
2	30,427	50,090	1937879	28656	42,121
Total		100,000	3868810	68033	100,000