Organocatalytic Asymmetric Synthesis of 5-(trialkylsilyl)cyclohex-2-enones and the Transformation into useful Building Blocks

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1. General methods and materials

General Methods. NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 MHz and 100 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a MicroMass LCT spectrometer using electrospray (ES^+) ionization techniques. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ dip. Purification of reaction products was carried out by flash chromatography (FC) using silica-gel (Fluka) or Iatrobeads 6RS-8060. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AS/AD or Daicel Chiralcel OD/OJ columns).

Materials. Commercially available starting materials and solvents were used without further purification and the catalyst[1] was prepared according to previously described procedures. The β-ketoesters[2] **7a**-**d** and the α,β-unsaturated aldehydes[3] **8a**,**b** were synthesized according to literature methods.

2. Optimization of the reaction conditions

The optimization of the reaction conditions was carried out for the second reaction step (the decarboxylation-aldol condensation-reaction) as the Michael-addition of the β-ketoester **7a** to the α,β-unsaturated aldehyde **8a** normally took place with full conversion overnight (checked by ^{1}H-NMR-spectroscopy) (Scheme 1, Table 1).

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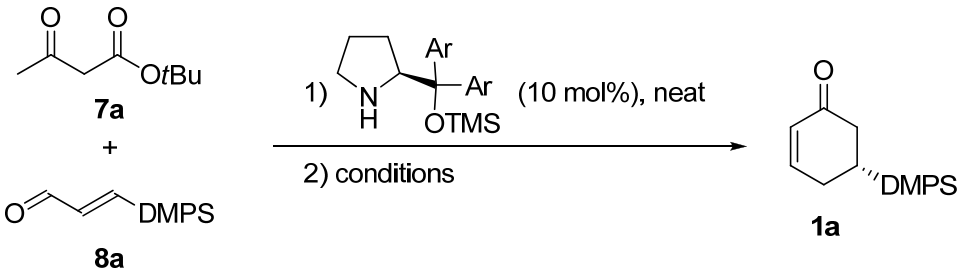
[1] Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794.
[2] (a) Welch, S. C.; Asserq, J.-M.; Loh, J.-P.; Glase, S. A. *J. Org. Chem.* **1987**, *52*, 1440. (b) Graalfs, H.; Frohlich, R.; Wolff, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, 1057.
[3] (a) Ostwald, R.; Chavant, P.-Y.; Stadtmüller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143. (b) Hwu, J. R.; Furth, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 8834.



Scheme 1: *Optimization of the reaction conditions*

Table 1: *Optimization of the decarboxylation-aldol condensation-reaction step*

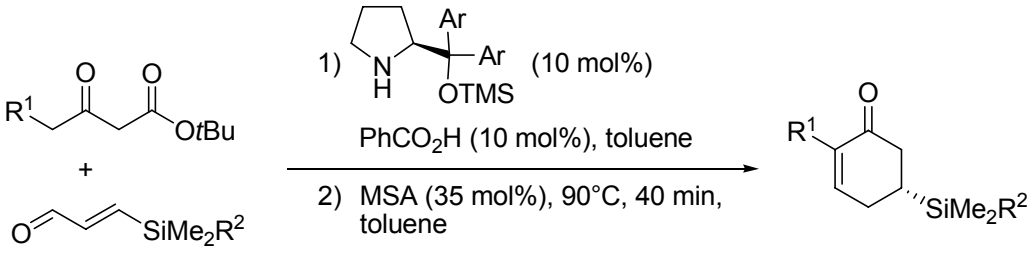
En-try	Acid[a]	Solvent	c (reac-tion) [mmol/ml]	Acid [mol%]	Time [min]	T [°C]	Yield[b] [%]	ee[c] [%]
1	TSA	Toluene	1.00	20	6 d	RT	traces	n.d.
2	TSA	Toluene	1.00	20	120 min	75	35	96
3	TSA	Toluene	0.50	20	17 h	80	17	92
4	TSA	Toluene	0.50	20	17 h	80	21	93
5	**TSA**	**Toluene**	**1.00**	**20**	**30 min**	**90**	**42**	**98**
6	TSA	Toluene	0.50	20	15 min	120	26	28 (+)
7	TSA	Toluene	1.00	15	30 min	90	35	95
8	TSA	Toluene	1.00	10	240 min	90	24	96
9	TFA	CH_2Cl_2	1.00	20	2 d	RT	-	-
10	TFA	Toluene	0.50	20	240 min	75	-	-
11	TFA	Toluene	0.50	150	60 min	75	traces	-

[a] Reaction conditions: 1) aldehyde (0.25 mmol), ketoester (0.25 mmol), catalyst (10 mol%), neat, 15-17 h. 2) Acid (10-20 mol%), solvent. [b]Isolated yield after column chromatography. [c]Determined after chiral HPLC. TSA = *p*-toluene sulfonic acid, TFA = trifluoroacetic acid.

The first optimizations of the decarboxylation-aldol condensation step showed that the yield of the cyclohexenone **1a** depended on a fine tuning of time, temperature and amount of acid. Low yields of the desired product were observed at long reaction times, low loadings of acid and high temperatures (Table 1, entries 2-8). At room

temperature only traces of the product were detected (Table 1, entry 1). With TFA no formation of the product took place (Table 1, entries 9-11). The best yield of 42% with an enantioselectivity of 98% ee was achieved with TSA after stirring for 30 min at 90 °C (Table 1, entry 5). That led to a further optimization of the reaction conditions.

3. Synthesis of 5-(trialkylsilyl)cyclohex-2-enones



Scheme 2: Synthesis of 5-(trialkylsilyl)cyclohex-2-enones

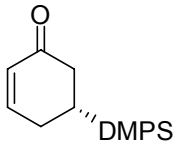
General procedure: Benzoic acid (0.10 mmol, 12 mg, 10 mol%) and the catalyst (0.10 mmol, 60 mg, 10 mol%) were dissolved in toluene (0.50 mL). Then the aldehyde (1.00 mmol) and the β-ketoester (1.5 mmol, 1.5 eq.) were added and the solution was stirred at room temperature overnight. Toluene (3.5 mL) and MSA (0.35 mmol, 23 µL, 35 mol%) were added and the solution was heated at 90 °C for 40 min. The mixture was directly purified by FC.

Synthesis of (*R*)-5-(dimethyl(phenyl)silyl)cyclohex-2-enone (10 mmol scale): Benzoic acid (1.0 mmol, 0.12 g, 10 mol%) and the catalyst (1.0 mmol, 0.60 g, 10 mol%) were dissolved in toluene (5.0 mL). Then (*E*)-3-(dimethyl(phenyl)silyl)acrylaldehyde (10.0 mmol, 1.90 g) and *tert*-butyl 3-oxobutanoate (15.0 mmol, 2.45 ml, 1.5 eq.) were added and the solution was stirred at room temperature overnight. Toluene (35 mL) and MSA (3.5 mmol, 0.24 mL, 35 mol%) were added and the solution was heated at 90 °C for 40 min. Then water (40 mL) and Et_2O (20 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with sat. NaCl solution (80 mL), dried (Na_2SO_4), filtered and concentrated

under reduced pressure. The residue was purified by FC (SiO_2, eluent 3/1, pentane/Et_2O) to obtain (*R*)-5-(dimethyl(phenyl)silyl)cyclohex-2-enone (5.9 mmol, 1.36 g, 59%).

Synthesis of (*R*)-5-(trimethylsilyl)cyclohex-2-enone (10 mmol scale): Benzoic acid (1.0 mmol, 0.12 g, 10 mol%) and the catalyst (1.0 mmol, 0.60 g, 10 mol%) were dissolved in toluene (5.0 mL). Then (*E*)-3-(dimethyl(phenyl)silyl)acrylaldehyde (10.0 mmol, 1.90 g) and *tert*-butyl 3-oxobutanoate (15.0 mmol, 2.45 mL, 1.5 eq.) were added and the solution was stirred at room temperature overnight. Toluene (35 mL) and MSA (3.5 mmol, 0.24 mL, 35 mol%) were added and the solution was heated at 90 °C for 40 min. After cooling the mixture was filtered through SiO_2 eluting with 99/1 pentane/Et_2O. The product was recovered by eluting with 1/4 pentane/Et_2O. After careful evaporation the residue was purified by FC (SiO_2, eluent 4/1, pentane/Et_2O) to obtain (*R*)-5-(trimethylsilyl)cyclohex-2-enone (6.1 mmol, 1.03 g, 61%).

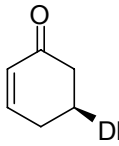
(*R*)-5-(dimethyl(phenyl)silyl)cyclohex-2-enone (1a)



The product was obtained following the general procedure as a yellow oil (0.57 mmol, 131 mg, 57%) after FC (SiO_2, eluent 3/1, pentane/Et_2O). The ee was determined by HPLC using a Chiralpak AS column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 17.4 min, τ_{minor} = 21.6 min (99% ee). $[\alpha]^{20}_D$ = -4.8 (*c* = 0.49, CH_2Cl_2, 99% ee). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52-7.44 (m, 2H), 7.43-7.34 (m, 3H), 6.98 (ddd, *J* = 10.1, 5.5, 2.5 Hz, 1H), 6.00-5.94 (m, 1H), 2.47-2.41 (m, 1H), 2.33-2.12 (m, 3H), 1.70-1.60 (m, 1H), 0.33 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.2, 151.5, 136.2, 134.0, 129.6, 129.5, 128.1, 38.7, 27.0, 23.0, -5.2, -5.4. HRMS calculated for: $[C_{14}H_{18}NaOSi]^+$ 253.1025; found: 253.1029. The spectral data are in accordance to literature data.[4]

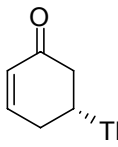
[4] Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811.

(*S*)-5-(dimethyl(phenyl)silyl)cyclohex-2-enone (1b)



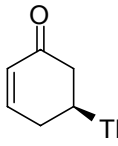
The product was obtained following the general procedure as a yellow oil (0.55 mmol, 126 mg, 55%) after FC (SiO_2, eluent 3/1, pentane/Et_2O). The ee was determined by HPLC using a Chiralpak AS column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 21.6 min, τ_{minor} = 17.5 min (99% ee). $[\alpha]^{20}_D$ = +3.9 (*c* = 0.50, CH_2Cl_2, 99% ee). The spectral data were identical to compound **1a**.

(*R*)-5-(trimethylsilyl)cyclohex-2-enone (1c)



The product was obtained following the general procedure as a yellow oil (0.65 mmol, 109 mg, 65%) after FC (SiO_2, eluent 4/1, pentane/Et_2O). The ee was determined by HPLC using two Chiralcel OJ columns [hexane/*i*PrOH (99:1)]; flow rate 0.5 mL/min; τ_{major} = 26.1 min, τ_{minor} = 28.0 min (99% ee). $[\alpha]^{20}_D$ = -6.3 (*c* = 1.0, CH_2Cl_2, 99% ee). ^{1}H NMR ($CDCl_3$) δ 7.04 (ddd, *J* = 10.1, 5.5, 2.4 Hz, 1H), 6.03-5.98 (m, 1H), 2.43 (ddt, *J* = 16.3, 3.7, 1.1 Hz, 1H), 2.37-2.28 (m, 1H), 2.26-2.13 (m, 2H), 1.43 (dddd, *J* = 15.1, 11.7, 4.6, 3.7 Hz, 1H), 0.02 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 200.4, 151.6, 129.5, 38.7, 26.9, 23.2, -3.7. HRMS calculated for $[C_9H_{16}NaOSi]^+$: 191.0868; found: 191.0867. The spectral data are in accordance to literature data.[5]

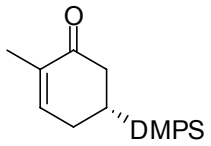
(*S*)-5-(trimethylsilyl)cyclohex-2-enone (1d)



The product was obtained following the general procedure as a yellow oil (0.69 mmol, 116 mg, 69%) after FC (SiO_2, eluent 4/1, pentane/Et_2O). The ee was determined by HPLC using two Chiralcel OJ columns [hexane/*i*PrOH (99:1)]; flow rate 0.5 mL/min; τ_{major} = 28.1 min, τ_{minor} = 26.8 min (99% ee). $[\alpha]^{20}_D$ = +7.9 (*c* = 0.52, CH_2Cl_2, 99% ee). The spectral data were identical to compound **1c**.

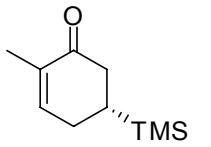
[5] (a) Hamon, D. P. G.; Hayball, P. J.; Massy-Westropp, R. A; Newton, J. L.; Tamblyn, J. G. *Tetrahedron: Asym.* **1996**, *7*, 263. (b) Asaoka, M; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669. (c) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811.

(*R*)-5-(dimethyl(phenyl)silyl)-2-methylcyclohex-2-enone (1e)



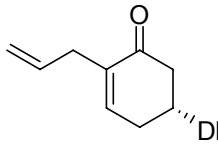
The product was obtained following the general procedure as a yellow oil (0.50 mmol, 123 mg, 50%) after FC (SiO_2, eluent 9/1, pentane/Et_2O). The ee was determined by HPLC using two Chiralpak AS columns [hexane/*i*PrOH (95:5)]; flow rate 0.5 mL/min; τ_{major} = 22.6 min, τ_{minor} = 20.8 min (99% ee). $[\alpha]^{20}_D$ = -18.7 (*c* = 0.50, CH_2Cl_2, 99% ee). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52-7.45 (m, 2H), 7.41-7.33 (m, 3H), 6.74-6.71 (m, 1H), 2.45, (ddd, *J* = 16.3, 3.6, 1.3 Hz, 1H), 2.30-2.11 (m, 3H), 1.73 (dt, *J* = 2.8, 1.4 Hz, 3H), 1.64 (dddd, *J* = 14.7, 11.2, 5.3, 3.6 Hz, 1H), 0.31 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.4, 146.3, 136.4, 135.2, 134.0, 129.5, 128.0, 38.9, 27.2, 23.6, 16.1, -5.2, -5.3. HRMS calculated for $[C_{15}H_{20}NaOSi]^+$: 267.1181; found: 267.1171. The spectral data are in accordance to literature data.[6]

(*R*)-5-(trimethylsilyl)-2-methylcyclohex-2-enone (1f)



The product was obtained following the general procedure as a yellow oil (0.42 mmol, 76 mg, 42%) after FC (SiO_2, eluent 9/1, pentane/Et_2O). The ee was determined by HPLC using two Chiralpak AS columns [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 21.6 min, τ_{minor} = 19.5 min (98% ee). $[\alpha]^{20}_D$ = -26.5 (*c* = 0.51, CH_2Cl_2, 98% *ee*). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.80-6.76 (m, 1H), 2.44 (ddd, *J* = 16.4, 3.7, 1.3 Hz, 1H), 2.34-2.11 (m, 3H), 1.77 (dt, *J* = 2.7, 1.4 Hz, 3H), 1.47-1.37 (m, 1H), 0.01 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.7, 146.4, 135.2, 38.9, 27.1, 23.8, 16.1, -3.7. HRMS calculated for $[C_{10}H_{18}NaOSi]^+$: 205.1025; found: 205.1028.

(*R*)-2-allyl-5-(dimethyl(phenyl)silyl)cyclohex-2-enone (1g)

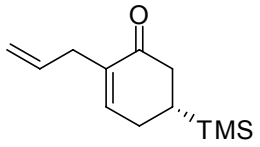


The product was obtained following the general procedure as a yellow oil (0.50 mmol, 134 mg, 50%) after FC (SiO_2, eluent 19/1 to 9/1, pentane/Et_2O). The ee was determined by HPLC using two Chiralpak AS columns [hexane/*i*PrOH (99:1)]; flow rate 0.5 mL/min; τ_{major} = 28.2 min, τ_{minor} = 25.1 min (99% ee). $[\alpha]^{20}_D$ = -20.2 (*c* = 0.49, CH_2Cl_2, 99% ee). ^{1}H

[6] Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044.

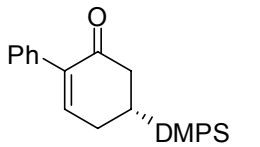
NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H), 7.40–7.35 (m, 3H), 6.73–6.69 (m, 1H), 5.85–5.70 (m, 1H), 5.06–4.96 (m, 2H), 2.95–2.85 (m, 2H), 2.47 (ddd, *J* = 16.2, 3.5, 1.2 Hz, 1H), 2.35–2.14 (m, 3H), 1.70–1.57 (m, 1H), 0.32 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 146.4, 137.4, 136.2, 135.7, 133.8, 129.3, 127.8, 116.1, 38.9, 33.4, 27.0, 23.2, -5.4, -5.5. HRMS calculated for $[C_{17}H_{22}NaOSi]^+$: 293.1338, found: 293.1334.

(*R*)-2-allyl-5-(trimethylsilyl)cyclohex-2-enone (1h)



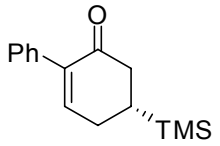
The product was obtained following the general procedure as a yellow oil (0.46 mmol, 95 mg, 46%) after FC (SiO_2, eluent 19/1, pentane/Et_2O). The ee was determined by HPLC using two Chiralpak AS columns [hexane/*i*PrOH (99:1)]; flow rate 0.5 mL/min; τ_{major} = 25.1 min, τ_{minor} = 22.1 min (99% ee). $[\alpha]^{20}_D$ = -29.6 (*c* = 0.53, CH_2Cl_2, 99% ee). ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (tdd, *J* = 5.2, 2.5, 1.3 Hz, 1H), 5.89-5.73 (m, 1H), 5.12-4.97 (m, 2H), 2.98-2.90 (m, 2H), 2.45 (ddd, *J* = 16.1, 3.5, 1.3 Hz, 1H), 2.39-2.28 (m, 1H), 2.27-2.16 (m, 2H), 1.48-1.37 (m, 1H), 0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 146.4, 137.4, 135.8, 116.1, 38.9, 33.4, 27.0, 23.4, -3.8. HRMS calculated for $[C_{12}H_{20}NaOSi]^+$: 231.1181; found: 231.1177.

(*R*)-5-(dimethyl(phenyl)silyl)-2-phenylcyclohex-2-enone (1i)



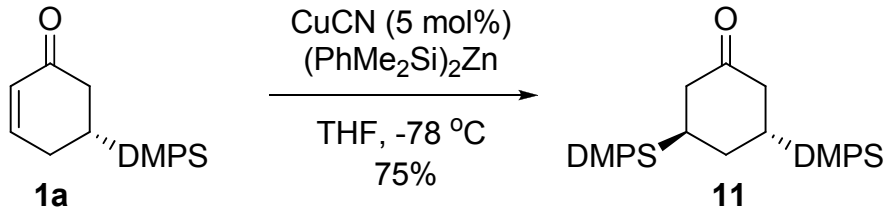
The product was obtained following the general procedure as a yellow oil (0.52 mmol, 160 mg, 52%) after FC (SiO_2, eluent 9/1 to 4/1, pentane/Et_2O). The ee was determined by HPLC using two Chiralpak AS columns [hexane/*i*PrOH (95:5)]; flow rate 0.5 mL/min; τ_{major} = 31.6 min, τ_{minor} = 26.5 min (99% ee). $[\alpha]^{20}_D$ = -11.9 (*c* = 0.53, CH_2Cl_2, 99% ee). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.49 (m, 2H), 7.44-7.36 (m, 3H), 7.36-7.22 (m, 5H), 7.00 (dd, *J* = 5.5, 2.8 Hz, 1H), 2.61 (ddd, *J* = 15.9, 3.5, 1.3 Hz, 1H), 2.52-2.43 (m, 1H), 2.43-2.32 (m, 2H), 1.83-1.74 (m, 1H), 0.37 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 148.6, 139.9, 136.6, 136.2, 134.0, 129.6, 128.6, 128.1, 127.6, 39.7, 27.8, 23.1, -5.2, -5.3. HRMS calculated for $[C_{20}H_{22}NaOSi]^+$: 329.1338; found: 329.1349.

(*R*)-5-(trimethylsilyl)-2-phenylcyclohex-2-enone (1j)



The product was obtained following the general procedure as a yellow solid (0.47 mmol, 115 mg, 47%) after FC (SiO_2, eluent 9/1, pentane/Et_2O). The ee was determined by HPLC using a Chiralcel OJ column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 12.9 min, τ_{minor} = 10.7 min (98% ee). $[\alpha]^{20}_D$ = -14.2 (*c* = 0.48, CH_2Cl_2, 98% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 7.06 (dd, *J* = 5.7, 2.7 Hz, 1H), 2.59 (ddd, *J* = 15.9, 3.6, 1.4 Hz, 1H), 2.56-2.46 (m, 1H), 2.45-2.34 (m, 2H), 1.64-1.52 (m, 1H), 0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 148.7, 139.9, 136.7, 128.6, 128.1, 127.6, 39.7, 27.7, 23.3, -3.6. HRMS calculated for $[C_{15}H_{20}NaOSi]^+$: 267.1181; found: 267.1186.

4. Synthesis of the A-ring ketone intermediate of 19-*nor*-1α,25-dihydroxyvitamin D_3



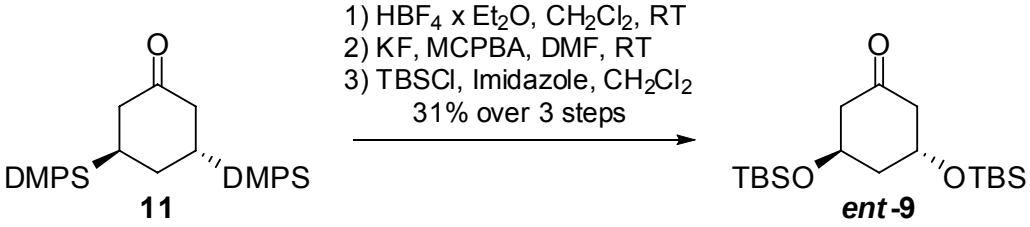
Scheme 3: Synthesis of (3S,5S)-3,5-bis(dimethyl(phenyl)silyl)cyclohexanone

4.1. Preparation of phenyldimethylsilyllithium: According to a procedure by Fleming[7] freshly cut lithium (70.6 mmol, 490 mg) was placed under N_2-atmosphere and washed with pentane (3 x 10 mL). 15 mL dry THF (15 mL) was added and the mixture was cooled to 0 °C. $PhMe_2SiCl$ (22.5 mmol, 3.75 mL) was then added, and the mixture was stirred at 0 °C for 6 h, after which the dark red mixture was placed at -20 °C and stored overnight. The solution was titrated by the standard double titration method (see ref.[7] for procedure).

4.2. Procedure: According to a procedure by Oestreich[8] 1 M $ZnCl_2$ in Et_2O (0.60 mmol, 0.60 mL, 1.2 eq.) was added at 0 °C to a 0.95 M solution of phenyldimethyl-

[7] Fleming, I.; Maiti, P.; Ramarao, C. *Org. Biomol. Chem.* **2003**, 3989
[8] Oestreich, M.; Weiner, B. *Synlett* **2004,** 2139

silyllithium (from the previous step) in THF (1.20 mmol, 1.3 mL, 2.4 eq.). After stirring for 15 min the solution was added to a suspension of Cu(I)CN (0.025 mmol, 2.2 mg, 5 mol%) in dry THF (2.8 mL) at -78 °C under N_2 atmosphere. The solution was heated to 0 °C and recooled to -78 °C, after which enone **1a** (0.50 mmol, 115 mg) in dry THF (1.1 mL) was slowly added. After 20 min NMR showed full conversion, and the reaction was quenched by addition of sat. NH_4Cl (2.8 mL). The aqueous layer was then extracted with Et_2O (3 x 10 mL), and the combined organic layers were washed with water (2 x 10 mL) and sat. NaCl solution (80 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FC (SiO_2, eluent 19/1 to 6/1, pentane/Et_2O) to obtain (3*S*,5*S*)-3,5-bis(dimethyl(phenyl)silyl)cyclohexanone as a pale, yellow solid (0.37 mmol, 137 mg, 75%). $[\alpha]^{20}_D$ = +75.1 (*c* = 0.57, CH_2Cl_2, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.30 (m, 10H), 2.30 (dd, *J* = 15.2, 5.8 Hz, 2H), 2.22 (dd, *J* = 15.2, 9.7 Hz, 2H), 1.71 (t, *J* = 7.1 Hz, 2H), 1.47-1.36 (m, 2H), 0.26 (s, 6H), 0.25 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.6, 137.1, 134.0, 129.4, 128.0, 41.2, 25.7, 23.6, -4.5. HRMS calculated for $[C_{22}H_{30}NaOSi_2]^+$: 389.1733; found: 389.1727.



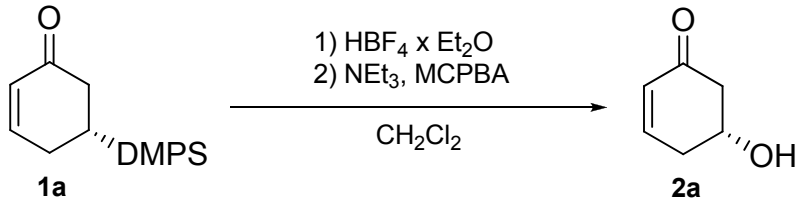
*Scheme 4: Synthesis of (3*R*,5*R*)-3,5-bis(*tert*-butyldimethylsilyloxy)cyclohexanone*

4.3. Procedure: According to a procedure by Fleming[9] **11** (0.33 mmol, 121 mg) was dissolved in CH_2Cl_2 (13 mL) and HBF_4 x Et_2O (6.5 mL) was added dropwise. The mixture was stirred overnight and cold KOH solution (5%, 32 mL) and CH_2Cl_2 (25 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with sat. NaCl solution (2 x 25 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield (3*S*,5*S*)-3,5-

[9] Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, E. J. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 317.

bis(fluorodimethylsilyl)cyclohexanone as a brown oil. The crude product was dissolved in dry DMF (4.4 mL) and added to anhyd. KF (0.99 mmol, 57.5 mg) under inert atmosphere. The mixture was cooled to 0 ^{o}C and *m*-CPBA (ca 77% pure, 1.32 mmol, 296 mg) in dry DMF (2.2 mL) was added dropwise. After stirring for 5 h at room temperature the reaction was estimated to be complete by NMR, after which the DMF was removed under high vacuum at 40 ^{o}C. CH_2Cl_2 (5 mL) was added giving a suspension, which was filtered and concentrated under reduced pressure. The residue mainly containing product, *m*-CPBA and DMF was dissolved in dry CH_2Cl_2 (2.3 mL) and TBSCl (2.3 mmol, 352 mg) was added at 0 ^{o}C. Imidazole (2.3 mmol, 159 mg) was then added in 3 portions at 2.5 min intervals. After 30 min the reaction was estimated to be complete by NMR, and the reaction was quenched by the addition of MeOH (1.5 mL). The reaction mixture was diluted with H_2O (15 mL) and CH_2Cl_2 (15 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were washed with sat. NaCl solution (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FC (SiO_2, eluent 99/1 to 19/1, pentane/EtOAc) to obtain (3*R*,5*R*)-3,5-bis(*tert*-butyldimethylsilyloxy)cyclohexanone as a yellow oil (0.10 mmol, 37 mg, 31% over three steps). $[\alpha]^{20}_{D}$ = +18.6 (*c* = 0.53, CH_2Cl_2, 99% ee). ^{1}H NMR (400 MHz, CDCl3) δ 4.38-4.31 (m, 2H), 2.54 (dd, *J* = 14.4, 3.9 Hz, 2H), 2.35 (dd, *J* = 14.5, 6.6 Hz, 2H), 1.94 (t, *J* = 5.3 Hz, 2H), 0.86 (s, 18H), 0.05 (s, 6H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 208.2, 66.9, 50.4, 42.2, 25.8, 18.1, -4.8, -4.8. HRMS calculated for $[C_{18}H_{38}NaO_3Si_2]^{+}$: 381.2257, found: 381.2258.

5. Synthesis of (*R*)-5-(*tert*-butyldimethylsilyloxy)cyclohex-2-enone

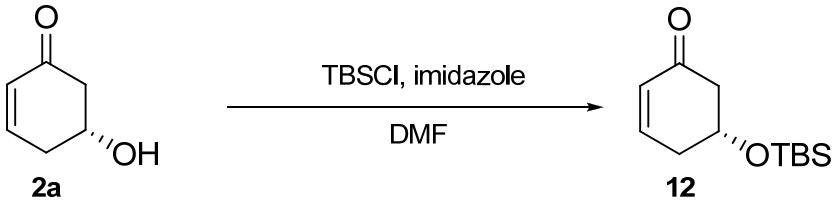


Scheme 5: Synthesis of 5-hydroxycyclohex-2-enone

5.1 Synthesis of 5-hydroxycyclohex-2-enone

According to a procedure by Fleming[9] (*R*)-5-(dimethyl(phenyl)silyl)cyclohex-2-enone (0.41 mmol, 95.4 mg) was dissolved in CH_2Cl_2 (8.2 mL) and HBF_4 x Et_2O (5 mL) was added dropwise. The mixture was stirred 5 h and cold KOH solution (5%, 50 mL) and CH_2Cl_2 (40 mL) were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield (*R*)-5-(fluorodimethylsilyl)cyclohex-2-enone as a brown oil. The crude product was dissolved in dry CH_2Cl_2 (3 mL) in a flame-dried Schlenk-tube equipped with a magnetic stirring bar. *m*-CPBA (ca 77% pure, 1.41 mmol, 315 mg) was added at 0 °C followed by Et_3N (0.48 mL, 67 µL) in 1 mL CH_2Cl_2. The mixture was allowed to reach room temperature and after stirring for 30 min, the reaction was diluted with 4 mL CH_2Cl_2 and quenched by the addition of 8 mL H_2O. The phases were separated and the organic layer was extracted with H_2O (2 x 8 mL). The combined aqueous layers were washed with Et_2O (10 mL) and evaporated under high vacuum at 30°C. The residue was purified by FC (SiO_2, eluent 1/1 to 3/7 pentane/EtOAc) to obtain (*R*)-5-hydroxycyclohex-2-enone as a clear oil (0.25 mmol, 28.3 mg, 61% over two steps) The *ee* was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 ml/min; τ_{major} = 24.6 min, τ_{minor} = 27.7 min (99% *ee*). $[\alpha]^{20}_D$ = -47.7 (*c* = 0.62, CH_2Cl_2, 99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (ddd, *J* = 10.0, 4.7, 3.5 Hz, 1H), 6.07 (dt, *J* = 10.1, 2.0 Hz, 1H), 4.32 (ddt, *J* = 8.8, 7.2, 4.3 Hz, 1H), 2.74 (dd, *J* = 16.0, 4.1 Hz, 1H), 2.74-2.60 (m, 1H), 2.52 (dd, J = 16.2, 9.0, Hz, 1H),

2.48-2.38 (m, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 198.5, 147.1, 130.1, 66.9, 47.3, 34.6. HRMS calculated for $[C_6H_8NaO_2]^+$: 135.0422, found: 135.0425.



2a **12**

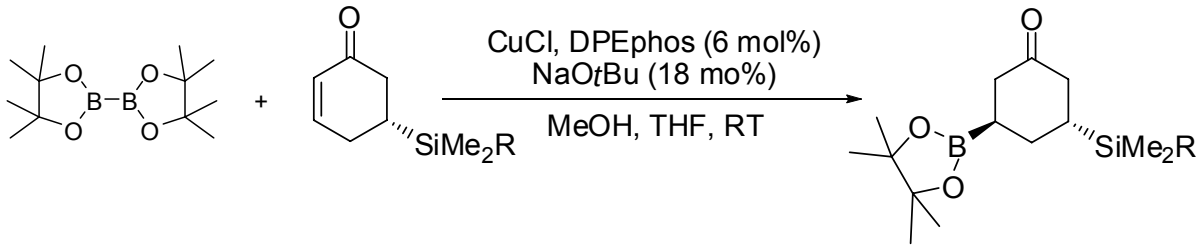
*Scheme 6: Synthesis of 5-(*tert-*butyldimethylsilyloxy)cyclohex-2-enone*

5.2 Synthesis of 5-(*tert*-butyldimethylsilyloxy)cyclohex-2-enone

According to a procedure by Honda[10] **2a** (0.20 mmol, 22.0 mg) was dissolved in DMF (1 mL) and imidazole (0.39 mmol, 26.7 mg) was added followed by TBSCl (0.39 mmol, 59.1 mg). After stirring at room temperature for 90 min the reaction was estimated to be complete by NMR, and the reaction was quenched by the addition of MeOH (8-10 drops). After diluting with Et_2O (10 mL) and H_2O (10 mL) the layers were separated, and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with H_2O (2 x 10 mL) and sat. NaCl solution (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FC (SiO_2, eluent 99/1 to 4/1 pentane/Et_2O) to obtain (*R*)-5-(tert-butyldimethylsilyloxy)cyclohex-2-enone as a clear oil (0.17 mmol, 39.1 mg, 88%) $[\alpha]^{20}_D$ = -10.9 (*c* = 0.54, CH_2Cl_2, 99% *ee*). ^{1}H NMR (400 MHz, CDCl3) δ 6.87 (ddd, *J* = 10.1, 5.1, 3.3 Hz, 1H), 6.10-6.02 (m, 1H), 4.23 (ddt, *J* = 9.6, 7.7, 4.4 Hz, 1H), 2.66 (dd, *J* = 16.0, 4.1 Hz, 1H), 2.63-2.55 (m, 1H), 2.48 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.38 (ddt, *J* = 18.3, 7.5, 2.8 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 198.8, 147.1, 130.2, 67.6, 48.2, 35.7, 25.8, 18.1, -4.6, -4.7. HRMS calculated for $[C_{12}H_{22}NaO_2Si]^+$: 249.1287; found: 249.1292.

[10] Honda, T.; Endo, K. *J. Chem. Soc., Perkin Trans. 1*, **2001**, *22*, 2915.

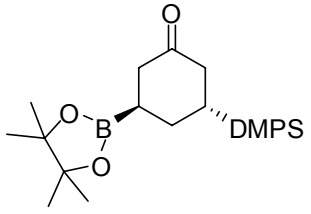
6. Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trialkylsilyl)cyclohexanones



Scheme 7: Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trialkylsilyl)cyclohexanones

General procedure: According to a procedure by Yun[11] Cu(I)Cl (0.03 mmol, 3 mg, 6 mol%), DPEphos (0.03 mmol, 16 mg, 6 mol%) and sodium *tert*-butanolate (0.09 mmol, 9 mg, 18 mol%) were suspended in THF (0.4 mL) in a Schlenk tube under Ar atmosphere and stirred 30 min at room temperature. Then bis(pinacolato)diboron (0.55 mmol, 140 mg, 1.1 eq.) and THF (0.3 mL) were added. After 10 min stirring at room temperature 5-(trialkylsilyl)-2-cyclohexenone (0.50 mmol), MeOH (2.00 mmol, 0.04 ml) and THF (0.3 mL) were added. After stirring overnight at room temperature the mixture was filtered over a pad of celite eluting with EtOAc:pentane (1:1, 80 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by FC.

Synthesis of (3*R*,5*S*)-3-(dimethyl(phenyl)silyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexanone (10a)

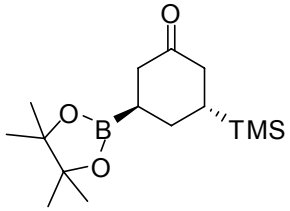


The product was obtained following the general procedure as colourless oil (0.46 mmol, 164 mg, 92%) with diastereomeric ratio of *trans*:*cis* = 82:18 after FC (Iatrobeads, eluent 5/1, pentane/EtOAc). $[\alpha]^{20}_{D}$ = +43.8 (c = 1.0, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.51-7.44 (m, 2H), 7.39-7.32 (m, 3H), 2.51-2.43 (m, 1H), 2.39-2.22 (m, 2H), 2.07 (t, J = 14.0,

[11] Mun, S; Lee, J.-Eon; Yun, J. *Org. Lett.* **2006**, *8*, 4887.

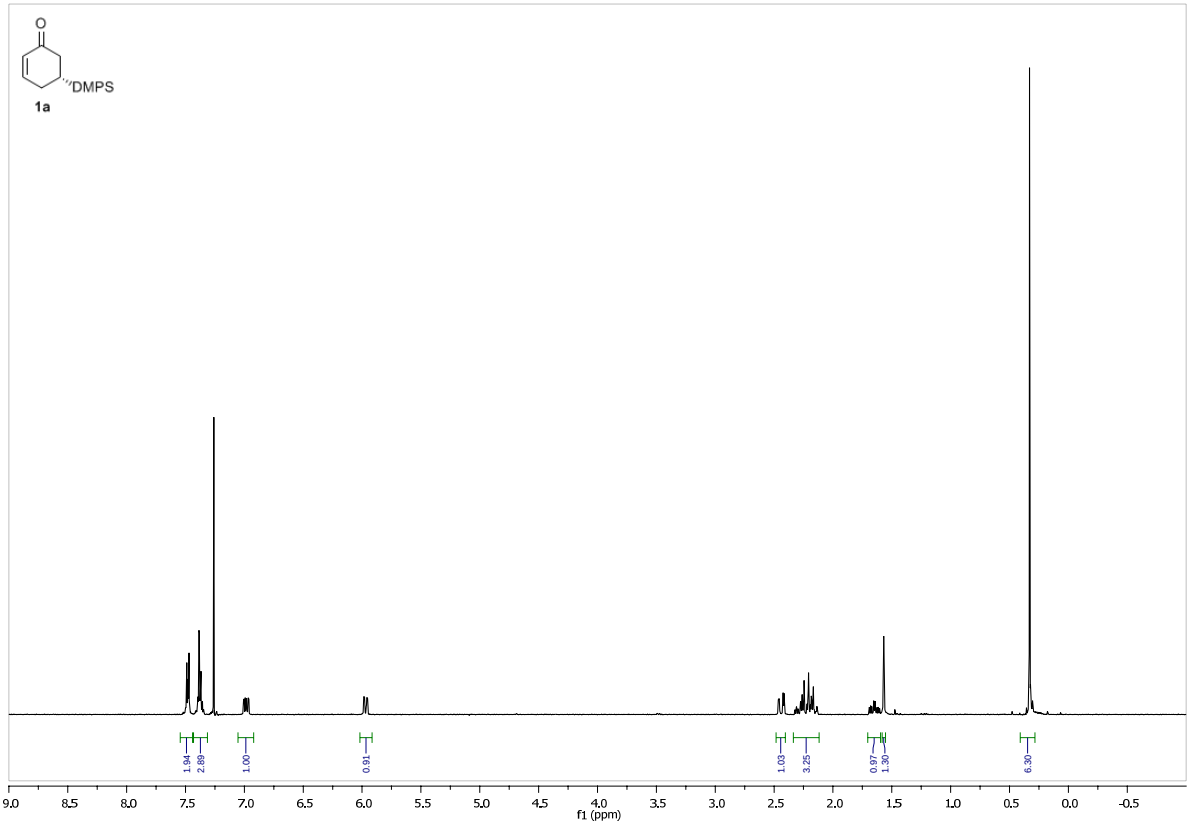
1H), 1.99-1.91 (m, 1H), 1.84-1.77 (m, 1H), 1.64-1.54 (m, 1H), 1.44-1.33 (m, 1H), 1.21 (s, 6H), 1.20 (m, 6H), 0.29 (s, 3H), 0.28 (s, 3H). ^{13}C-NMR (100 MHz, CDCl3): δ 212.3, 136.8, 133.8, 129.1, 127.7, 83.4, 42.0, 41.9, 26.9, 25.2, 24.8, 24.6, -5.0, -5.3 (resonance for Cα to boron not observed). HRMS calculated for $[C_{20}H_{31}BNaO_3Si]^+$: 381.2033, found: 381.2028.

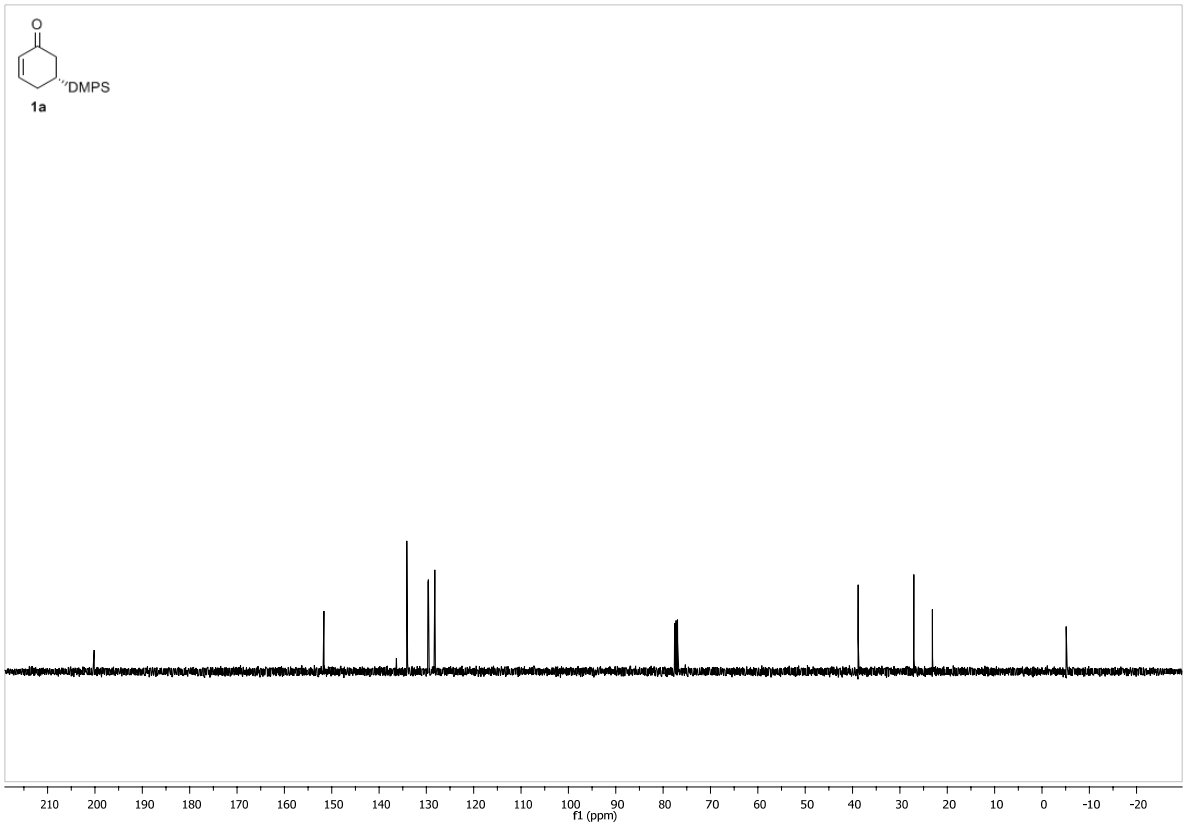
Synthesis of (3*S*,5*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trimethylsilyl)cyclohexanone (10b)



The product was obtained following the general procedure as colourless oil (0.43 mmol, 127 mg, 86%) with di-astereomeric ratio of *trans*:*cis* > 99:1 after FC (Iatrobeads, eluent 5/1, pentane/EtOAc). $[\alpha]^{20}_D$ = +58.8 (c = 1.0, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.52-2.43 (m, 1H), 2.35 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.27 (ddt, *J* = 14.3, 3.6, 1.6 Hz, 1H), 2.07 (t, *J* = 13.9 Hz, 1H), 1.92 (dt, *J* = 13.4, 3.8 Hz, 1H), 1.81 (dt, *J* = 11.2, 4.3 Hz, 1H), 1.68-1.54 (m, 1H), 1.21 (s, 6H), 1.19 (s, 6H), 1.10 (ddt, *J* = 13.3, 12.1, 3.8 Hz, 1H), -0.02 (s, 9H). ^{13}C-NMR (100 MHz, CDCl3): δ 212.7, 83.4, 42.0, 41.9, 26.8, 25.7, 24.8, 24.5, -3.6 (resonance for Cα to boron not observed). HRMS calculated for $[C_{15}H_{29}BNaO_3Si]^+$: 319.1877, found: 319.1878.

7. ^{1}H- and ^{13}C-NMR spectra of all relevant compounds

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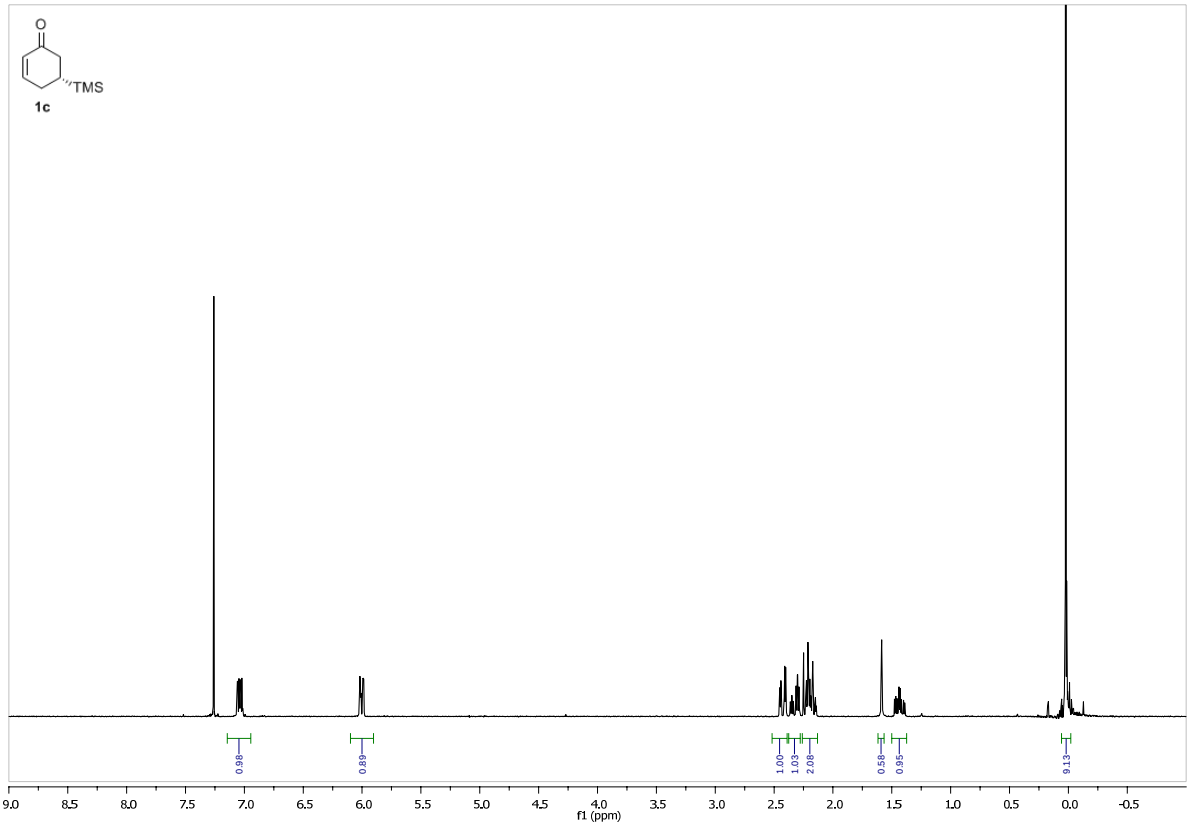
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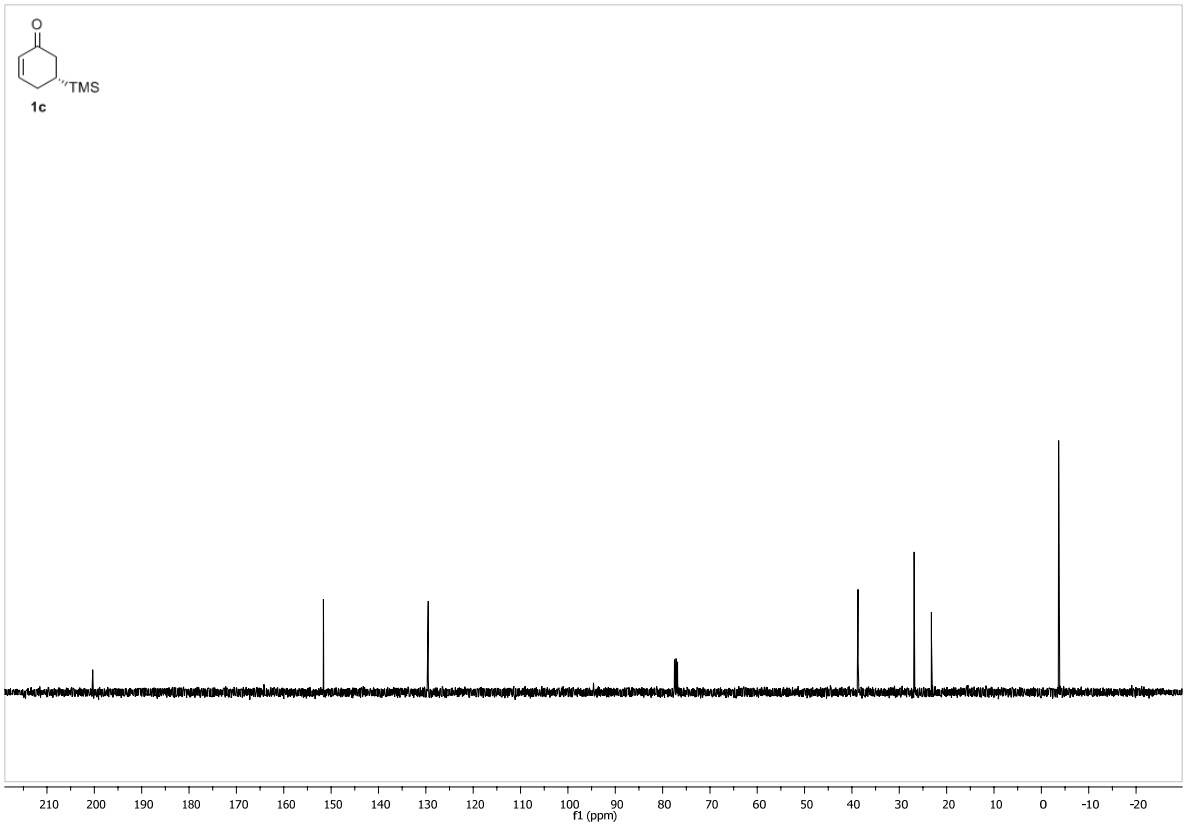
1.03
2.08
0.58
0.95
9.13
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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TMS
1c
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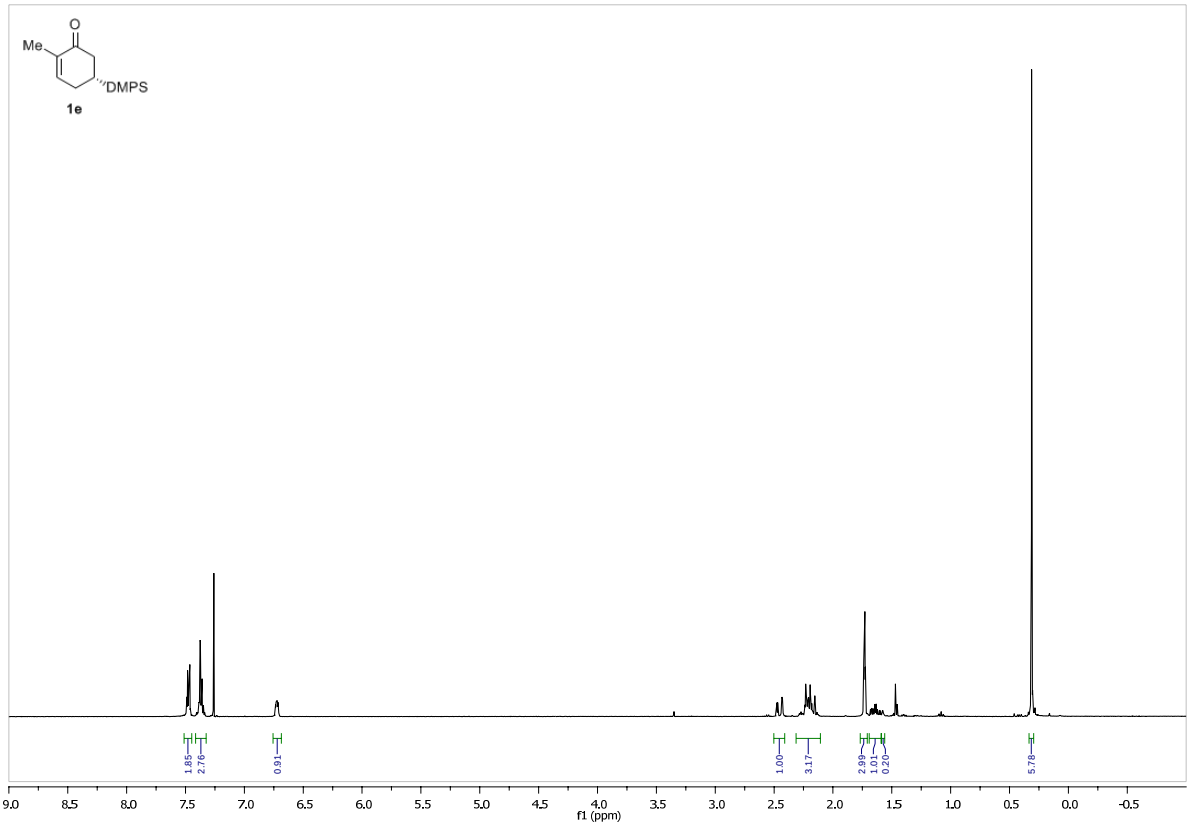
f1 (ppm)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Me
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1.00
3.17
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1.01
0.20
5.78
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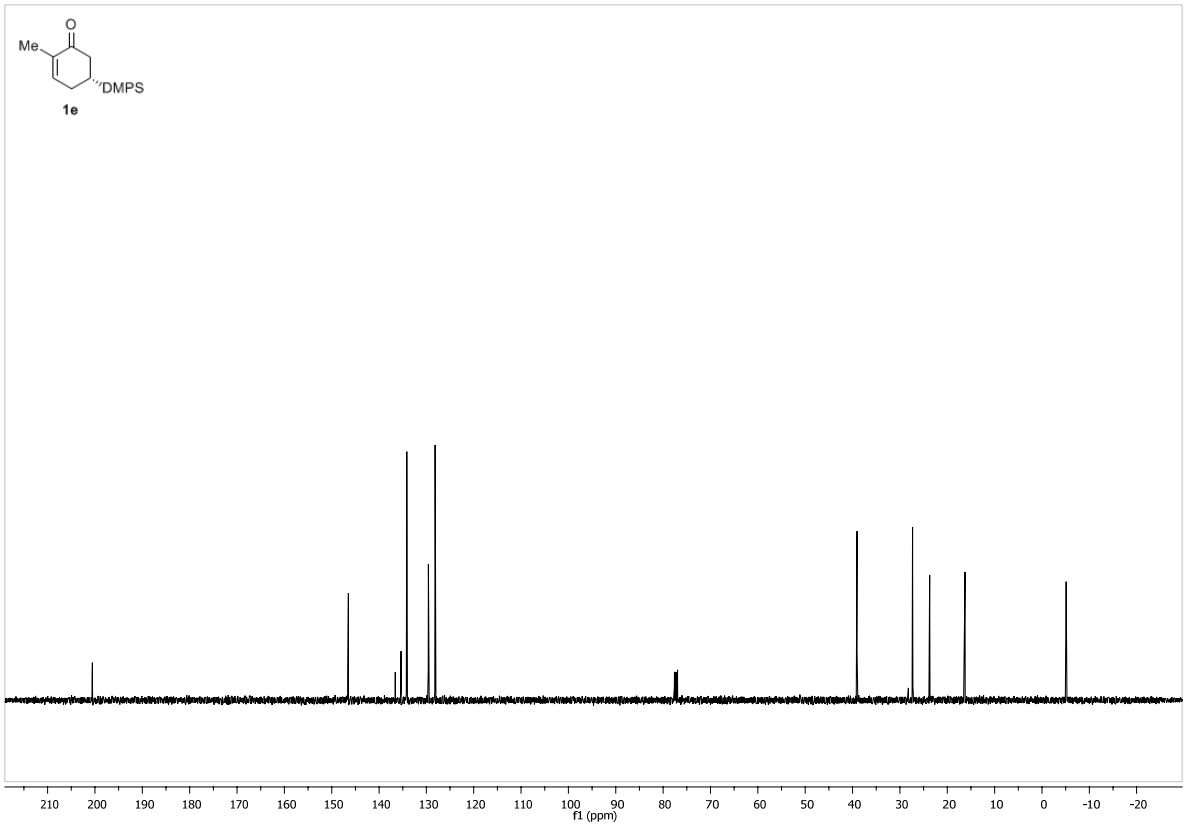
f1 (ppm)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O
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1e
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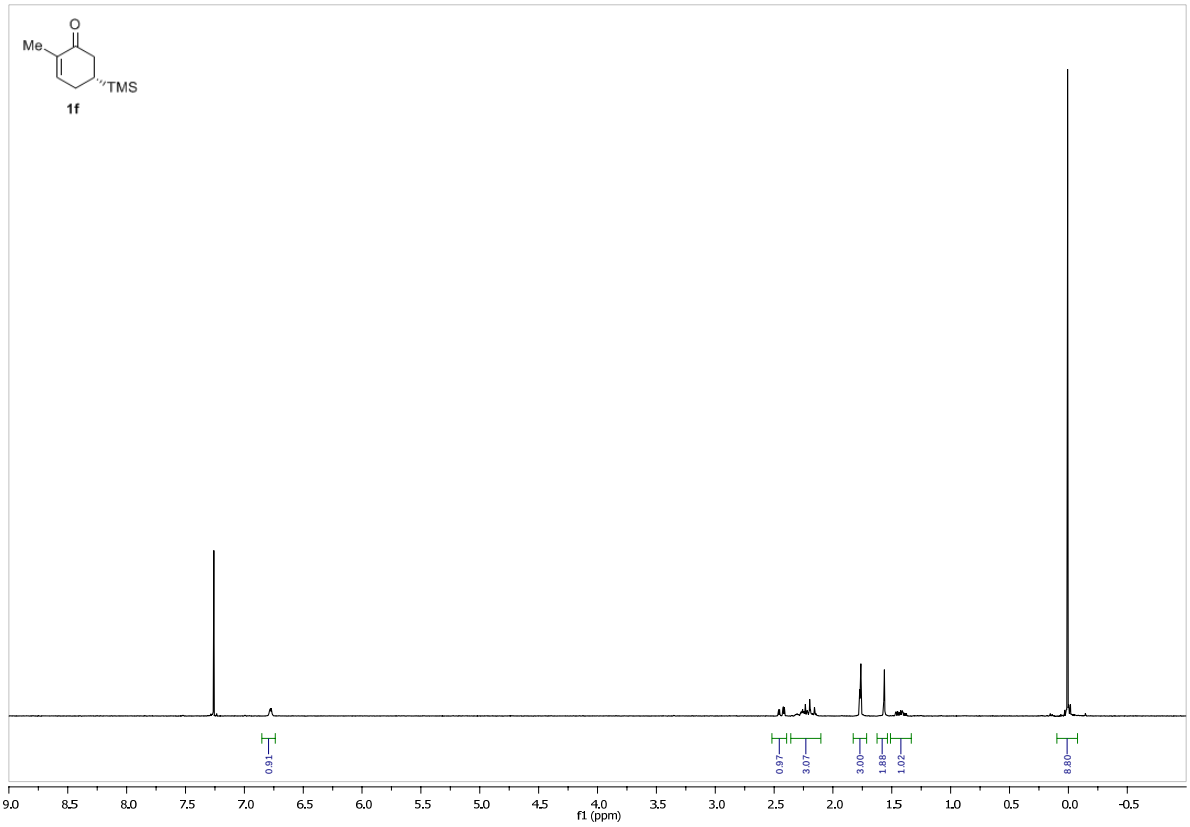
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1.02
8.80
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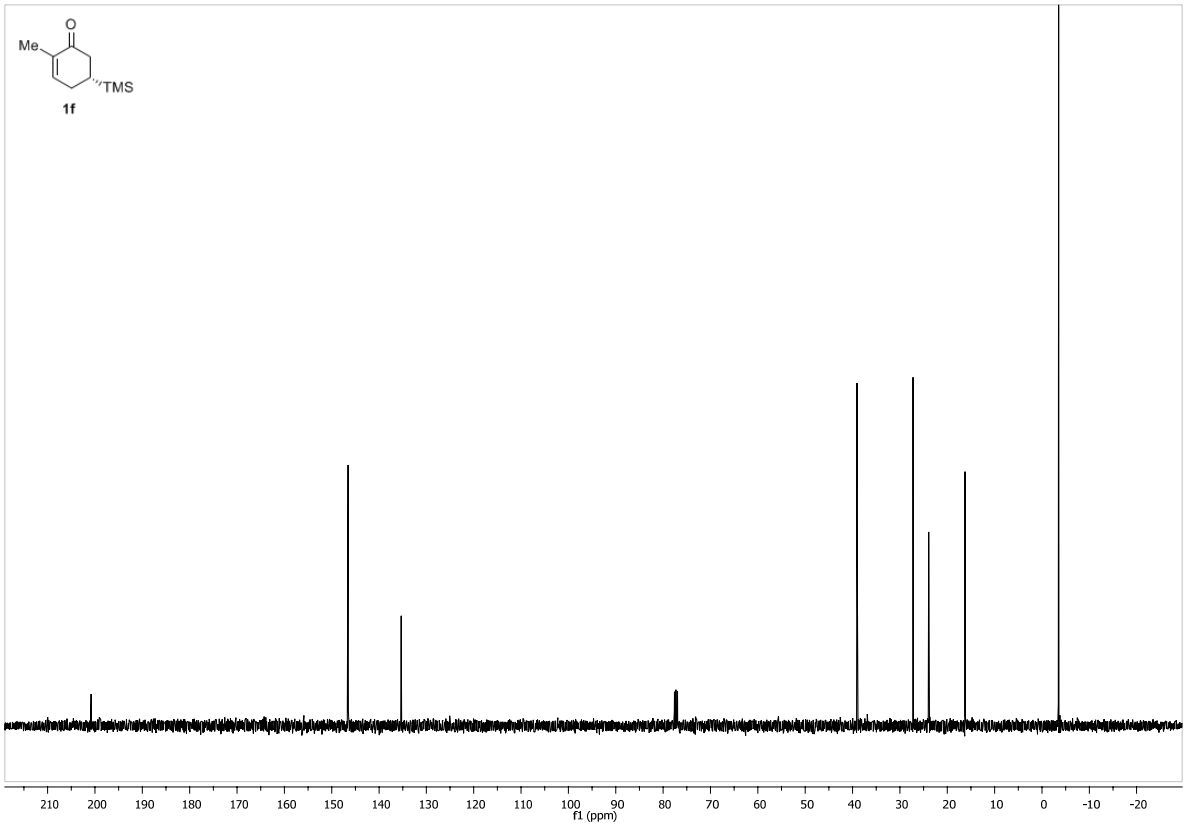
f1 (ppm)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O
TMS
1f
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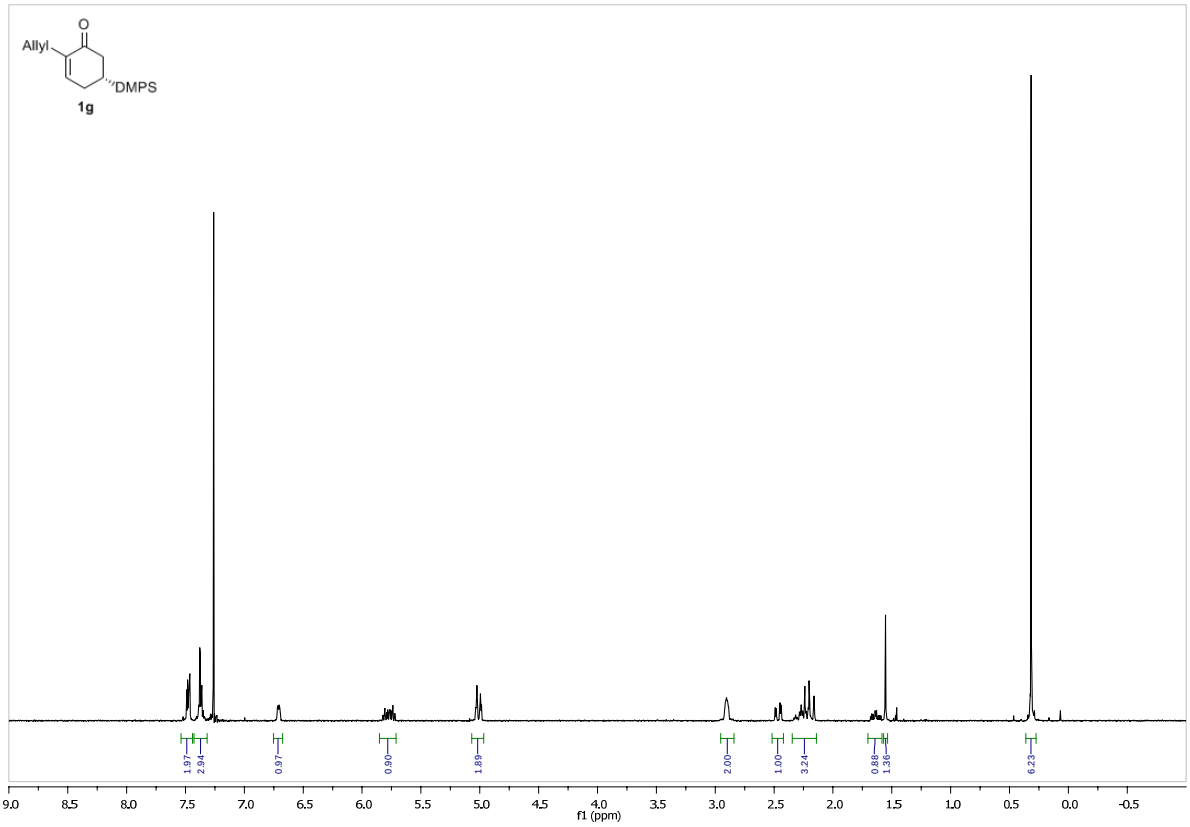
f1 (ppm)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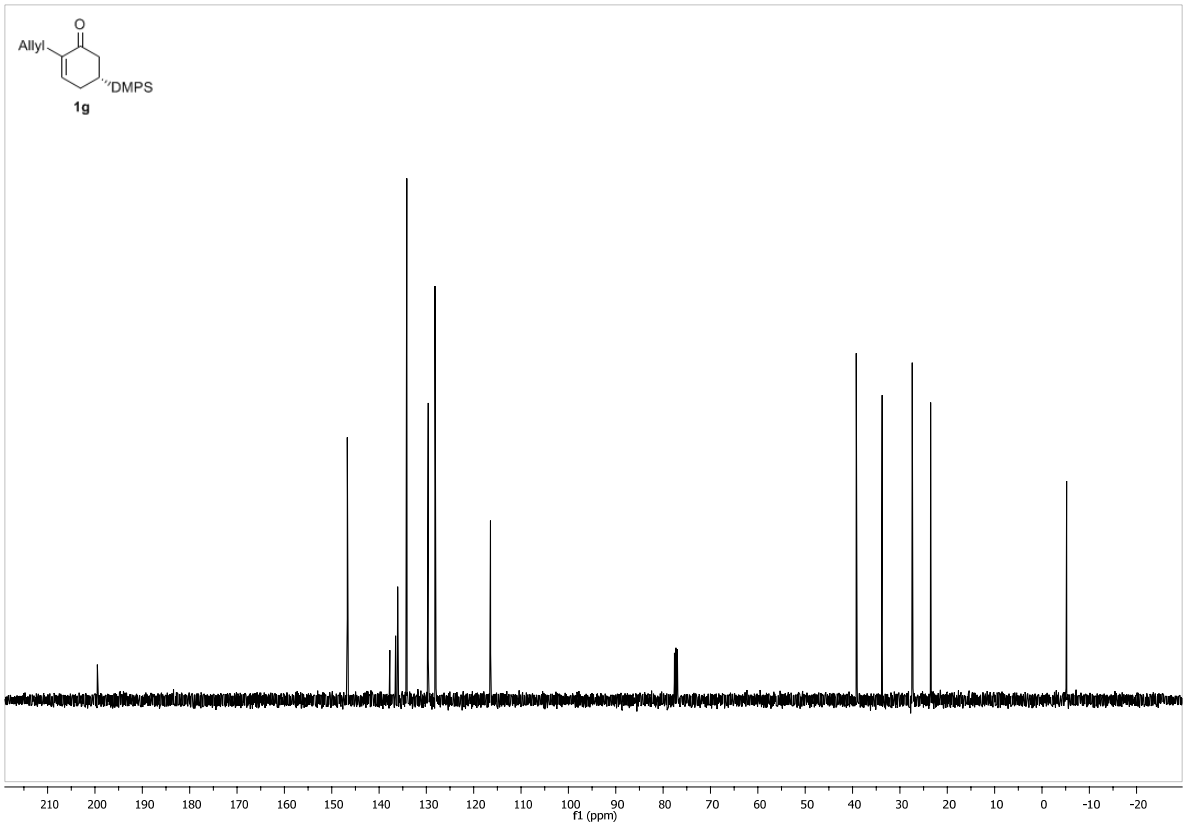
0.90
1.89
2.00
1.00
3.24
0.88
1.36
6.23
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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DMPS
1g
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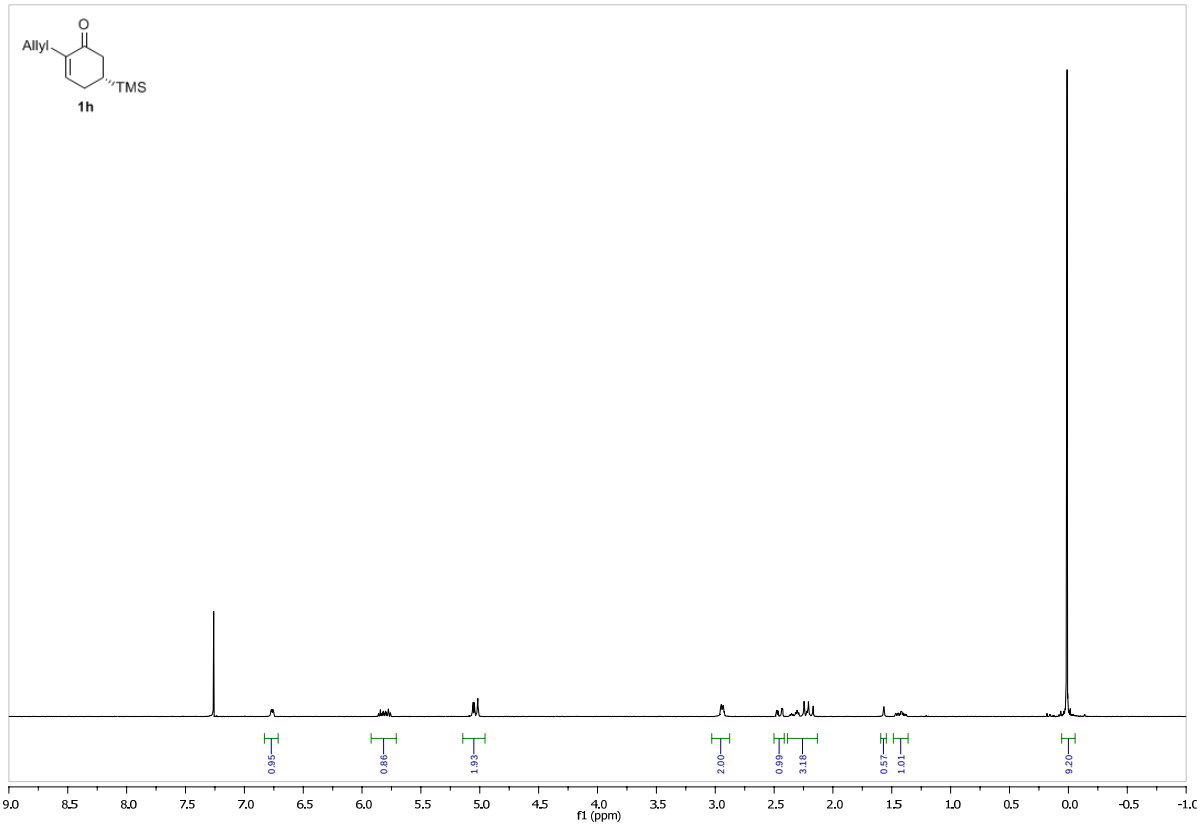
f1 (ppm)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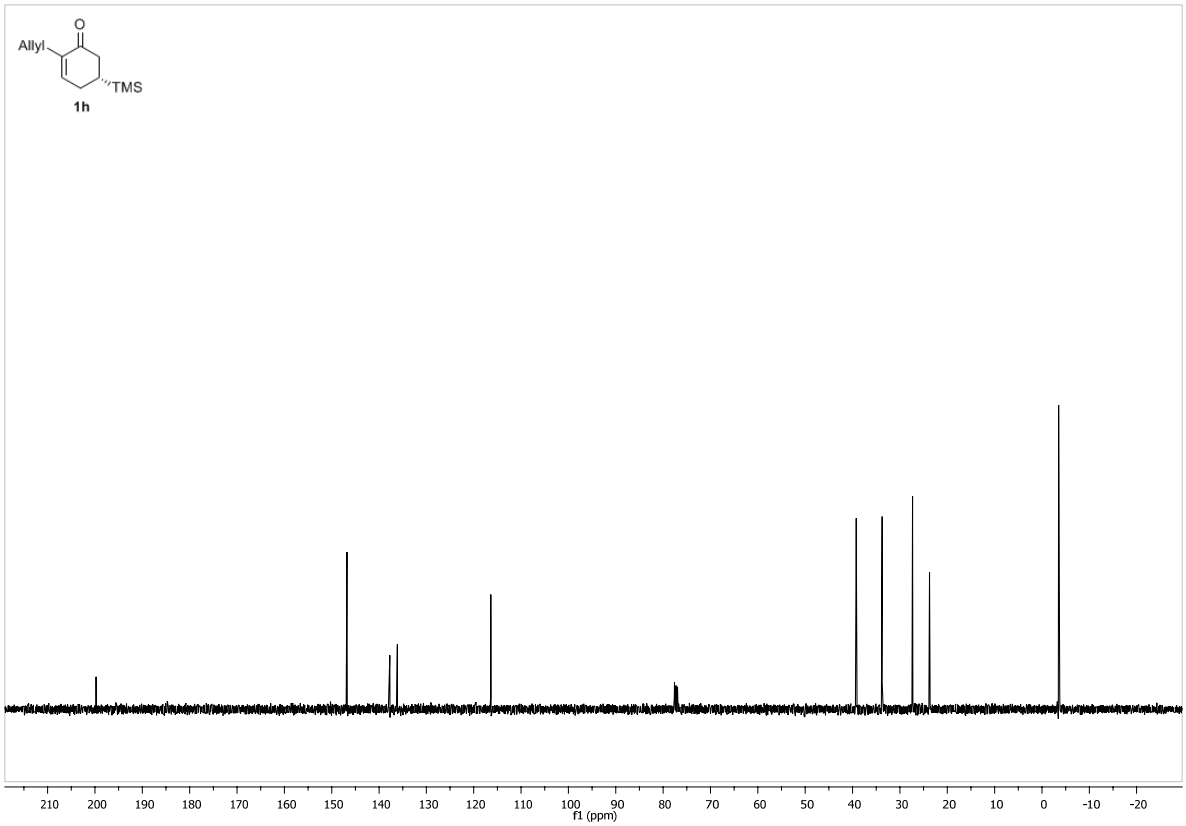
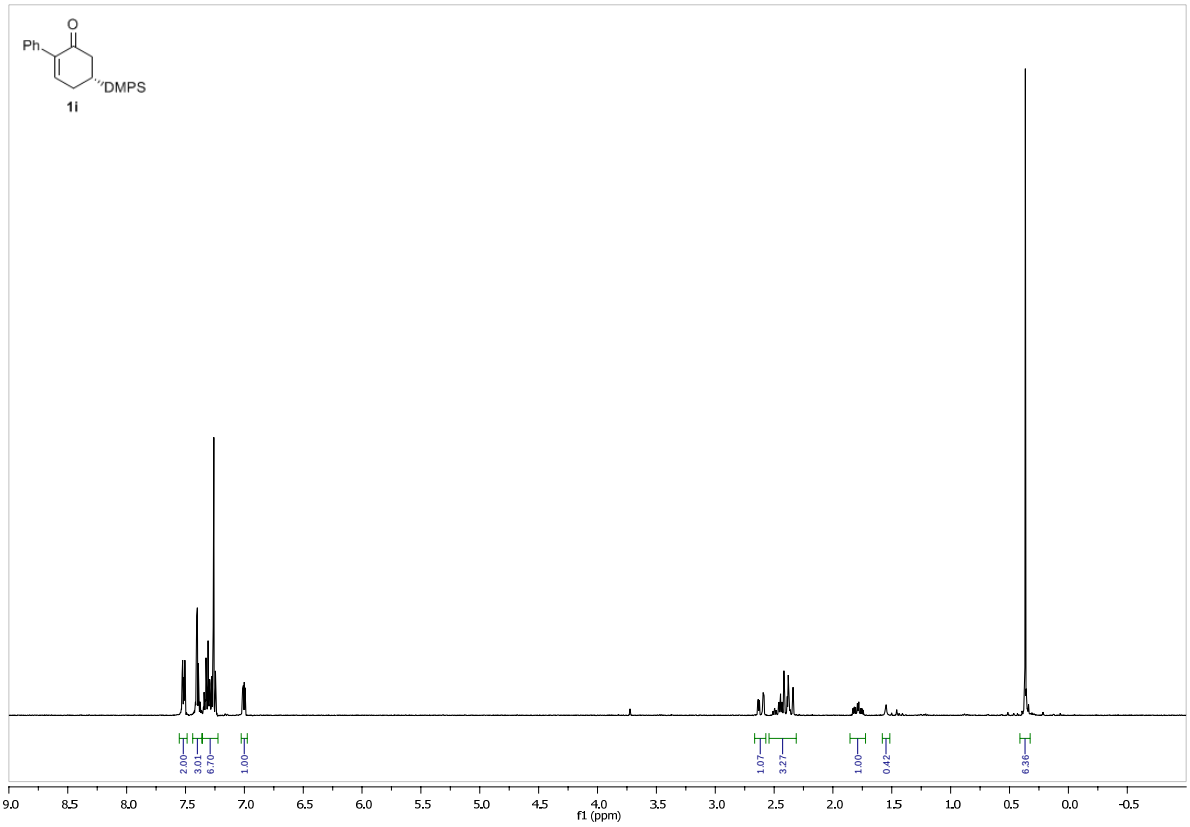
1.93
2.00
0.99
3.18
0.57
1.01
9.20
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


Allyl
TMS
1h
f1 (ppm)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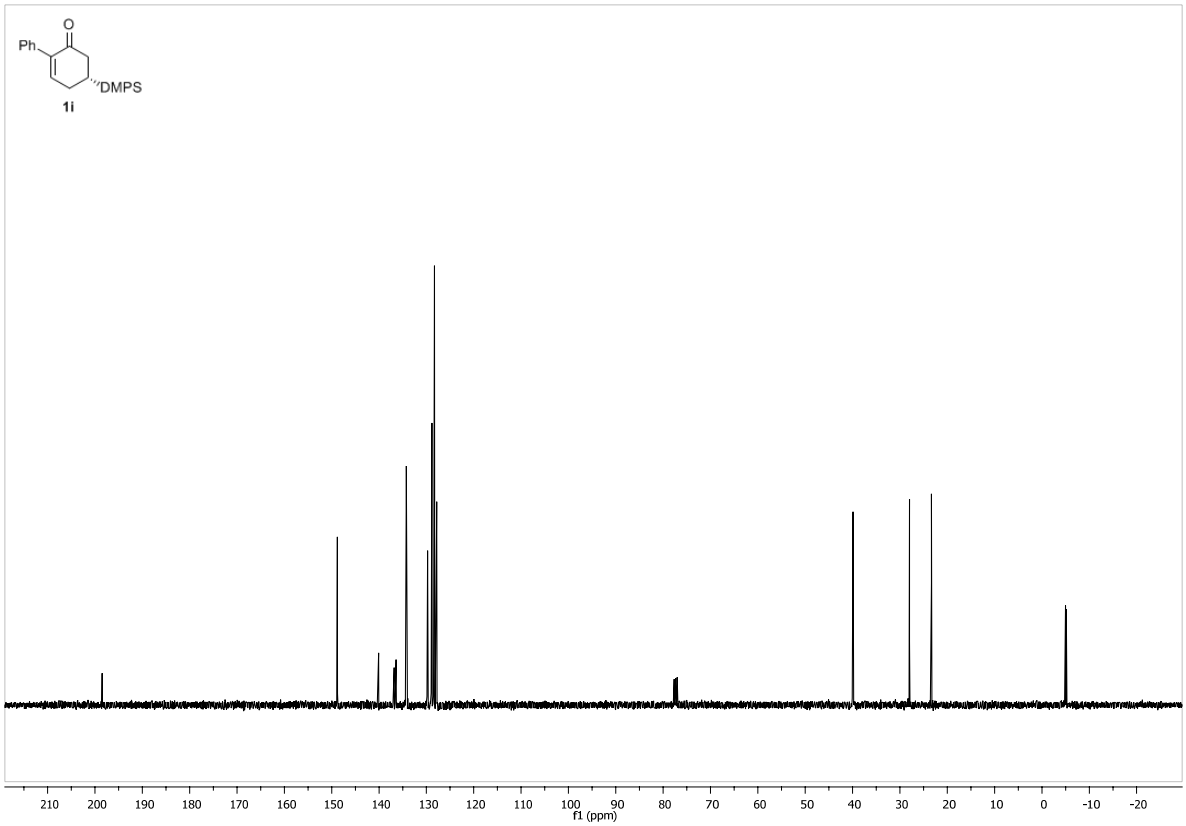
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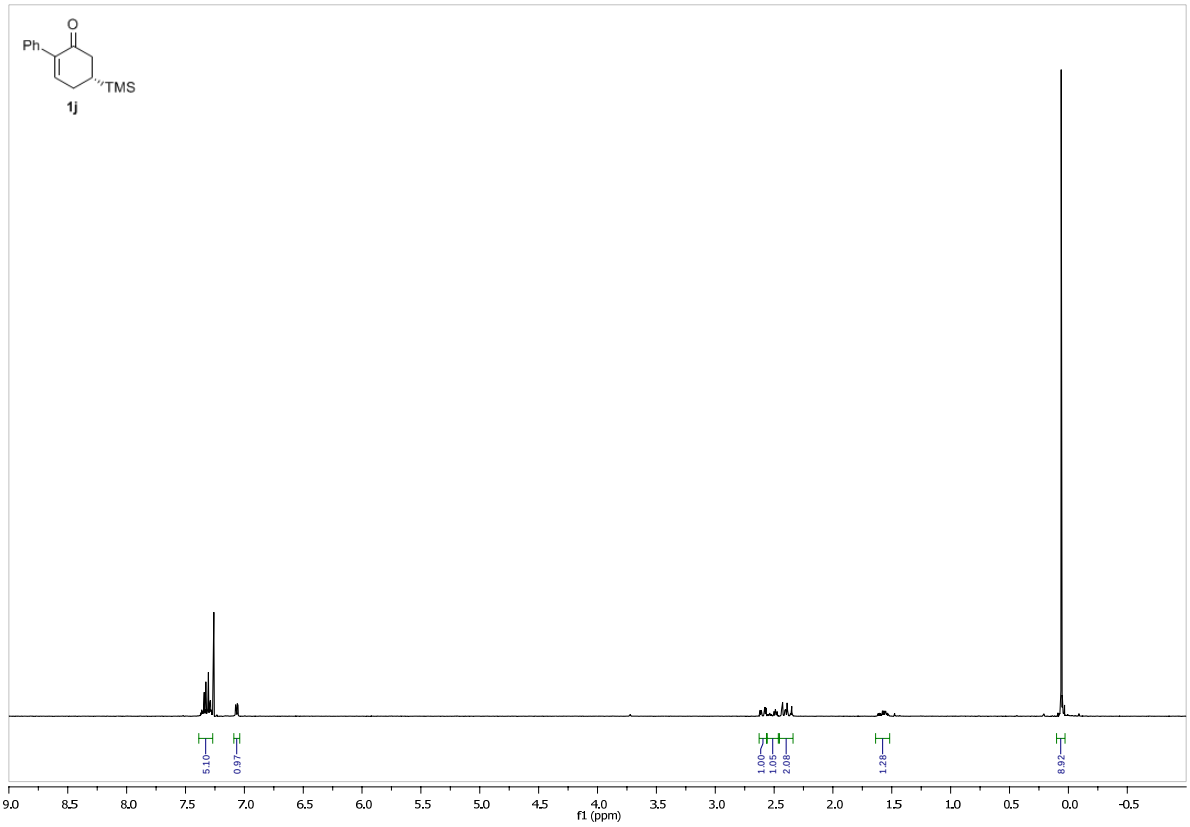
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2.08
1.28
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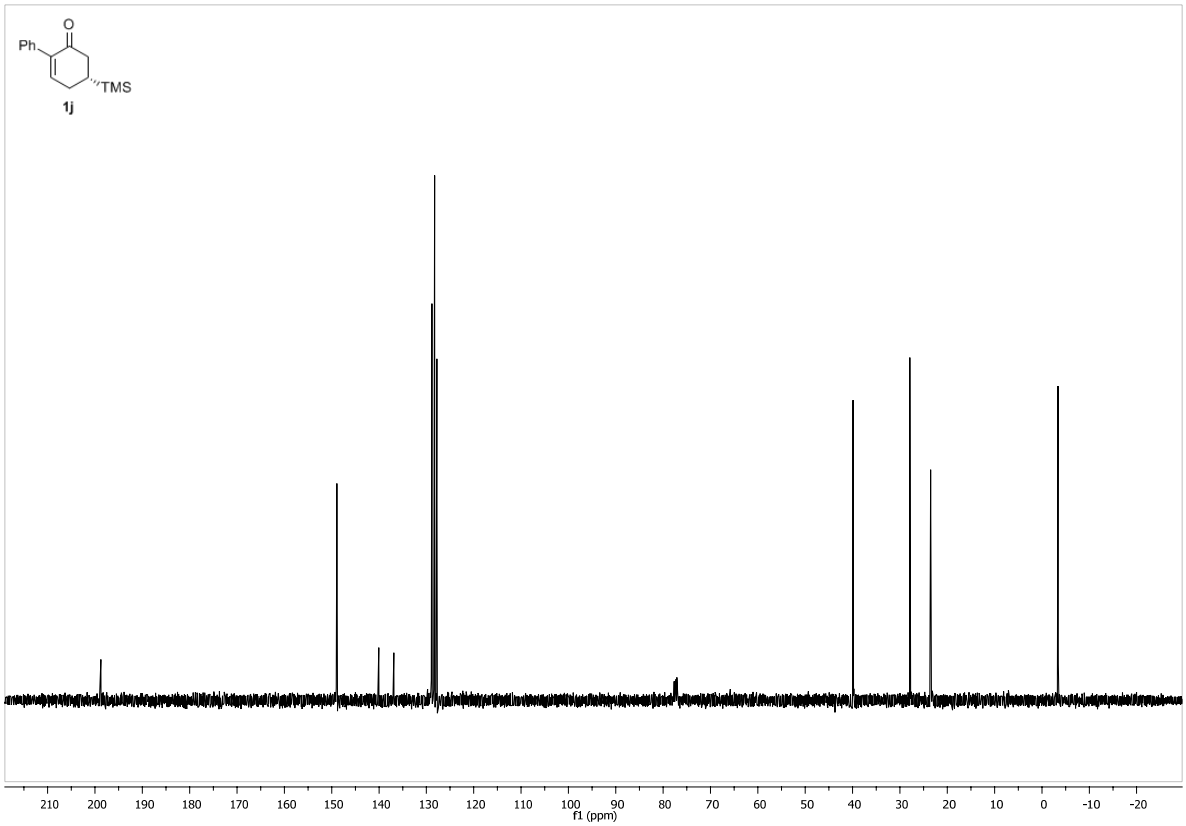
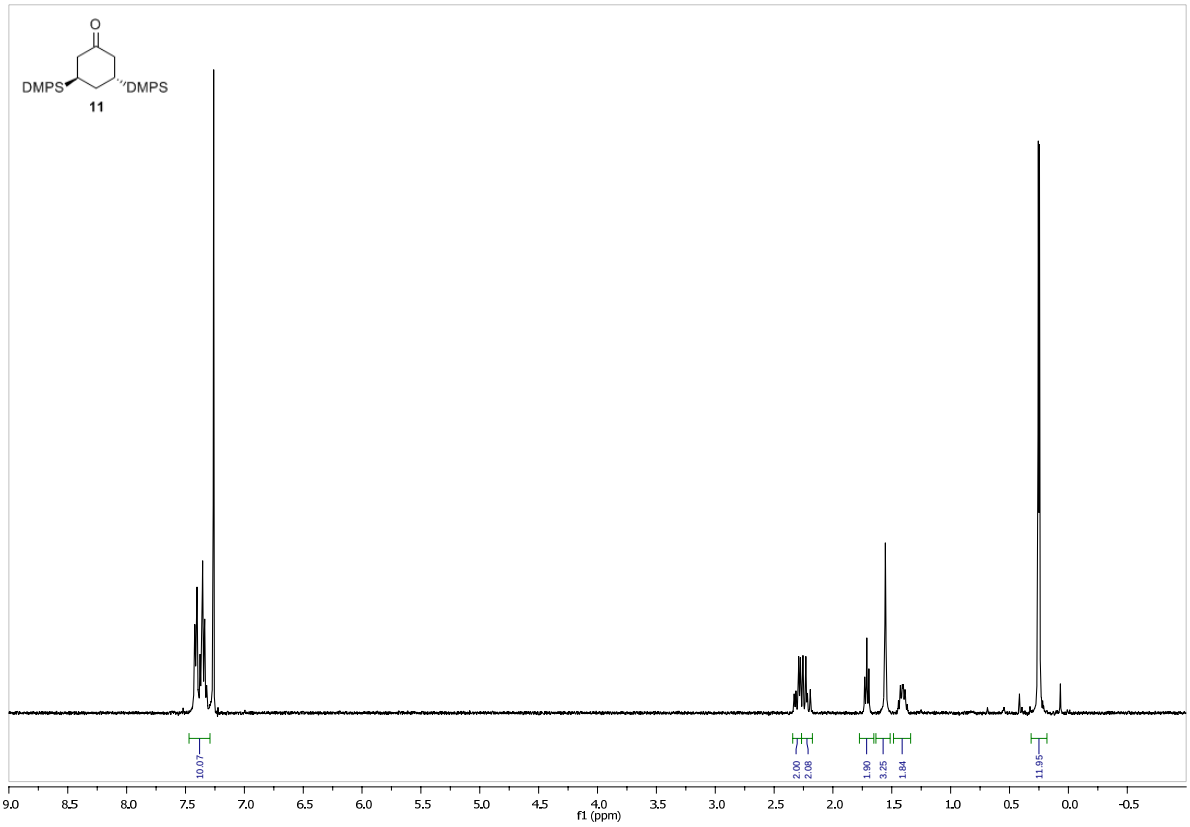
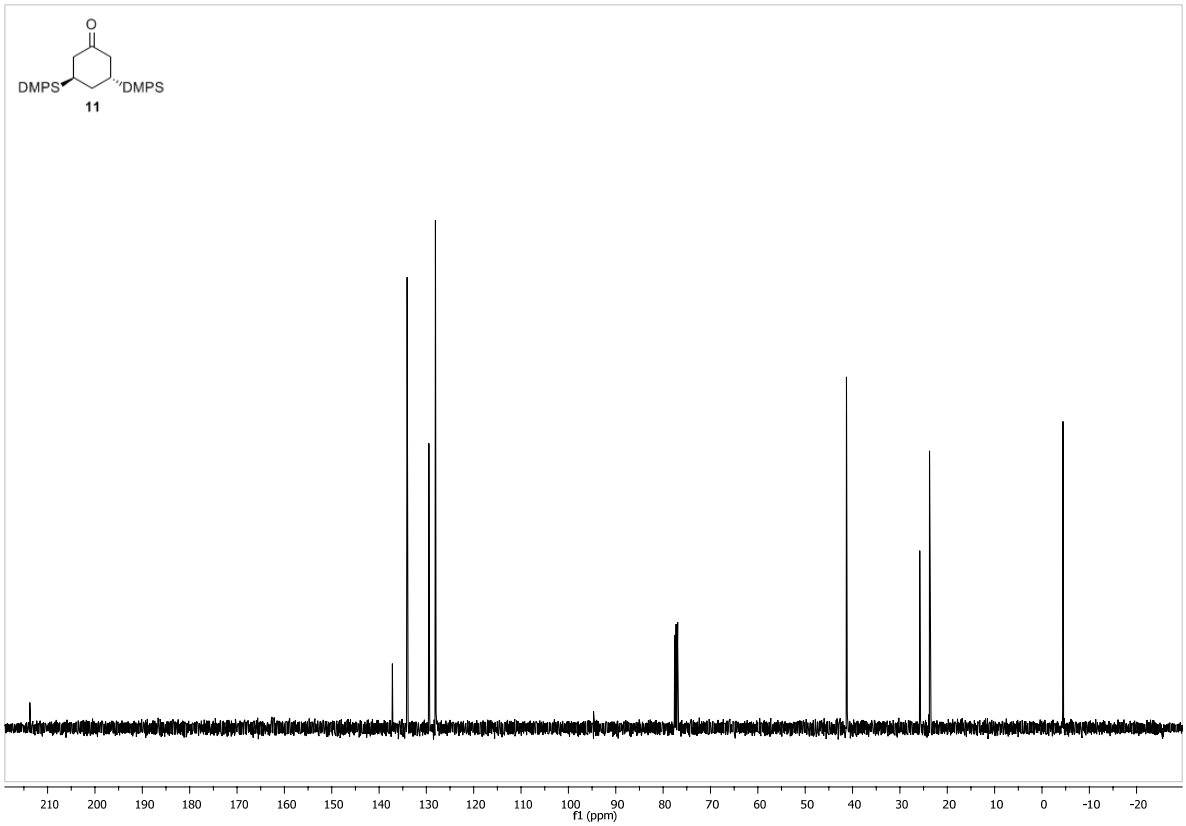
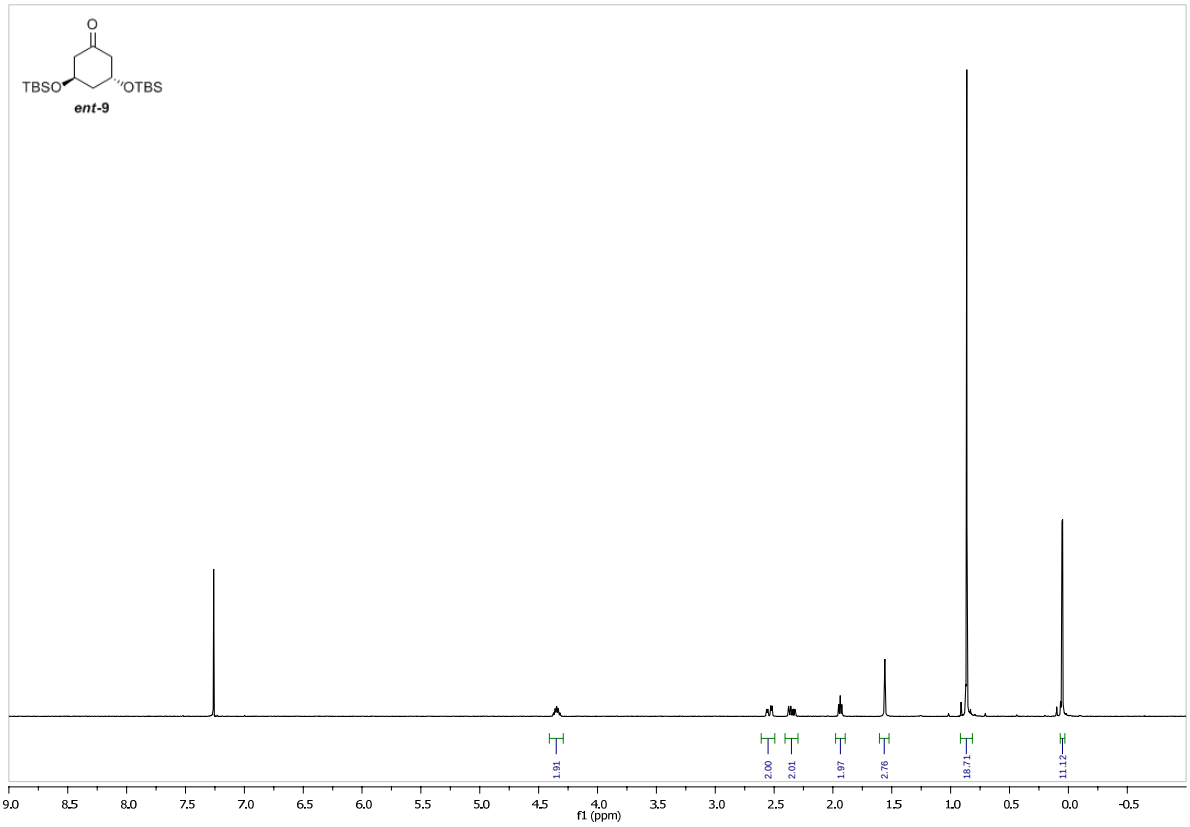
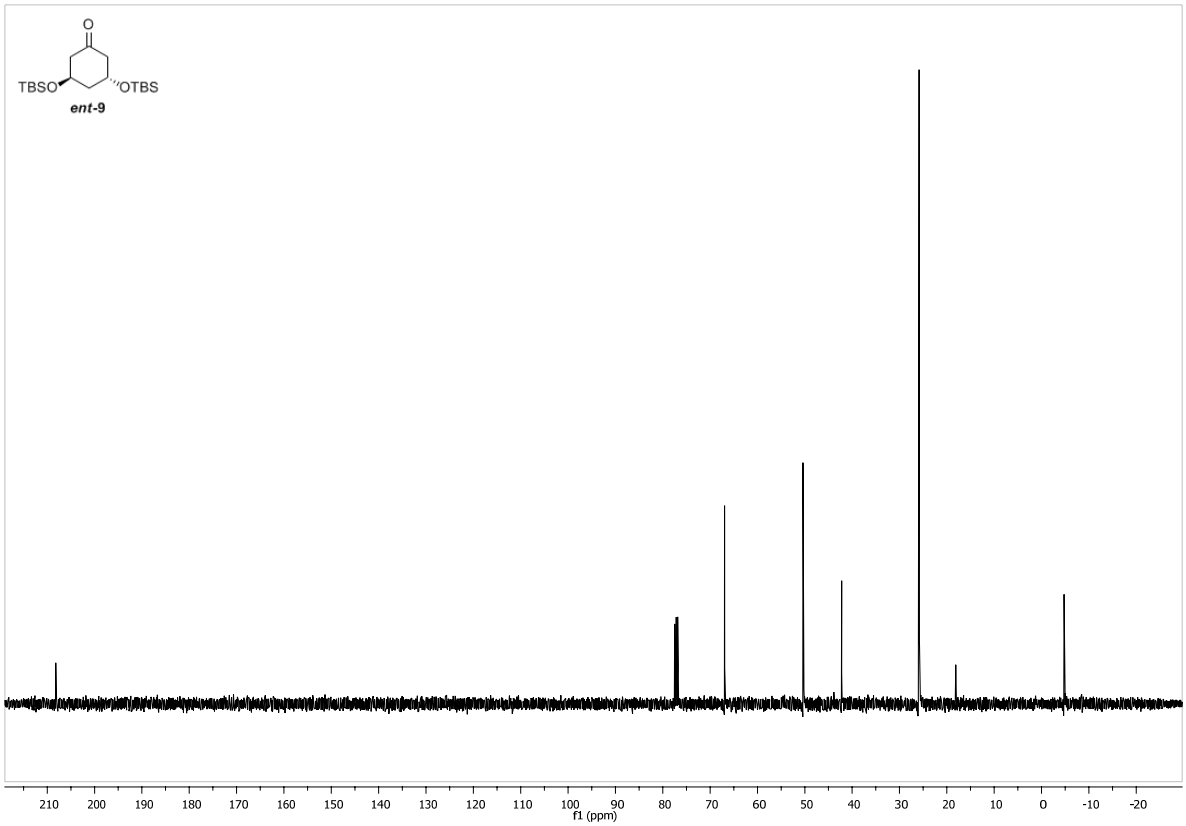
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

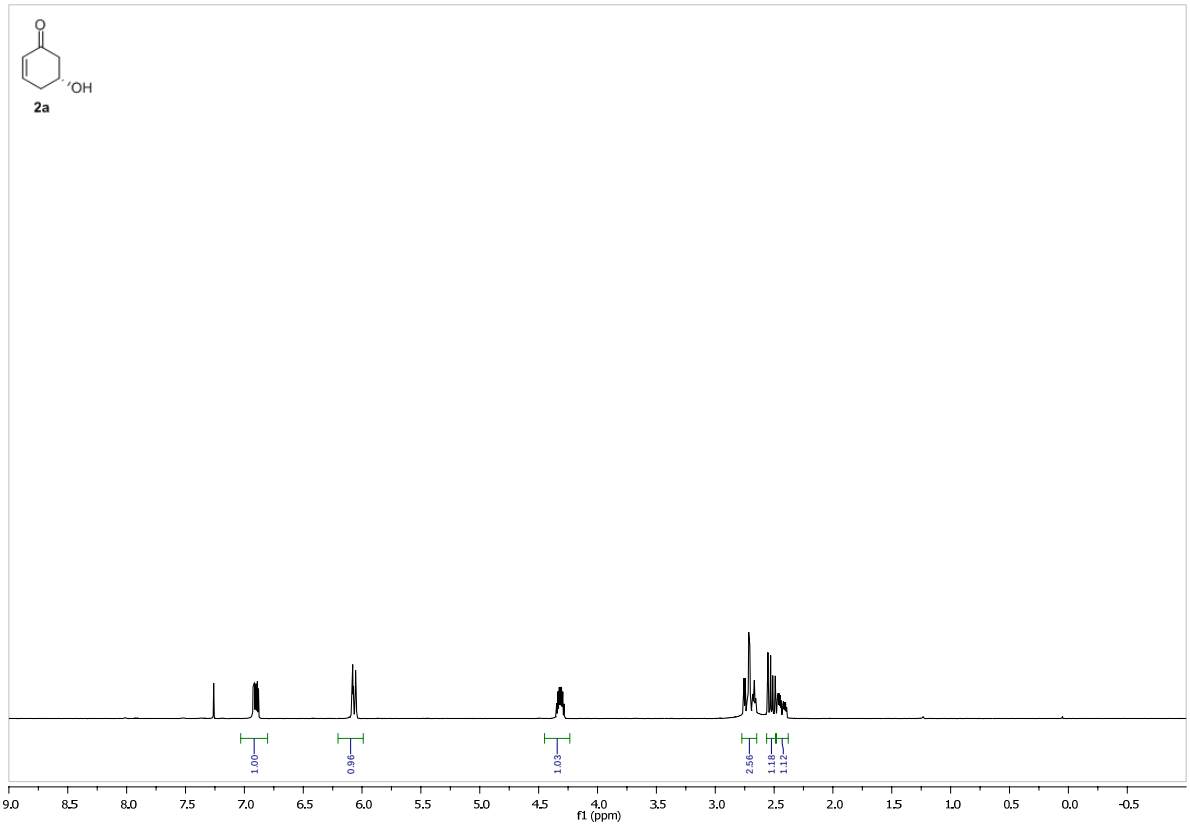

Ph
O
TMS
1j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

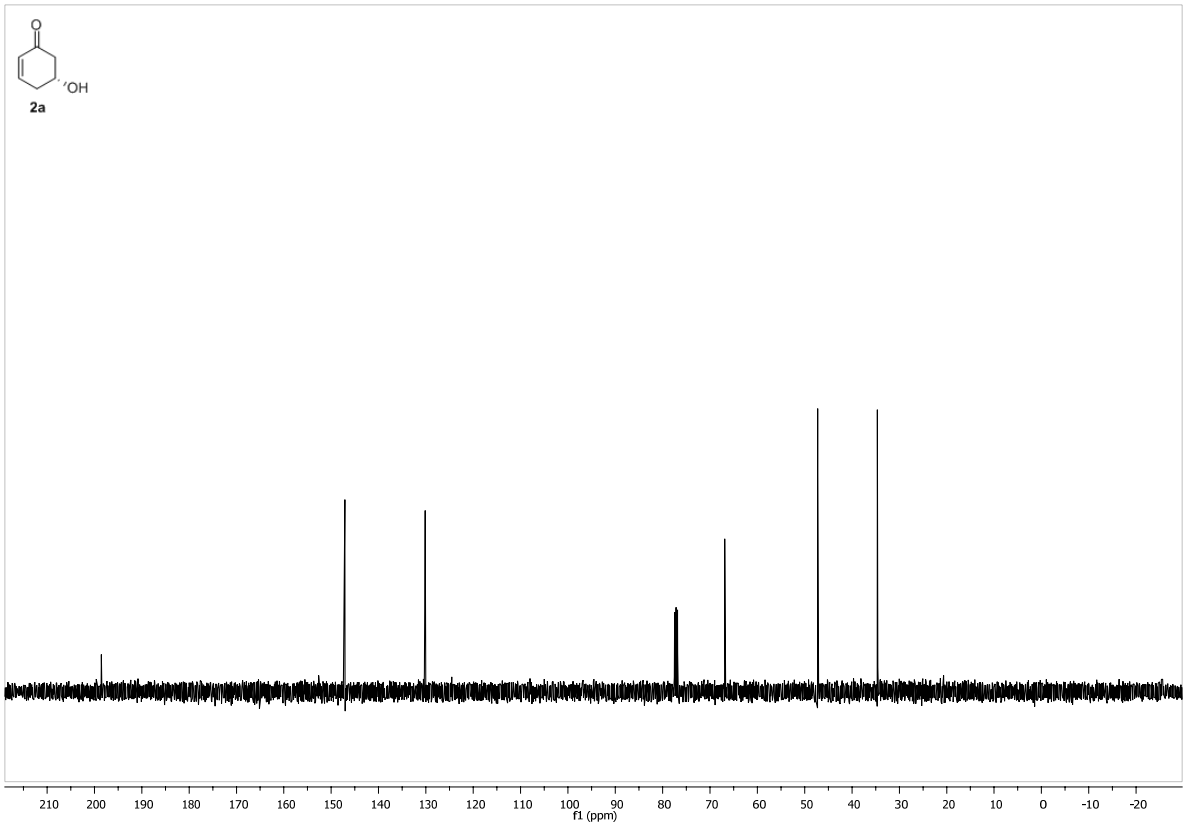

O
DMPS
DMPS
11
10.07
2.00
2.08
1.90
3.25
1.84
11.95
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

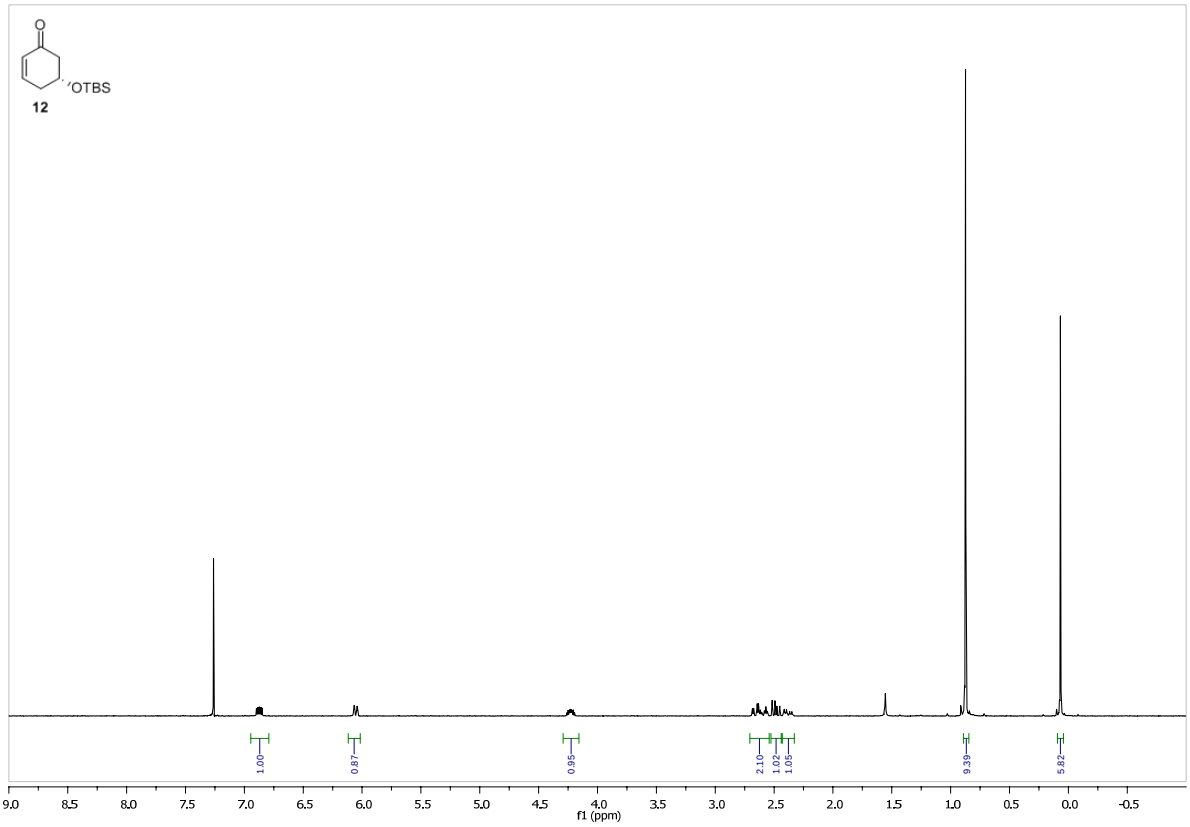

DMPS
DMPS
11
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

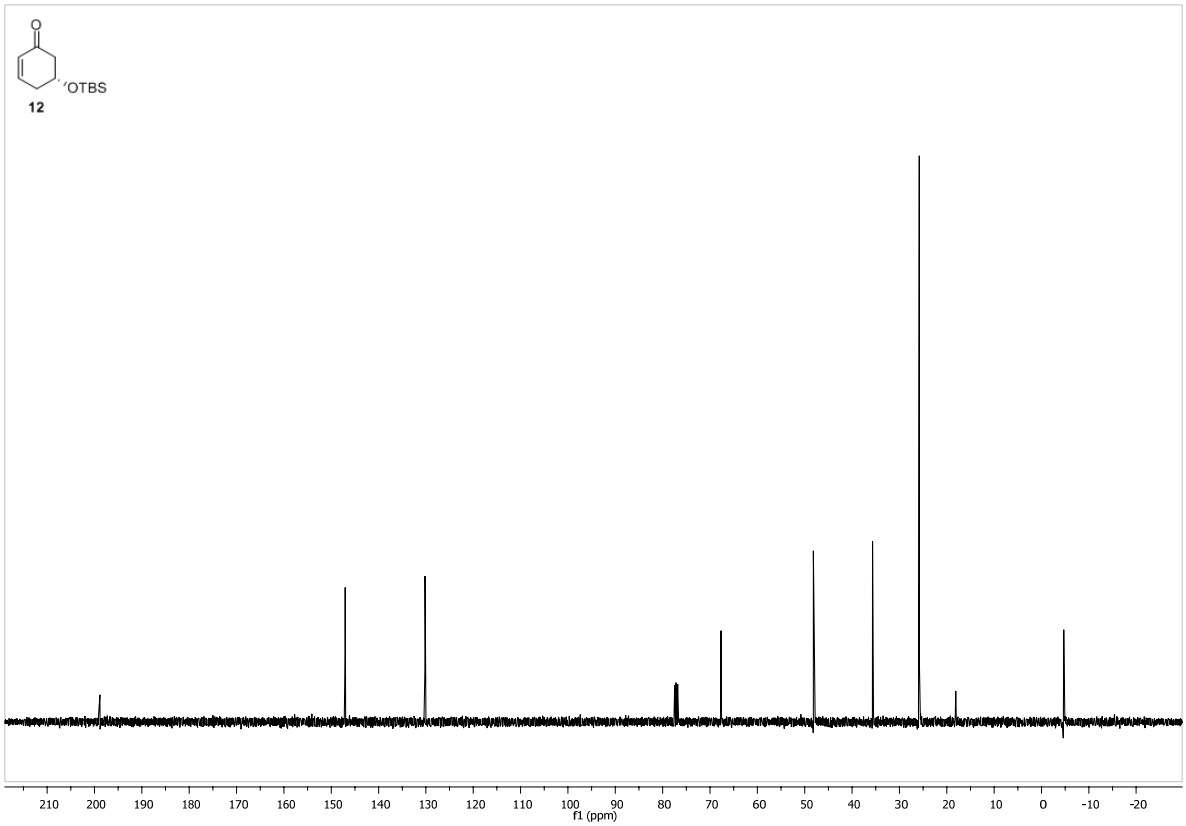

TBSO
OTBS
ent-9
1.91
2.00
2.01
1.97
2.76
18.71
11.12
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

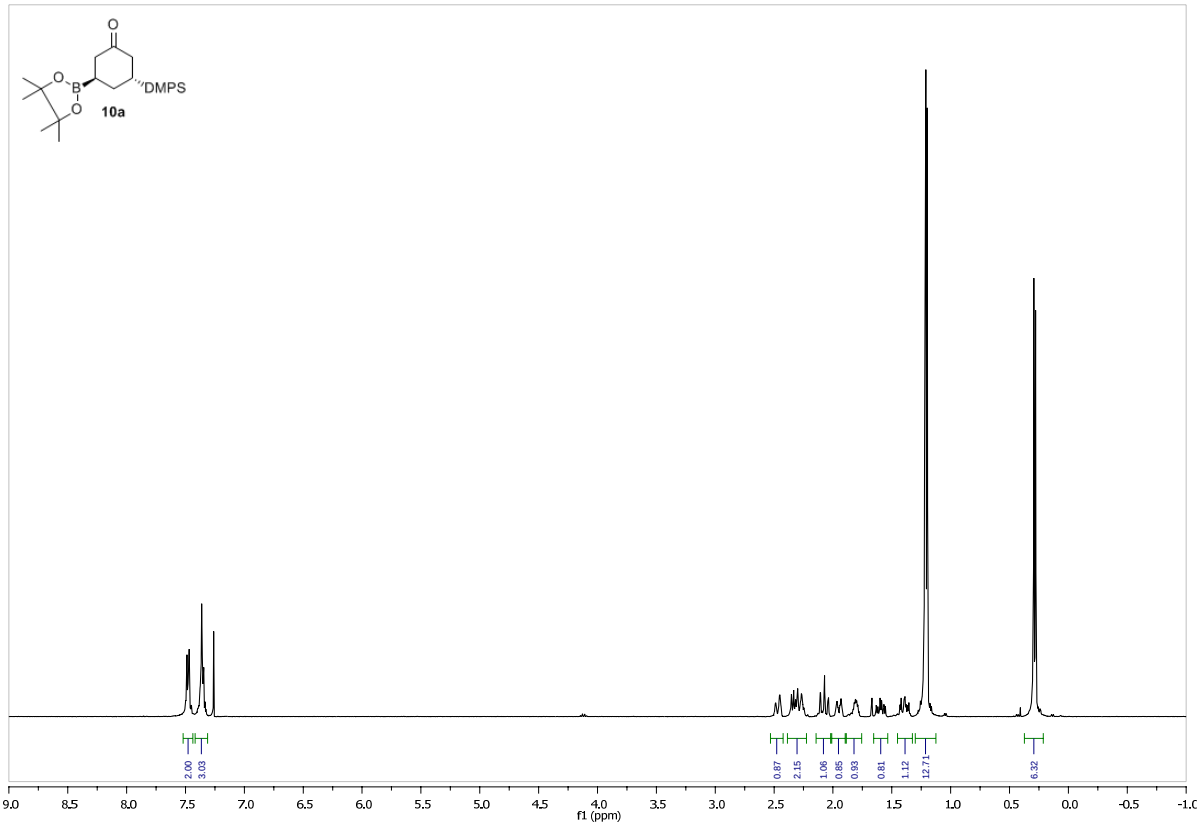

TBSO
OTBS
ent-9
f1 (ppm)

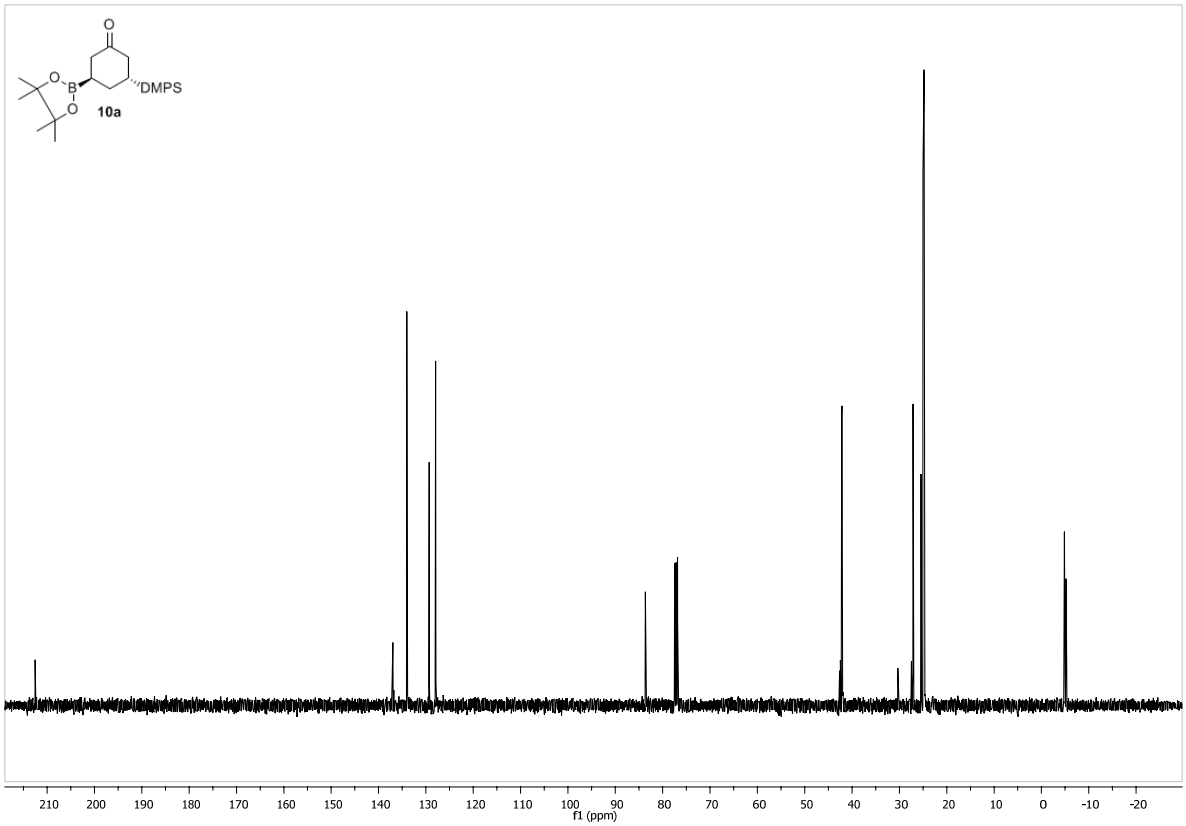

OH
2a
1.00
0.96
1.03
2.56
1.18
1.12
f1 (ppm)

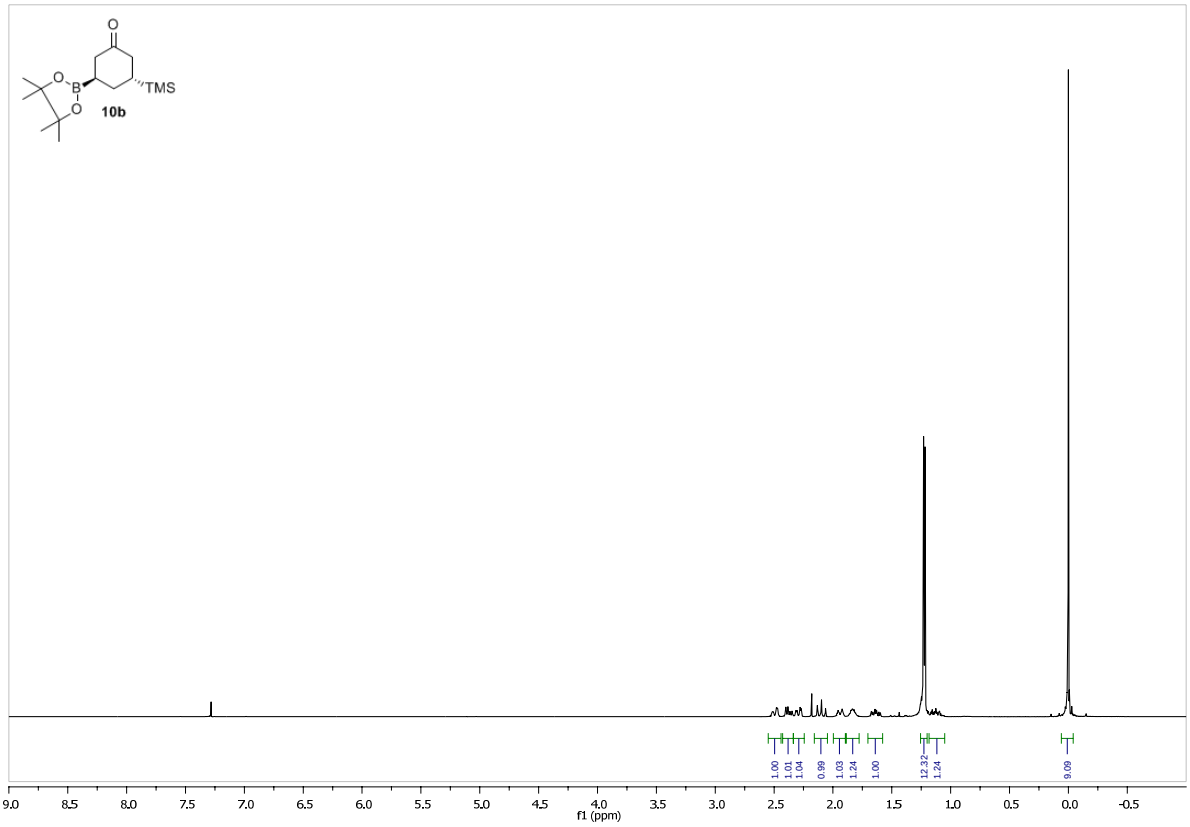

OH
2a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

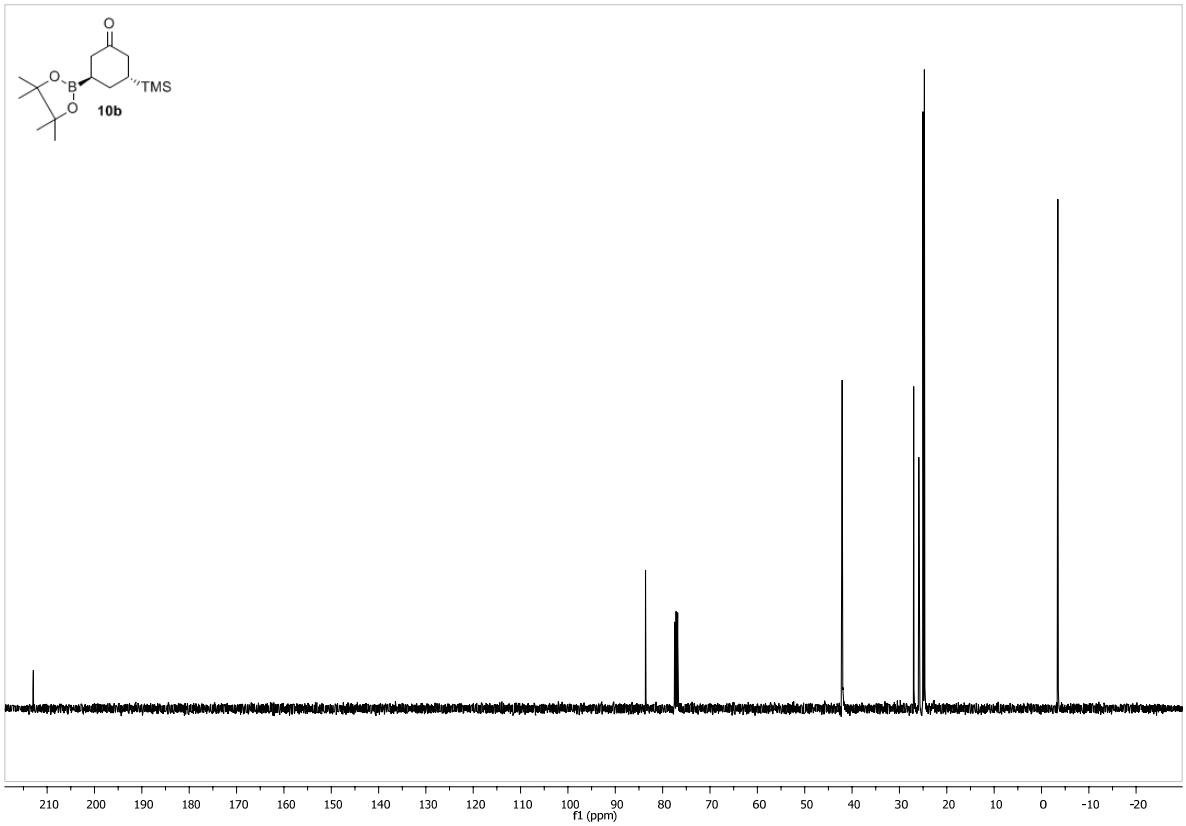

OTBS
12
1.00
0.87
0.95
2.10
1.02
1.05
9.39
5.82
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OTBS
12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


DMPS
10a
2.00
3.03
0.67
2.15
1.06
0.85
0.93
0.81
1.12
12.71
6.32
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


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


TMS
10b
1.00
1.01
1.04
0.99
1.03
1.24
1.00
12.32
1.24
9.09
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


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