Electronic Supplementary Material (ESI) for ChemComm.


# Electronic Supplementary Information

# Intramolecular Hydroalkoxylation Catalyzed inside a Self-assembled Cavity of an Enzyme-like Host Structure

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## 1. General information

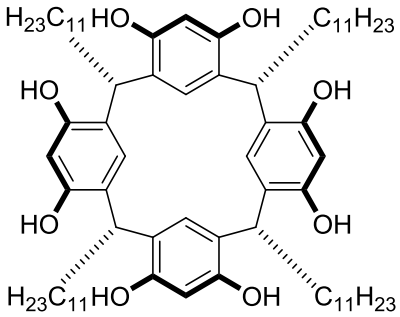
**Experimental:** Reactions were carried out under an atmosphere of argon unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 $F_{254}$ glass-baked plates, which were analyzed after exposure to standard staining solutions (basic $KMnO_4$ or vanillin). $^1$H NMR spectra were recorded at 250 MHz, 360 MHz or 500 MHz, using a Bruker AV 250, AV 360 and AV 500 spectrometer respectively. $^{13}$C NMR spectra were recorded at 91 MHz on a Bruker AV 360 MHz spectrometer. Chemical shifts of $^1$H NMR and $^{13}$C NMR (measured at 298 K) are given in ppm by using $CHCl_3$ and $CDCl_3$ as references (7.26 ppm and 77.16 ppm respectively). Coupling constants (*J*) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet). GC analyses were done on an Agilent GC6890 instrument equipped with a FID detector and a HP-5 capillary column (length = 29.5 m). Hydrogen was used as the carrier gas and the constant-flow mode (flow rate = 1.8 mL/min) with a split ratio of 1:20 was used. The following temperature-program was used: 60 °C for 3 min, 15 °C/min to 250 °C, and 250 °C for 5 min. Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution mass spectra were obtained using either the electron impact ionization (EI) technique on a Thermo Finnigan MAT 95 mass spectrometer or the electrospray ionization (ESI) technique on a Thermo Finnigan LTQ FT mass spectrometer. Sonication was performed in a VWR Ultrasonic Cleaner USC-300TH.

**Sources of chemicals:** Anhydrous $CH_2Cl_2$, $Et_2O$ and THF were taken from a solvent drying system (MBraun SPS-800). THF was further dried by distillation from sodium/benzophenone under argon atmosphere. $CDCl_3$ (99.8%) was purchased from Deutero GmbH. Anhydrous ethanol, anhydrous toluene, lithium aluminium hydride, 2,6-dimethyl-5-heptenal, methylmagnesium chloride solution in $Et_2O$, allylmagnesium bromide solution in $Et_2O$, ethynylmagnesium bromide solution in THF, dodecylmagnesium bromide solution in $Et_2O$, 3,3-dimethyallyl bromide, potassium *tert*-butoxide, diisobutylaluminium hydride solution in cyclohexane, phthalide, methyllithium solution in $Et_2O$, imidazole, *tert*-butyldimethylsilyl chloride solution in toluene, 1-bromo-11-hydroxyundecane, methyltriphenylphosphonium bromide, *n*-butyllithium solution in hexanes, ethylene glycol, boron trifluoride diethyl etherate, trifluoromethanesulfonic acid, *tert*-butyl hydroperoxide solution in decane and sodium bis(2-methoxyethoxy) aluminium hydride (Red-Al®) solution in toluene were purchased from Sigma-Aldrich. Silica gel (0.040-0.063 mm, 230-400 mesh ASTM), anhydrous iron(III) chloride, tetramethylethylenediamine, dimethyl malonate and sodium hydride (60%

suspension in paraffin oil) were purchased from Merck KGaA. Sodium sulfate and magnesium sulfate were purchased from AppliChem. Vanadyl acetylacetonate and ammonium chloride were purchased from ABCR and Grüssing respectively. Cyclopentanone and *n*-decane were purchased from Fluka. $CHCl_3$ (stabilized with 50 ppm amylene), nerol, resorcinol, 6-methylhept-5-en-2-one, ε-caprolactone, 4-penten-1-ol and dodecanal were purchased from Alfa Aesar. 4-Hexen-1-ol was purchased from SAFC. *n*-Hexane (HPLC grade) was purchased from VWR. Hydrochloric acid (37%), isopropyltriphenylphosphonium iodide, isopropenylmagnesium bromide solution in THF, tetrabutylammonium fluoride solution in THF, acetic acid and tetrabutylammonium bromide were purchased from Acros Organics. Methanol, pentane, $Et_2O$ and EtOAc were purchased from Brenntag and distilled prior to use. Chemicals were used without further purification, unless stated otherwise.

**General:** Transfer of liquids with a volume ranging from 1 to 10 µL or from 10 to 100 µL was performed with a Microman M1 pipette (Gilson, systematic error: 1.40% - 1.60%) equipped with 10 µL or 100 µL pipette tips respectively. For reactions with catalyst **I**, only glass pipettes and syringes with stainless steel cannula from Unimed were used in the preparation to prevent contamination with silicone grease, which is visible at 0.07 ppm in the $^1$H NMR spectrum. The weighing of tetrabutylammonium bromide, solid substrates and substrates with unknown density for the preparation of stock solutions was performed using a M3P Sartorius microbalance.

## 2. Synthesis of *C*-undecylcalix[4]resorcinarene (1)




$C_{72}H_{112}O_8$
1105.68 g/mol

Resorcin[4]arene **1** was synthesized according to modified literature procedures.[1,2] To a stirred solution of 99.9 % ethanol (54 mL) and 37% aqueous HCl (18 mL), resorcinol (14.3 g, 129 mmol, 1.0 eq.) was added. After complete dissolution and cooling to 0 °C, a solution of dodecanal (29.9 mL, 129 mmol, 1.0 eq.) in 99.9% ethanol (36 mL) was added dropwise into the reaction mixture over the course of 1 h. The resulting solution was allowed to warm to rt and subsequently refluxed at 100 °C for 18 h. The dark red solution was then allowed to cool

to rt whereby a yellow precipitate formed. The precipitate was dispersed in cold methanol, filtered and subsequently washed with cold methanol until the washings were light yellow. The solid was crystallized twice from methanol (50 mL and 28 mL respectively). In order to remove remaining yellow impurities, the solid was moistened with cold methanol and then washed extensively with distilled water (6 × 50 mL). The crystalline material was dried under reduced pressure (16 mbar) at rt using a rotary evaporator. The drying process was continued until the residual methanol was completely removed and a satisfactory water content was obtained. Compound **1** (17.4 g, 15.7 mmol, 49%) was obtained as a white to slightly yellowish powder. After dissolving **1** (11.0 mg) in $CDCl_3$ (0.50 mL), a water content of 11-12 eq. $H_2O$/hexamer **I** was determined via integration of the $^1H$ NMR spectrum. The spectroscopic data matched those reported in the literature.[3]

General remark: If the water content is too low, a gel like mixture is obtained upon addition of $CDCl_3$.

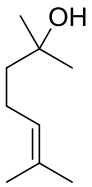
The catalytic activity of hexamer **I** in intramolecular hydroalkoxylations was reproduced when commercially available *C*-undecylcalix[4]resorcinarene **1** (monohydrate; methanol-free; purchased from Sigma Aldrich) was employed.

## 3. Substrate syntheses

Compounds **3b** and **3h** were prepared according to published procedures.[4,5] Their spectroscopic data matched those reported in the literature.[6,5]

**General procedure for the addition of Grignard reagents to 6-methylhept-5-en-2-one:** According to a modified literature procedure,[7] 6-methylhept-5-en-2-one (1.0 eq.) was dissolved in anhydrous THF (0.23 M) and cooled to 0 °C. A solution of the Grignard reagent (2.0-2.5 eq.) was then added dropwise and the reaction mixture was stirred for 15 min at 0 °C. After additional stirring at rt (1-3 h), the reaction was carefully quenched with saturated aqueous $NH_4Cl$ and extracted with $Et_2O$ (3 ×). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under vacuum. The crude product was subsequently purified via flash column chromatography (pentane/$Et_2O$).

**2,6-Dimethylhept-5-en-2-ol (3a)**




$C_9H_{18}O$
142.24 g/mol

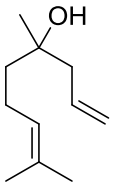
According to the general procedure for the addition of Grignard reagents, methylmagnesium chloride (1.5 M in $Et_2O$, 5.28 mL, 7.92 mmol, 2.5 eq.) was added to 6-methylhept-5-en-2-one (0.47 mL, 3.17 mmol, 1.0 eq.) and the mixture was stirred for 3 h at rt. After flash column chromatography (silica gel, pentane/$Et_2O$ = 5/1), alcohol **3a** (315 mg, 2.21 mmol, 70%) was obtained as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ [ppm] = 5.13 (m, 1H), 2.11 - 2.02 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.54 - 1.48 (m, 2H), 1.22 (s, 6H).

**TLC**: $R_f$ = 0.59 (pentane/$Et_2O$ = 1/2) [$KMnO_4$].

The spectroscopic data matched those reported in the literature.[8]

**4,8-Dimethylnona-1,7-dien-4-ol (3d)**




$C_{11}H_{20}O$
168.28 g/mol

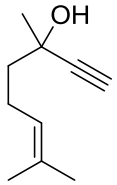
According to the general procedure for the addition of Grignard reagents, allylmagnesium bromide (1.0 M in $Et_2O$, 3.60 mL, 2.0 eq.) was added to 6-methylhept-5-en-2-one (0.27 mL, 1.80 mmol, 1.0 eq.) and the mixture was stirred for 1 h at rt. After flash column chromatography (silica gel, pentane/$Et_2O$ = 5/1), alcohol **3d** (164 mg, 975 µmol, 54%) was obtained as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ [ppm] = 5.93 - 5.81 (m, 1H), 5.20 - 5.05 (m, 3H), 2.30 - 2.20 (m, 2H), 2.10 - 2.00 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.55 - 1.45 (m, 2H), 1.18 (s, 3H).

**TLC**: $R_f$ = 0.33 (pentane/$Et_2O$ = 5/1) [$KMnO_4$].

The spectroscopic data matched those reported in the literature.[9]

**3,7-Dimethyloct-6-en-1-yn-3-ol (3c)**




$C_{10}H_{16}O$
152.24 g/mol

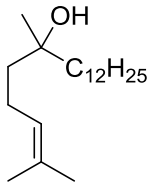
According to a modified literature procedure,[10] 6-methylhept-5-en-2-one (0.35 mL, 2.38 mmol, 1.0 eq.) was dissolved in anhydrous THF (7 mL) and cooled to 0 °C. After slow addition of ethynylmagnesium bromide (0.5 M in THF, 7.13 mL, 3.57 mmol, 1.5 eq.), the mixture was stirred for 2 h at 0 °C. The reaction was subsequently quenched with saturated aqueous $NH_4Cl$ (10 mL) and extracted with $Et_2O$ (3 × 30 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/$Et_2O$ = 10/1) to afford alcohol **3c** (290 mg, 1.91 mmol, 80%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$[ppm] = 5.22 - 5.14 (m, 1H), 2.46 (s, 1H), 2.36 - 2.24 (m, 1H), 2.24 - 2.12 (m, 1H), 1.74 - 1.68 (m, 2H), 1.70 (s, 3H), 1.66 (s, 3H), 1.50 (s, 3H).

**TLC**: $R_f$ = 0.73 (pentane/$Et_2O$ = 2/1) [$KMnO_4$].

The spectroscopic data matched those reported in the literature.[10]

**2,6-Dimethyloctadec-2-en-6-ol (5)**




$C_{20}H_{40}O$
296.54 g/mol

To a stirred solution of dodecylmagnesium bromide (1.0 M in $Et_2O$, 6.34 mL, 6.34 mmol, 2.0 eq.) in anhydrous $Et_2O$ (4.79 mL) at 0 °C was added a solution of 6-methylhept-5-en-2-one (0.47 mL, 3.17 mmol, 1.0 eq.) in anhydrous $Et_2O$ (10 mL) dropwise. After 1 h of stirring at 0 °C, the reaction mixture was refluxed for 2 h, followed by 1 h of stirring at rt. Upon completion, the reaction was quenched by the addition of saturated aqueous $NH_4Cl$ at 0 °C and extracted with $Et_2O$ (3 × 50 mL). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The crude product was purified

by flash column chromatography (pentane/$Et_2O$ = 10/1 → 5/1) to yield compound **5** (609 mg, 2.05 mmol, 65%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$[ppm] = 5.17 - 5.09 (m, 1H), 2.09 - 1.98 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.51 - 1.41 (m, 4H), 1.34 - 1.21 (m, 20H), 1.16 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H).

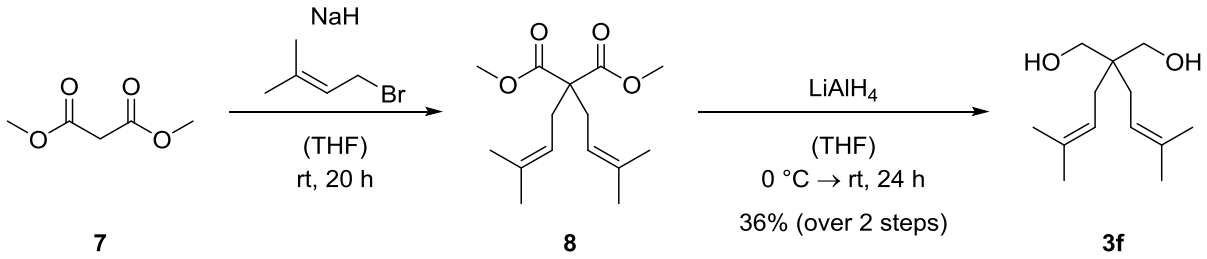
**$^{13}$C NMR** (91 MHz, $CDCl_3$): $\delta$[ppm] = 131.8, 124.7, 73.0, 42.2, 41.7, 32.1, 30.4, 29.8 (6C), 29.5, 27.0, 25.9, 24.1, 22.9, 17.8, 14.3.

**HRMS** (EI): calcd. for $C_{20}H_{38}^+$ [$(M-H_2O)^+$]: 278.2973, found: 278.2976.

**IR** (ATR): $\tilde{\nu}$ [$cm^{-1}$] = 3377, 2959, 2922, 2852, 1464, 1375, 1300, 1112, 984, 918, 837, 721.

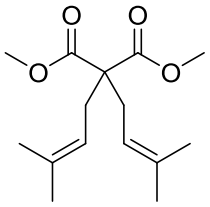
**TLC**: $R_f$ = 0.18 (pentane/$Et_2O$ = 5/1) [$KMnO_4$].

**Synthesis of diol 3f:**




**Scheme S1.** Synthesis of diol **3f**.

**Dimethyl 2,2-bis(3-methylbut-2-en-1-yl)malonate (8)**



$C_{15}H_{24}O_4$
268.35 g/mol

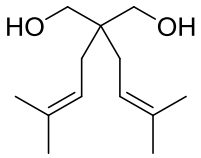
To a stirred solution of dimethyl malonate (**7**) (500 mg, 3.78 mmol, 1.0 eq.) in anhydrous THF (12 mL) was added NaH (60% suspension in paraffin oil, 282 mg, 11.73 mmol, 3.1 eq.) at 0 °C, and the reaction mixture was stirred for 20 min at rt. To the reaction mixture was added 3,3-dimethylallyl bromide (1.05 mL, 9.08 mmol, 2.4 eq.), and the mixture was subsequently stirred for 21 h at rt. The reaction was quenched by the addition of saturated aqueous $NH_4Cl$, and this mixture was extracted with EtOAc (3 × 20 mL) and washed with

brine. The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under vacuum. The crude alkylation product **8** was used without further purification in the next step as shown in scheme S1.

**$^1$H NMR** (360 MHz, $CDCl_3$): $\delta$ [ppm] = 4.99 - 4.89 (m, 2H), 3.69 (s, 6H), 2.58 (d, *J* = 7.5 Hz, 4H), 1.68 (s, 6H), 1.59 (s, 6H).

**TLC**: $R_f$ = 0.48 (pentane/$Et_2O$ = 10/1) [$KMnO_4$].

**2,2-Bis(3-methylbut-2-en-1-yl)propane-1,3-diol (3f)**




$C_{13}H_{24}O_2$
212.33 g/mol

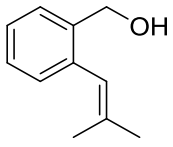
To a stirred solution of the crude alkylation product **8** (1.00 g, 3.78 mmol, 1.0 eq.) in anhydrous THF (12 mL) was carefully added $LiAlH_4$ (323 mg, 8.51 mmol, 2.3 eq.) in multiple portions at 0 °C, and the reaction mixture was stirred over night at rt. The reaction was quenched by the addition of $MgSO_4 \cdot 10H_2O$ and the precipitate was separated by filtration. After thoroughly washing the precipitate with $Et_2O$, the crude product was obtained via concentration under vacuum. Purification by flash column chromatography (pentane/EtOAc = 3/1) yielded diol **3f** (286 mg, 1.35 mmol, 36% over two steps) as a white solid.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ [ppm] = 5.22 - 5.15 (m, 2H), 3.58 (s, 4H), 2.01 (d, *J* = 7.7 Hz, 4H), 1.85 (s, 2H), 1.72 (s, 6H), 1.74 (s, 6H).

**TLC**: $R_f$ = 0.24 (pentane/EtOAc = 3/1) [$KMnO_4$].

The spectroscopic data matched those reported in the literature.[11]

**(2-(2-Methylprop-1-en-1-yl)phenyl)methanol (3g)**




$C_{11}H_{14}O$
162.23 g/mol

To a mixture of potassium *tert*-butoxide (1.40 g, 12.46 mmol, 4.0 eq.) in anhydrous toluene (28 mL) was added isopropyltriphenylphosphonium iodide (5.38 g, 12.46 mmol, 4.0 eq.) in one portion at rt. The dark red suspension was stirred for 30 min at rt before a solution of 1,3-

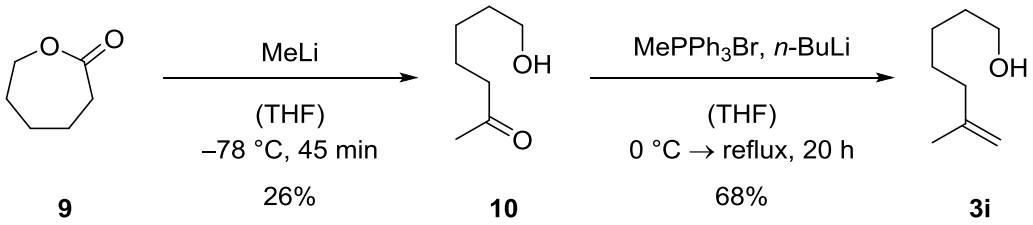
dihydroisobenzofuran-1-ol (424 mg, 3.11 mmol, 1.0 eq.) – prepared according to a published procedure[12] and used crude without further purification – in toluene (14 mL) was added slowly to the reaction mixture. The orange suspension was stirred for 4 h at rt at which point TLC showed full conversion of the starting material. The reaction was quenched with saturated aqueous $NH_4Cl$ (20 mL) and extracted with $Et_2O$ (3 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL), dried over $Na_2SO_4$, filtered and concentrated under vacuum. To remove most of the formed triphenylphosphin oxide, the residue was suspended in a mixture of pentane and $Et_2O$ (2/1) and the supernatant liquid was decanted. After repeating this process several times, the combined organic phases were again concentrated under reduced pressure. The crude product was then purified by flash column chromatography (pentane/$Et_2O$ = 5/1) to afford alcohol **3g** (283 mg, 1.74 mmol, 35% over two steps) as a colorless oil.

**$^1$H NMR** (360 MHz, $CDCl_3$): $\delta$ [ppm] = 7.44 - 7.36 (m, 1H), 7.30 - 7.20 (m, 2H), 7.19 - 7.12 (m, 1H), 6.33 (s, 1H), 4.65 (s, 2H), 1.92 (s, 3H), 1.70 (s, 3H).

**TLC**: $R_f$ = 0.21 (pentane/$Et_2O$ = 5/1) [$KMnO_4$].

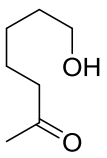
The spectroscopic data matched those reported in the literature.[13]

**Synthesis of alcohol 3i:**




**Scheme S2.** Synthesis of alcohol **3i**.

**7-Hydroxyheptan-2-on (10)**




$C_7H_{14}O_2$
130.19 g/mol

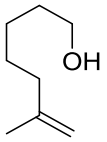
ε-Caprolactone (**9**) (0.65 mL, 6.13 mmol, 1.0 eq.) was dissolved in anhydrous THF (18 mL). The solution was brought to –78 °C, whereupon methyllithium (1.6 M in $Et_2O$, 4.22 mL, 6.75 mmol, 1.1 eq.) was added dropwise over a 20 min span. The mixture was stirred for

45 min at –78 °C and then quenched with saturated aqueous $NH_4Cl$. The crude product was extracted with $Et_2O$ (3 × 30 mL) and the combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under vacuum. Purification via flash column chromatography (pentane/EtOAc = 1/1) afforded the monomethylated product **10** (211 mg, 1.62 mmol, 26%) as a colorless oil. Product **10** was used in the next step as shown in scheme S2.

**$^1$H NMR** (250 MHz, $CDCl_3$): $\delta$[ppm] = 3.64 (t, $J$ = 6.4 Hz, 2H), 2.44 (t, $J$ = 7.3 Hz, 2H), 2.13 (s, 3H), 1.67 - 1.50 (m, 4H), 1.44 - 1.30 (m, 2H).

The spectroscopic data matched those reported in the literature.[14]

**6-Methylhept-6-en-1-ol (3i)**




$C_8H_{16}O$
128.22 g/mol

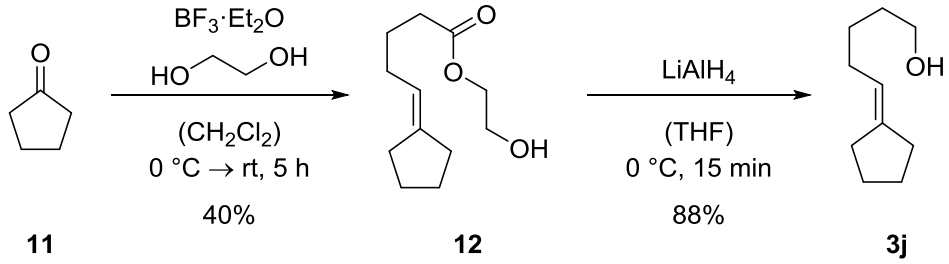
To a suspension of methyltriphenylphosphonium bromide (1.74 g, 4.86 mmol, 3.0 eq.) in anhydrous THF (8 mL) was added *n*-butyllithium (2.5 M in hexanes, 1.94 mL, 4.86 mmol, 3.0 eq.) dropwise at –78 °C. The cold bath was subsequently removed, and the solution was allowed to warm towards rt over a period of 20 min. After cooling to 0 °C, a solution of ketone **10** (211 mg, 1.62 mmol, 1.0 eq.) in anhydrous THF (2 mL) was added dropwise and the reaction mixture was stirred for 10 min at 0 °C. The mixture was then heated to reflux and stirred for 20 h. After cooling to 0 °C, saturated aqueous $NH_4Cl$ was added to quench the reaction. The crude product was extracted with $Et_2O$ and the combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The organic mixture was purified via flash column chromatography (pentane/$Et_2O$ = 2/1) to give alcohol **3i** (141 mg, 1.10 mmol, 68%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$[ppm] = 4.71 - 4.69 (m, 1H), 4.68 - 4.65 (m, 1H), 3.65 (t, $J$ = 6.6 Hz, 2H), 2.02 (t, $J$ = 7.5 Hz, 2H), 1.71 (s, 3H), 1.62 - 1.55 (m, 2H), 1.50 - 1.42 (m, 2H), 1.40 - 1.32 (m, 2H).

**TLC**: $R_f$ = 0.30 (pentane/$Et_2O$ = 2/1) [$KMnO_4$].

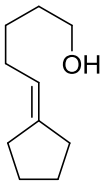
The spectroscopic data matched those reported in the literature.[15]

**Synthesis of alcohol 3j:**




**Scheme S3.** Synthesis of alcohol **3j**.

**5-Cyclopentylidenepentan-1-ol (3j)**



$C_{10}H_{18}O$
154.25 g/mol

To a solution of ester **12** (253 mg, 1.19 mmol, 1.0 eq.) – prepared according to a published procedure[16] in one step from cyclopentanone (**11**), as shown in scheme S3 – in anhydrous THF (13 mL) was added $LiAlH_4$ (141 mg, 3.72 mmol, 3.1 eq.) at 0 °C. The mixture was stirred for 15 min at that temperature, before the reaction was quenched by successive addition of water (0.56 mL) and 15% NaOH (0.14 mL). After 15 min of stirring at rt, $MgSO_4$ was added and the mixture was again stirred for 15 min at rt. The suspension was then filtered and the filtrate was concentrated under vacuum. Purification of the crude product via flash column chromatography (pentane/$Et_2O$ = 2/1) yielded alcohol **3j** (162 mg, 1.05 mmol, 88%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$[ppm] = 5.34 - 5.30 (m, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.32 - 2.36 (m, 2H), 2.25 - 2.18 (m, 2H), 2.11 - 2.04 (m, 2H), 1.89 - 1.80 (m, 2H), 1.62 - 1.54 (m, 2H), 1.52 - 1.43 (m, 2H), 1.40 - 1.30 (m, 2H).

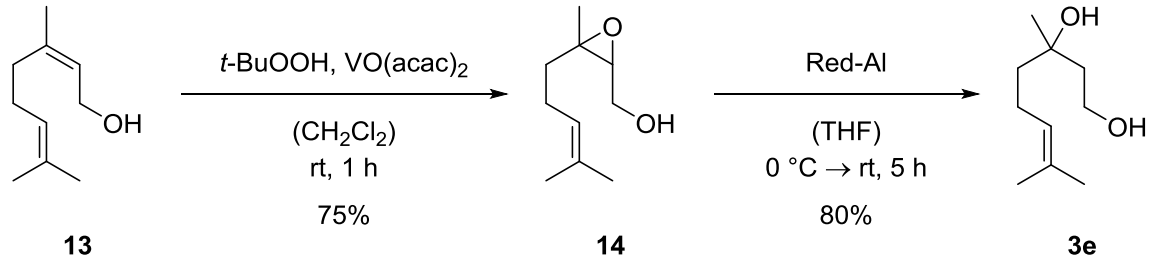
**$^{13}$C NMR** (91 MHz, $CDCl_3$): $\delta$[ppm] = 144.9, 123.4, 63.2, 35.2, 32.9, 32.6, 31.3, 27.8, 25.8, 23.6.

**HRMS** (EI): calcd. for $C_{10}H_{18}O^+$ [$(M)^+$]: 154.1358, found: 154.1341.

**IR** (ATR): $\tilde{\nu}$ [$cm^{-1}$] = 3327, 3042, 2929, 2855, 1697, 1652, 1613, 1458, 1436, 1338, 1296, 1070, 1050, 963, 814.

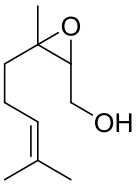
**TLC**: $R_f$ = 0.26 (pentane/$Et_2O$ = 2/1) [$KMnO_4$].

**Synthesis of diol 3e:**




**Scheme S4.** Synthesis of diol **3e**.

**(+/-)-2,3-Epoxynerol (14)**




$C_{10}H_{18}O_2$
170.25 g/mol

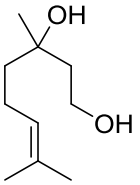
To a stirred solution of nerol (**13**) (0.34 mL, 1.94 mmol, 1.0 eq.) in anhydrous $CH_2Cl_2$ (5.6 mL) was added vanadyl acetylacetonate (51.6 mg, 194 μmol, 0.1 eq.) in one portion. After slow addition of *tert*-butyl hydroperoxide (5.5 M in decane, 0.46 mL, 2.53 mmol, 1.3 eq.), the reaction mixture was stirred for 1.5 h at rt. The reaction was subsequently quenched by the addition of 50% aqueous $Na_2S_2O_3$ (5.6 mL) and the crude product was extracted with $Et_2O$ (3 × 6 mL). The combined organic phases were successively washed with water (2 × 6 mL) and brine (1 × 6 mL), dried over $Na_2SO_4$ and concentrated under vacuum. Purification via flash column chromatography (pentane/$Et_2O$ = 1/1) yielded (+/-)-2,3-epoxynerol (**14**) (249 mg, 1.46 mmol, 75%) as a colorless oil. (+/-)-2,3-Epoxynerol (**14**) was used in the next step as shown in scheme S4.

**$^1$H NMR** (360 MHz, $CDCl_3$): $\delta$ [ppm] = 5.16 - 5.04 (m, 1H), 3.88 - 3.75 (m, 1H), 3.72 - 3.60 (m, 1H), 2.96 (dd, *J* = 6.8 Hz, 4.5 Hz, 1H), 2.24 - 1.98 (m, 2H), 1.72 - 1.62 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.54 - 1.42 (m, 1H), 1.34 (s, 3H).

**TLC**: $R_f$ = 0.03 (pentane/$Et_2O$ = 5/1) [$KMnO_4$].

The spectroscopic data matched those reported in the literature.[17]

**3,7-Dimethyloct-6-ene-1,3-diol (3e)**




$C_{10}H_{20}O_2$
172.27 g/mol

To a stirred solution of (+/-)-2,3-epoxynerol (**14**) (150 mg, 881 μmol, 1.0 eq.) in anhydrous THF (3 mL) was added sodium bis(2-methoxyethoxy) aluminium hydride (3.5 M in toluene, 264 μL, 925 μmol, 1.1 eq.) dropwise at 0 °C. The reaction mixture was stirred for 5 h at rt, at which point TLC indicated full conversion. After dilution with $Et_2O$ (1 mL), the reaction was quenched by successive addition of water (1.1 mL) and 2N HCl (1.1 mL). The crude product was subsequently extracted with $Et_2O$ (3 × 30 mL) and washed with brine. The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under vacuum. After flash column chromatography (pentane/EtOAc = 2/1), diol **3e** (122 mg, 708 μmol, 80%) was obtained as a colorless oil.

**$^1$H NMR** (360 MHz, $CDCl_3$): $\delta$ [ppm] = 5.20 - 5.07 (m, 1H), 3.98 - 3.80 (m, 2H), 2.40 - 2.15 (s, 2H), 2.14 - 1.96 (m, 2H), 1.86 - 1.76 (m, 1H), 1.72 - 1.50 (m, 3H), 1.69 (s, 3H), 1.63 (s, 3H), 1.26 (s, 3H).

**TLC**: $R_f$ = 0.42 (pentane/EtOAc = 1/1) [$KMnO_4$].

The spectroscopic data matched those reported in the literature.[18]

## 4. Intramolecular hydroalkoxylation: determination of yields

**General procedure (small scale, NMR analysis):** *C*-Undecylcalix[4]resorcinarene **1** (11.0 mg, 9.95 μmol, 6.0 eq.) was weighed directly into a NMR tube. After addition of $CDCl_3$ (0.50 mL), the mixture was homogenized in an ultrasonic water bath for 10 min at 40 °C. After cooling the clear yellow solution to 0 °C, the substrate (16.6 μmol, 10.0 eq.) was added in one portion and the sample was immediately subjected to NMR spectroscopy to determine the initial ratio between substrate and hexamer **I** (internal standard). Following the acquisition of the $^1$H NMR spectrum, the NMR tube was kept at 30 °C (±1 °C) using a thermostated heating block made from alumina. The progress of the reaction was monitored via GC. For this purpose, at specified intervals, a small sample (approximately 10 μL) of the reaction mixture was diluted with *n*-hexane (0.1 mL) and subjected to GC analysis. After full

conversion of the starting material or complete equilibration, a $^1$H NMR spectrum of the reaction mixture was measured in order to determine the yield of the reaction via integration. All measurements were performed on a Bruker AV 500 spectrometer.

Multiple parallel hydroalkoxylations were conducted using a *C*-undecylcalix[4]resorcinarene **1** stock solution in $CDCl_3$. The stock solution was prepared by homogenizing a mixture of *C*-undecylcalix[4]resorcinarene **1** and $CDCl_3$ (less than full capacity) in a 1 mL-, 2 mL- or 5 mL-volumetric flask in an ultrasonic water bath for 10 min at 40 °C. The volumetric flask was then filled up to the calibration mark with $CDCl_3$ and again homogenized by agitation to give a clear yellow solution. Solid substrates and substrates with unknown density were added as a stock solution in $CDCl_3$ (20 μL, 829 mmol/L, 16.6 μmol). The small contribution of a substrate with unknown density to the volume of the stock solution was neglected. In all cases the amount of added $CDCl_3$ was adjusted to maintain an overall $CDCl_3$ volume of 0.50 mL. Cooling the catalyst solution to 0 °C prior to substrate addition only served to prevent conversion between substrate addition and acquisition of the initial $^1$H NMR spectrum and is therefore not needed for general synthetic application. In case of overlap of the water signal with the product signal of interest, water saturated $CDCl_3$ (0.2 mL) was added to the sample to induce a shift of the water signal. After agitation, the sample was then again subjected to NMR spectroscopy. The water saturated $CDCl_3$ was prepared by adding distilled water (25 μL) to $CDCl_3$ (5.0 mL). After mixing by agitation and allowing the mixture to equilibrate for 30 min, the $CDCl_3$-phase was directly used. Concerning GC analysis, the addition of *n*-hexane (0.1 mL) to a small sample (approximately 10 μL) of the reaction mixture results in termination of the reaction in this sample.

For NMR analysis, the yields were calculated by employing the following equations (4.1 - 4.3).

$$n(sm)_0 = \frac{(I_{sm})_0}{(I_{sm})_{0,exp}} = x \tag{4.1}$$

$$n(p)_n = \frac{(I_p)_n}{(I_p)_{exp}} = z \tag{4.2}$$

$$yield(p) = \left(\frac{z}{x}\right) \cdot 100\% \tag{4.3}$$

$n(sm)_0$ = amount of starting material in the initial measurement; $n(p)_n$ = amount of product in the n-th measurement (full conversion/equilibrium reached); $(I_{sm})_0$ = integral of a characteristic starting material resonance (usually olefinic proton resonance) in the initial measurement, after normalizing an integral value of a hexamer **I** resonance (methine group = 24H, *o*-aromatic proton = 24H or $CH_2$ group next to the methine group = 48H); $(I_{sm})_{0,exp}$ = expected integral of the corresponding resonance assuming 10.0 eq. of starting material; $(I_p)_n$ = integral of a characteristic product resonance (usually $CH_2$ group next to oxygen) in the n-th measurement, after normalizing an integral value of a hexamer **I** resonance; $(I_p)_n$ = expected integral of the corresponding resonance assuming complete and selective conversion of 10.0 eq. of substrate to the cyclic ether.

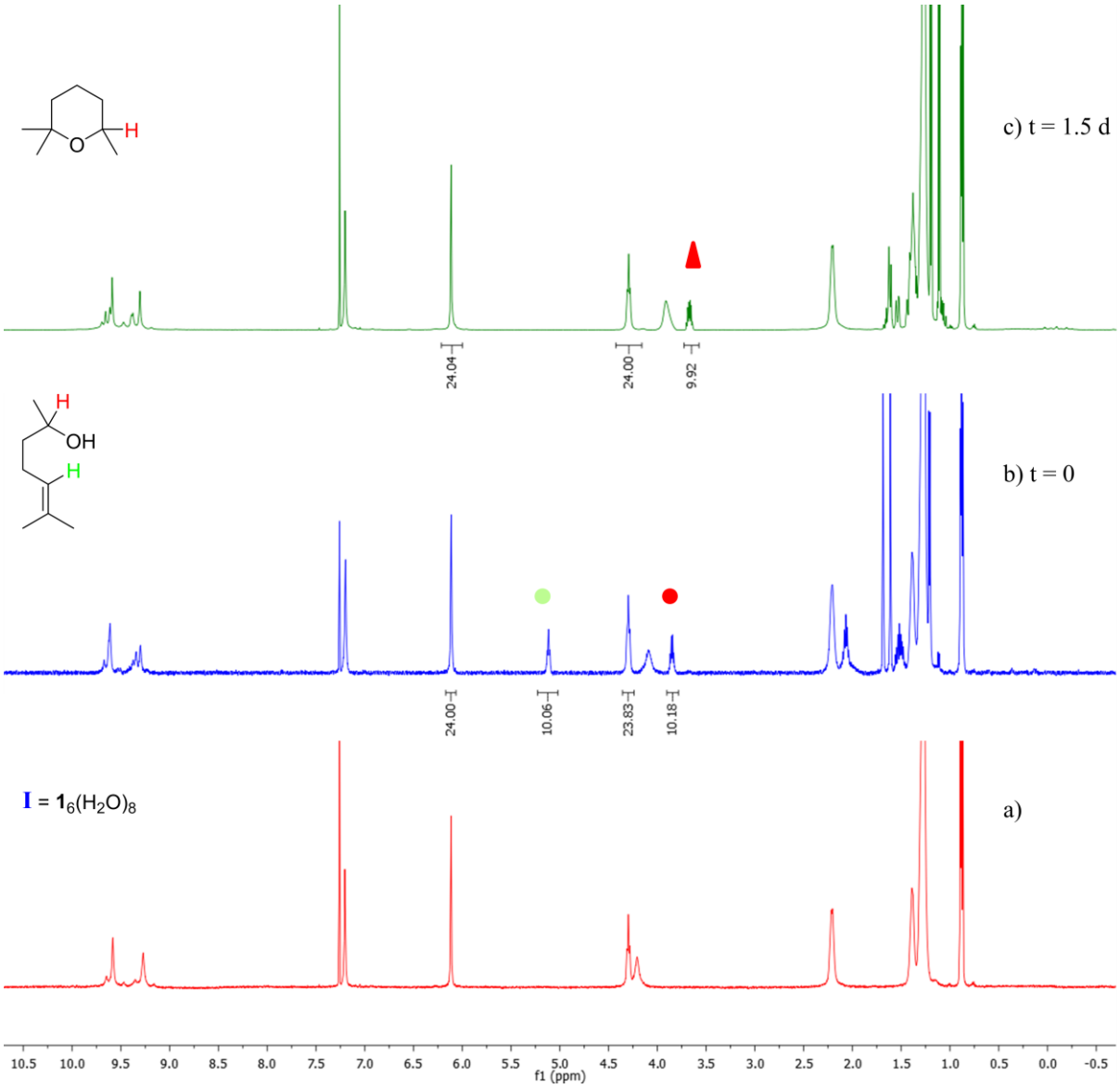



**Figure S1.** NMR-based yield determination of the intramolecular hydroalkoxylation of substrate **3b**. a) Hexamer **I**; b) hexamer **I** + substrate **3b** at t = 0; c) hexamer **I** + cyclic ether **4b** at t = 1.5 d (the resonance left to the marked signal represents water).

If possible, multiple resonances were taken into account (e.g. Figure S1 b)). The calculated mean values were then used for the equations.

**General procedure (small scale, GC analysis):** Cyclic ethers that could not be analyzed by NMR due to signal overlap with the catalyst were analyzed by GC. For this purpose, *C*-undecylcalix[4]resorcinarene **1** (11.0 mg, 9.95 μmol, 6.0 eq.) was weighed directly into a NMR tube. After addition of $CDCl_3$ (0.50 mL), the mixture was homogenized in an ultrasonic water bath for 10 min at 40 °C. After allowing the solution to cool to rt, *n*-decane (internal standard) (2.59 μL, 13.3 μmol, 8.0 eq.) and the substrate (16.6 μmol, 10.0 eq.) were added in one portion and the mixture was immediately sampled. The small sample (approximately 10 μL) was diluted with *n*-hexane (0.1 mL) and subjected to GC analysis (initial sample). The NMR tube was kept at 30 °C (±1 °C) using a thermostated heating block made from alumina. The progress of the reaction was monitored via GC at specified intervals until full conversion was observed. In order to precisely calculate the conversion and yield, GC-response factors to *n*-decane as internal standard (IS) were determined for the investigated substrates and their corresponding products. Stock solutions of *n*-decane, substrates and products were prepared as described in Table S1, utilizing $CDCl_3$ as the solvent. 20 μL aliquots of *n*-decane stock solution (166 mmol/L) were added to 20 μL, 40 μL or 100 μL aliquots of analyte (166 mmol/L). After dilution with $CDCl_3$ to a total volume of 0.50 mL, analyte to *n*-decane ratios of 1, 2 or 5 were obtained. For cyclic ether **6**, 20 μL aliquots of *n*-decane stock solution (166 mmol/L) were added to 10 μL, 20 μL or 40 μL aliquots of analyte (166 mmol/L). After dilution with $CDCl_3$ to a total volume of 0.50 mL, analyte to *n*-decane ratios of 0.5, 1 or 2 were obtained. The concentrations of analytes matched the range observed in the hydroalkoxylation reactions.

**Table S1.** Preparation of stock solutions.

| Compound | Molar mass [g/mol] | Density [mg/mL] | Pure compound | $CDCl_3$ [µL] |
|---|---|---|---|---|
| ***n*-Decane** | 142.29 | 730 | 12.0 µL | 359 |
| **Substrate 3a** | 142.24 | 845 | 8.0 µL | 279 |
| **Substrate 5** | 296.54 | 856[a] | 12.0 µL | 197 |
| **Cyclic ether 4a** | 142.24 | - | 5.695 mg[b] | 242 |
| **Cyclic ether 6** | 296.54 | - | 4.299 mg[b] | 87.4 |

[a] Determined as reported below; [b] measured on a M3P Sartorius microbalance.

The density of substrate **5** was determined by measuring the weight of defined volumes of substrate **5** on a microbalance (Table S2).

**Table S2.** Determination of the density of substrate **5**.

| Substrate 5 [µL] | Weight [mg] | Density [mg/mL] | Mean value [mg/mL] |
|---|---|---|---|
| **4.0** | 3.421 | 855 | |
| **6.0** | 5.166 | 861 | 856 ± 4.6 |
| **50.0[a]** | 42.6 | 852 | |

[a] Measured on a Sartorius CP224S balance.

Approximately 10 µL of each sample was diluted with 0.1 mL *n*-hexane and subjected to GC analysis. The response factors were calculated according to equation 4.4 and are listed in Table S3.

$$RF = \frac{(A_x \cdot C_{IS})}{(A_{IS} \cdot C_X)} \qquad (4.4)$$

RF = response factor; $A_x$ = GC area of analyte; $A_{IS}$ = GC area of internal standard; $C_x$ = concentration of analyte; $C_{IS}$ = concentration of internal standard.

For GC analysis, conversions and yields were calculated by employing the following equations (4.3, 4.5 - 4.8).

$$n(sm)_0 = \frac{(A_{sm})_0}{RF_{sm} \cdot (A_{IS})_0} = x \tag{4.5}$$

$$n(sm)_n = \frac{(A_{sm})_n}{RF_{sm} \cdot (A_{IS})_n} = y \tag{4.6}$$

$$conversion(sm) = \left(\frac{x - y}{x}\right) \cdot 100\% \tag{4.7}$$

$$n(p)_n = \frac{(A_p)_n}{RF_p \cdot (A_{IS})_n} = z \tag{4.8}$$

$n(sm)_n$ = amount of starting material in the n-th measurement; $(A_{sm})_0$ = area of starting material in the initial measurement; $(A_{IS})_0$ = area of internal standard in the initial measurement; $(A_{sm})_n$ = area of starting material in the n-th measurement; $(A_{IS})_n$ = area of internal standard in the n-th measurement; $(A_p)_n$ = area of product in the n-th measurement; $RF_{sm}$ = response factor of starting material; $RF_p$ = response factor of product.

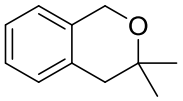
**Table S3.** Response factors.

| Compound | $C_x/C_{IS}$ | $A_x/A_{IS}$ | RF | Mean value |
|---|---|---|---|---|
| **Substrate 3a** | 1 | 0.835 | 0.84 | 0.85 |
| | 2 | 1.708 | 0.85 | |
| | 5 | 4.325 | 0.87 | |
| **Substrate 5** | 1 | 2.031 | 2.03 | 2.07 |
| | 2 | 4.116 | 2.06 | |
| | 5 | 10.525 | 2.11 | |
| **Cyclic ether 4a** | 1 | 0.718 | 0.72 | 0.72 |
| | 2 | 1.436 | 0.72 | |
| | 5 | 3.560 | 0.71 | |
| **Cyclic ether 6** | 0.5 | 0.935 | 1.87 | 1.92 |
| | 1 | 1.936 | 1.94 | |
| | 2 | 3.896 | 1.95 | |

**General procedure (large scale, isolation):** In order to characterize hydroalkoxylation products not previously reported in literature and to obtain material for response factor determination large scale reactions (8-30 × NMR scale) were performed. In a general large scale reaction, *C*-undecylcalix[4]resorcinarene **1** (330.0 mg, 298 μmol, 6.0 eq.) was weighed into a 25 mL round bottom flask, $CDCl_3$ (15 mL) was added and the mixture was homogenized in an ultrasonic water bath for 10 min at 40 °C. After allowing the solution to cool to rt, the substrate (497 μmol, 10.0 eq.) was added in one portion and the flask was sealed with a glass stopper (caution: small overpressure). The round bottom flask was then kept at 30 °C (±1 °C) using a thermostated paraffin oil bath until GC indicated full conversion of the starting material. The mixture was subsequently poured onto a packed silica column ($SiO_2$ = 50 mL) and the $CDCl_3$ was separated by washing with pentane (~50 mL). Following this, the corresponding cyclic ether was eluted using a mixture of pentane and $Et_2O$. In all cases, staining of the cyclic ether was performed utilizing vanillin stain (strong heating required). Subsequent solvent evaporation under vacuum (800-850 mbar at 40 °C) then gave the purified cyclization product. For most substrates, a significantly reduced yield was obtained due to the volatility of the corresponding cyclic ether. Isolation of the cyclization product was performed for all substrates listed in Table 1 (see manuscript) except for substrate **3b**. For substrate **3b**, the structure of the cyclization product was confirmed by comparing the $^1$H NMR spectrum of the reaction mixture (see Figure S1 c)) with literature data[19] and by GC analysis (retention time shift).

The spectroscopic data of the cyclizations products **4a**[20], **4c**[20], **4d**[20], **4e**[21], **4f**[22], and **4h**[20] matched those reported in the literature.

**3,3-Dimethylisochromane (4g)**




$C_{11}H_{14}O$
162.23 g/mol

According to the general procedure, *C*-undecylcalix[4]resorcinarene **1** (330.0 mg, 298 μmol, 6.0 eq.) and substrate **3g** (80.7 mg, 497 μmol, 10.0 eq.) were dissolved in $CDCl_3$ (15 mL) and kept at 30 °C for 6 d (full conversion). Flash column chromatography (pentane/$Et_2O$ = 1/0 → 20/1) gave product **4g** (30.0 mg, 185 μmol, 37%) as a colorless oil.

**$^1$H NMR** (360 MHz, $CDCl_3$): $\delta$[ppm] = 7.22 - 7.13 (m, 2H), 7.12 - 7.05 (m, 1H), 7.04 - 6.96 (m, 1H), 4.80 (s, 2H), 2.72 (s, 2H), 1.29 (s, 6H).

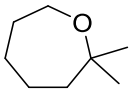
**$^{13}$C NMR** (91 MHz, $CDCl_3$): $\delta$[ppm] = 134.1, 133.2, 129.3, 126.5, 126.0, 124.0, 71.0, 63.2, 39.9, 26.6 (2C).

**HRMS** (EI): calcd. for $C_{11}H_{14}O^+$ $[(M)^+]$: 162.1045, found: 162.1030.

**IR** (ATR): $\tilde{\nu}$ [$cm^{-1}$] = 3064, 3045, 3023, 3005, 2972, 2928, 2896, 2869, 2834, 2712, 1604, 1586, 1496, 1454, 1425, 1380, 1366, 1339, 1284, 1255, 1212, 1193, 1181, 1127, 1106, 1079, 1036, 1004, 970, 881, 849, 774, 745, 734, 664.

**TLC**: $R_f$ = 0.30 (pentane/$Et_2O$ = 20/1) [vanillin].

**2,2-Dimethyloxepane (4i)**



$C_8H_{16}O$
128.22 g/mol

According to the general procedure, *C*-undecylcalix[4]resorcinarene **1** (330.0 mg, 298 μmol, 6.0 eq.) and substrate **3i** (63.8 mg, 497 μmol, 10.0 eq.) were dissolved in $CDCl_3$ (15 mL) and kept at 30 °C for 6 d (full conversion). Flash column chromatography (pentane/$Et_2O$ = 1/0 → 20/1) gave product **4i** (39.0 mg, 304 μmol, 61%) as a colorless oil.

**$^1$H NMR** (360 MHz, $CDCl_3$): $\delta$[ppm] = 3.57 - 3.49 (m, 2H), 1.66 - 1.44 (m, 8H), 1.16 (s, 6H).

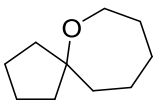
**$^{13}$C NMR** (91 MHz, $CDCl_3$): $\delta$[ppm] = 75.2, 62.9, 41.3, 32.1, 30.0, 28.3 (2C), 23.1.

**HRMS** (EI): calcd. for $C_8H_{16}O^+$ $[(M)^+]$: 128.1201, found: 128.1206.

**IR** (ATR): $\tilde{\nu}$ [$cm^{-1}$] = 2973, 2926, 2867, 2854, 1470, 1449, 1442, 1380, 1363, 1336, 1299, 1277, 1259, 1248, 1216, 1198, 1156, 1142, 1099, 1078, 1019, 997, 977, 957, 903, 841, 803, 696.

**TLC**: $R_f$ = 0.29 (pentane/$Et_2O$ = 20/1) [vanillin].

**6-Oxaspiro[4.6]undecane (4j)**



$C_{10}H_{18}O$
154.25 g/mol

According to the general procedure, *C*-undecylcalix[4]resorcinarene **1** (330.0 mg, 298 μmol, 6.0 eq.) and substrate **3j** (76.7 mg, 497 μmol, 10.0 eq.) were dissolved in $CDCl_3$ (15 mL) and

kept at 30 °C for 3 d (equilibrium reached). Flash column chromatography (pentane/$Et_2O$ = 1/0 → 20/1) gave product **4j** (38.7 mg, 251 μmol, 50%) as a colorless oil.

**$^1$H NMR** (360 MHz, $CDCl_3$): $\delta$[ppm] = 3.60 - 3.44 (m, 2H), 1.85 - 1.30 (m, 16H).

**$^{13}$C NMR** (91 MHz, $CDCl_3$): $\delta$[ppm] = 87.4, 63.7, 40.2, 39.1, 32.0, 29.8, 24.2.

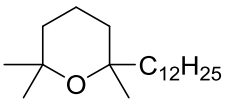
**HRMS** (EI): calcd. for $C_{10}H_{18}O^+$ [$(M)^+$]: 154.1358, found 154.1359.

**IR** (ATR): $\tilde{\nu}$ [$cm^{-1}$] = 2925, 2865, 2853, 2688, 1469, 1443, 1371, 1352, 1329, 1287, 1256, 1215, 1171, 1138, 1105, 1085, 1068, 1009, 974, 947, 901, 837, 806.

**TLC**: $R_f$ = 0.33 (pentane/$Et_2O$ = 20/1) [vanillin].

The reversibility of 6-oxaspiro[4.6]undecane (**4j**) formation was proven by subjecting the isolated ether to the standard reaction conditions described above. The cyclic ether **4j** slowly equilibrated to a mixture of **3j** and **4j**.

**2-Dodecyl-2,6,6-trimethyltetrahydro-2H-pyran (6)**




$C_{20}H_{40}O$
296.54 g/mol

According to the general procedure, *C*-undecylcalix[4]resorcinarene **1** (330.0 mg, 298 μmol, 6.0 eq.) and substrate **5** (148 mg, 497 μmol, 10.0 eq.) were dissolved in $CDCl_3$ (15 mL) and kept at 30 °C for 10 d (little conversion). Flash column chromatography (pentane/$Et_2O$ = 1/0 → 50/1) gave product **6** (19.0 mg, 64.1 μmol, 13%) as a colorless oil.

**$^1$H NMR** (360 MHz, $CDCl_3$): $\delta$[ppm] = 1.75 - 1.57 (m, 2H), 1.53 – 1.23 (m, 26H), 1.21 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 0.88 (t, $J$ = 6.7 Hz, 3H).

**$^{13}$C NMR** (91 MHz, $CDCl_3$): $\delta$[ppm] = 73.3, 71.2, 43.9, 37.1, 34.9, 32.1, 31.6, 30.5, 29.9, 29.9, 29.9 (3C), 29.8, 29.5, 27.6, 24.0, 22.9, 16.8, 14.3.

**HRMS** (EI): calcd. for $C_{19}H_{37}O^+$ [$(M\text{-}CH_3)^+$]: 281.2844, found: 281.2853.

**IR** (ATR): $\tilde{\nu}$ [$cm^{-1}$] = 2971, 2924, 2852, 1467, 1370, 1349, 1223, 1123, 1015.

**TLC**: $R_f$ = 0.34 (pentane/$Et_2O$ = 50/1) [vanillin].

## 5. Reaction times

To ensure reproducibility, all substrates were tested multiple (2-3) times. The high selectivity of the reactions was successfully reproduced. However, slight variations in the required reaction time were observed, probably due to small variations in water content, reaction temperature and concentration (evaporation of solvent when using a NMR tube as the reaction vessel). The mean values of the reaction times are listed in Table 1 and S4.

**Table S4.** Mean values of the required reaction times.

| Substrate | Mean value of reaction time [d] |
|---|---|
| **3a** | 3.5 |
| **3b** | 1.5 |
| **3c** | 1.8 |
| **3d** | 3.4 |
| **3e** | 0.7 |
| **3f** | 0.7 |
| **3g** | 5.5 |
| **3h** | 1.9 |
| **3i** | 5.0 |
| **3j** | 5.0 |

# 6. Control experiments

## 6.1 Blocked cavity

In order to verify that the reaction takes place inside the cavity of the hexamer, the conversion of all substrates was tested in the presence of a competing high affinity guest molecule that would act as an inhibitor by blocking the cavity. Based on previous reports[23], tetrabutyl-ammonium bromide ($Bu_4NBr$) (**2**) was chosen as the inhibitor. Furthermore, it has been reported that the acidity of the hexamer is increased upon encapsulation of $Bu_4NBr$ (**2**).[23] This improves the quality of the control experiment, since the background reaction outside the cavity may even be increased when the inhibitor is encapsulated. For the control reactions a small excess (1.5 eq. relative to hexamer **I**) of inhibitor **2** was used to ensure complete blocking of all cavities.

**General procedure (control experiment with $Bu_4NBr$ (2), NMR analysis):** An aliquot of a *C*-undecylcalix[4]resorcinarene **1** stock solution in $CDCl_3$ (11.0 mg, 9.95 μmol, 6.0 eq.) – prepared as described above – was added into a NMR tube. After addition of an aliquot of $Bu_4NBr$ (**2**) stock solution in $CDCl_3$ (2.49 μmol, 1.5 eq.), regular $CDCl_3$ was added until a total volume of 0.50 mL was obtained. Under agitation the sample was subsequently heated using a heat gun to ensure complete uptake of inhibitor **2**. After allowing the solution to cool to rt, the substrate (16.58 μmol, 10.0 eq.) was added in one portion and the sample was immediately subjected to NMR spectroscopy to determine the initial ratio between substrate and hexamer **I** (internal standard). Following the acquisition of the $^1$H NMR spectrum the NMR tube was kept at 30 °C (±1 °C) using a thermostated heating block made from alumina. A $^1$H NMR spectrum of the reaction mixture was measured after approximately the average reaction time (Table S4). The background conversion was then determined via integration of this $^1$H NMR spectrum. The measurements were performed on a Bruker AV 360 and AV 500 spectrometer.

For NMR analysis, the background conversions were calculated by employing the following equations (4.1, 4.7 and 4.9).

$$n(sm)_n = \frac{(I_{sm})_n}{(I_{sm})_{n,exp}} = y \qquad (4.9)$$

$(I_{sm})_n$ = integral of a characteristic starting material resonance (usually olefinic proton resonance) in the n-th measurement, after normalizing an integral value of a hexamer **I** resonance; $(I_{sm})_{n,exp}$ = expected integral of the corresponding resonance assuming no conversion of 10.0 eq. of the substrate;

**General procedure (control experiment with $Bu_4NBr$ (2), GC analysis):** If the background conversion could not be analyzed by NMR due to signal overlap with the catalyst, GC analysis was applied. For this purpose, an aliquot of a *C*-undecylcalix[4]resorcinarene **1** (11.0 mg, 9.95 μmol, 6.0 eq.) stock solution in $CDCl_3$ – prepared as described above – was added into a NMR tube. After addition of an aliquot of $Bu_4NBr$ (**2**) (2.49 μmol, 1.5 eq.) stock solution in $CDCl_3$, pure $CDCl_3$ was added until a total volume of 0.50 mL was obtained. Under agitation the sample was subsequently heated using a heat gun to ensure complete uptake of the inhibitor. After allowing the solution to cool to rt, *n*-decane (internal standard) (2.59 μL, 13.3 μmol, 8.0 eq.) and the substrate (16.58 μmol, 10.0 eq.) were added in one portion and the mixture was immediately sampled. The small sample (approximately 10 μL) was diluted with *n*-hexane (0.1 mL) and subjected to GC analysis (initial sample). The NMR tube was kept at 30 °C (±1 °C) using a thermostated heating block made from alumina. A GC sample of the reaction mixture was taken after approximately the average reaction time (Table S4). The background conversion was then determined utilizing the corresponding response factor.

For GC analysis, the background conversions were calculated by employing the equations above (4.5 - 4.7).

**General remark:** For the $Bu_4NBr$ (**2**) stock solution, a high dilution (~50.8 mmol/L or less) was used in order to ensure complete homogeneity. Furthermore, to check the quality of the *C*-undecylcalix[4]resorcinarene stock solution used for the control experiments, an aliquot of it was employed in a parallel hydroalkoxylation reaction without inhibitor **2** and the reaction rate was compared to previous measurements.

All substrates showed a significantly reduced conversion when exposed to the $Bu_4NBr$ (**2**)-blocked cavity (Table S5).

**Table S5.** Results of the control experiments with 1.5 eq. $Bu_4NBr$ (**2**) as inhibitor (NMR analysis).

| Compound | Background conv. [%] | Time [d] |
|---|---|---|
| **3a**[a] | 6.6 | 7 |
| **3b** | 8.4 | 1.5 |
| **3c** | 3.0 | 1.5 |
| **3d** | 8.2 | 3.5 |
| **3e** | 5.8 | 0.7 |
| **3f** | 7.6 | 0.7 |
| **3g** | 6.1 | 3.6 |
| **3h** | 3.8 | 1.5 |
| **3i** | 9.6 | 3.5 |
| **3j** | 3.7 | 3.5 |
| **5** | 8.2 | 13 |

[a] Analyzed via GC.

## 6.2 Without catalyst

Control experiments without catalyst were performed to rule out a background reaction, catalyzed by trace amounts of HCl/DCl, potentially formed by photodegradation of $CDCl_3$. The substrate (16.58 μmol, 10.0 eq.) and *n*-decane (internal standard) (2.59 μL, 13.3 μmol, 8.0 eq.) were dissolved in $CDCl_3$ (0.50 mL), kept at 30 °C and analyzed by GC. No cyclic ether formation was observed in all cases after 7 d.

### 6.3 With Brønsted acid in solution

To further prove that the catalyst does not act solely as a Brønsted acid, the conversion of substrate **3b** in the presence of acetic acid ($pK_a$ = 4.8; in water)[24] was explored. For that purpose, an aliquot of a stock solution of acetic acid in $CDCl_3$ (20 μL, 83.0 mmol/L, 1.66 μmol, 1.0 eq.), substrate **3b** (2.47 μL, 16.58 μmol, 10.0 eq.) and *n*-decane (internal standard) (2.59 μL, 13.3 μmol, 8.0 eq.) were dissolved in $CDCl_3$ (0.48 mL), kept at 30 °C and analyzed by GC. No cyclic ether formation was observed after 9 d.

## 7. Competition experiment

The control experiments provided strong evidence that the reaction is taking place inside the cavity. To provide additional evidence, a competition experiment between substrate **3a** and its longer derivative, substrate **5**, was investigated. Both substrates were shown to display a similar reactivity in solution.

**Procedure for competition experiment in solution:** To a solution of substrate **3a** (19.0 μL, 113 μmol, 10.0 eq.) and substrate **5** (39.2 μL, 113 μmol, 10.0 eq.) in $CHCl_3$ (3.4 mL) was added *n*-decane (17.6 μL, 90.4 μmol, 8.0 eq.) as an internal standard. At this point, a sample (approximately 10 μL) was diluted with *n*-hexane (0.1 mL) and subjected to GC analysis (initial sample). To start the reaction, TfOH (1.00 μL, 11.3 μmol, 1.0 eq.) was added and the reaction was stirred at rt. The process of the reaction was monitored via GC. For sampling, a small amount of the reaction mixture (approximately 10 μL) was diluted with $Et_2O$ (0.2 mL), washed with saturated aqueous $NaHCO_3$ and subjected to GC analysis. After 7 h, the ratio of conversion between substrate **3a** and substrate **5** was determined to be 46:54, attributing an even higher reactivity to the larger substrate in solution. The substrates were completely converted after 2 d with the cyclic ether being the main product in both cases. In order to minimize side reactions, the reaction was performed at a concentration that differs from the standard conditions.

**Procedure for competition experiment using catalyst I:** *C*-Undecylcalix[4]resorcinarene **1** (11.0 mg, 9.95 μmol, 6.0 eq.) was weighed directly into a NMR tube. After addition of $CDCl_3$ (0.50 mL), the mixture was homogenized in an ultrasonic water bath for 10 min at 40 °C. After allowing the solution to cool to rt, *n*-decane (internal standard) (1.29 μL, 6.63 μmol, 4.0 eq.), substrate **3a** (1.40 μL, 8.29 μmol, 5.0 eq.) and substrate **5** (2.87 mL, 8.29 μmol,

5.0 eq.) were added successively and the mixture was immediately sampled. The small sample (approximately 10 µL) was diluted with *n*-hexane (0.1 mL) and subjected to GC analysis (initial sample). The NMR tube was kept at 30 °C (±1 °C) using a thermostated heating block made from alumina. The progress of the reaction was monitored via GC at specified intervals until full conversion of substrate **3a** was observed. After 64 h, the ratio of conversion between substrate **3a** and substrate **5** was determined to be 92:8 (Figure S2).

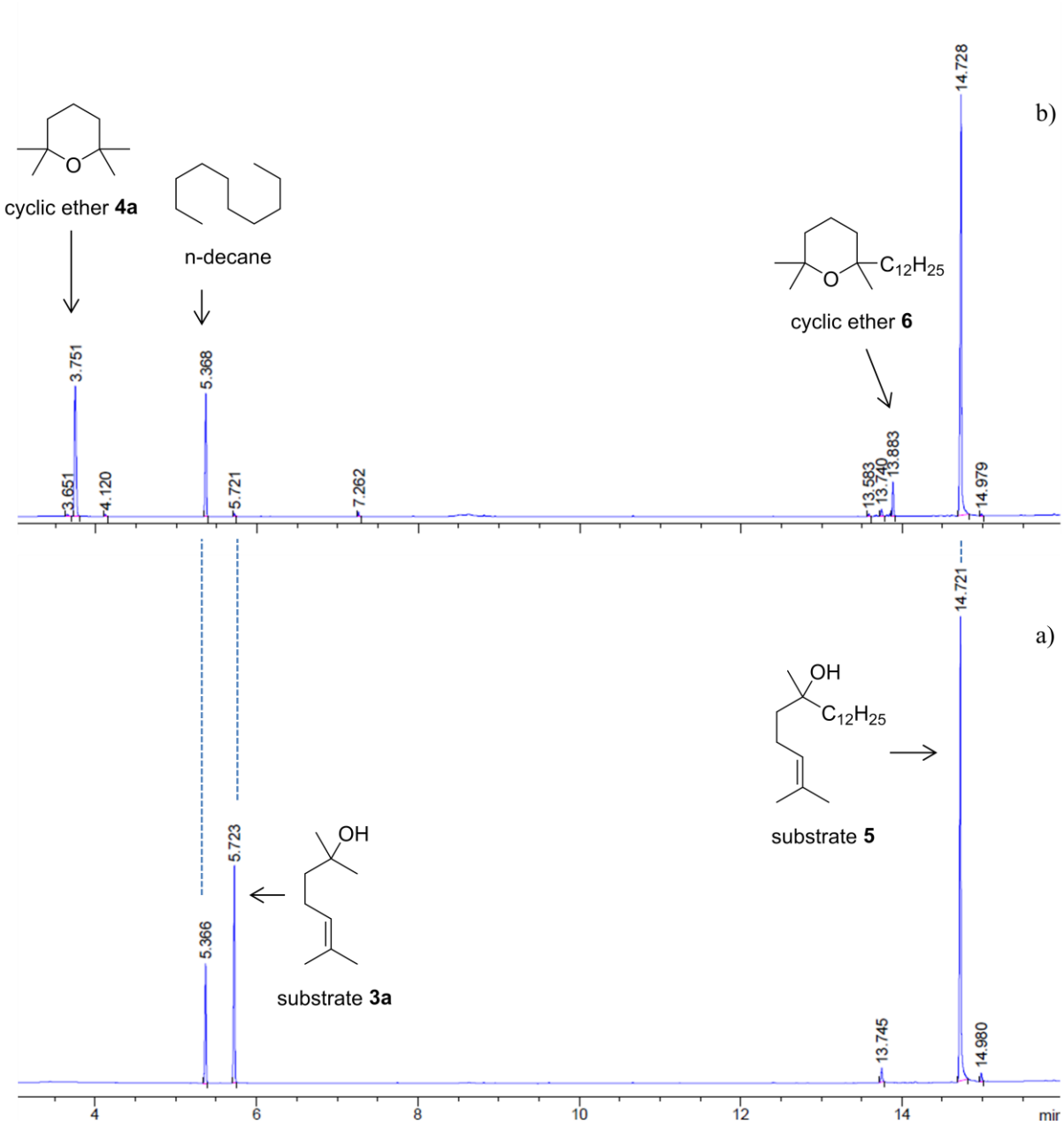



**Figure S2.** GC traces of the competition reaction with catalyst **I**. a) Measured directly after addition of the substrates; b) measured after 64 h reaction time.

## 8. Water content

In order to investigate, if the hexamer-catalyzed intramolecular hydroalkoxylation reaction is hindered by an excess of water, *C*-undecylcalix[4]resorcinarene **1** (11.0 mg, 9.95 μmol, 6.0 eq.) was dissolved in regular $CDCl_3$ (0.50 mL) and water saturated $CDCl_3$ (0.50 mL) respectively. The water saturated $CDCl_3$ was prepared by adding distilled water (25 μL) to $CDCl_3$ (5.0 mL). After mixing by agitation and allowing the mixture to equilibrate for 30 min, the $CDCl_3$-phase was directly used. Both samples were subjected to NMR spectroscopy to determine the water content via integration using the integral of the methine group (4.30 ppm, t, $J$ = 7.7 Hz, 24H) or the *o*-aromatic proton (6.11 ppm, s, 24H) of the hexamer **I** as the reference. The water contents were determined to be 11 eq. and 30 eq. $H_2O$/hexamer **I**. After successive addition of *n*-decane (internal standard) (2.59 μL, 13.3 μmol, 8.0 eq.) and substrate **3a** (2.79 μL, 16.58 μmol, 10.0 eq.), the mixtures were immediately sampled. Following this, the reactions were kept at 30 °C (±1 °C) for 24 h. GC samples of both mixtures were prepared and the difference in conversion after 24 h was determined via GC analysis. The conversion of substrate **3a** was 5 times slower in water saturated $CDCl_3$ than in regular $CDCl_3$. However, the water content did not significantly influence the selectivity of the reaction.

## 9. Substrate concentration

To explore the influence of substrate concentration on the reaction rate, different amounts of substrate **3a** (5.0 eq., 10.0 eq., 15.0 eq. or 20.0 eq.) were added to a solution of *C*-undecyl-calix[4]resorcinarene **1** (11.0 mg, 9.95 μmol, 6.0 eq.) and *n*-decane (internal standard) (2.59 μL, 13.3 μmol, 8.0 eq.) in $CDCl_3$ (0.50 mL). Immediately after substrate addition, a GC sample was taken from each mixture. After 24 h at 30 °C (±1 °C), a final GC sample was taken from each reaction to determine the respective conversions. The conversions after 24 h are summarized in Table S6, normalized to the conversion determined with 10.0 eq. of **3a**. Substrate concentration, however, showed no influence on the selectivity of the reaction.

**Table S6.** Influence of substrate concentration on the reaction rate.

| Substrate 3a [eq.] | Relative conversion after 24 h |
|---|---|
| **5.0** | 1.07 |
| **10.0** | 1.00 |
| **15.0** | 0.52 |
| **20.0** | 0.23 |

## 10. Unreactive substrates

In order to further evaluate the scope of the hexamer **I**-catalyzed intramolecular hydroalkoxylation, substrates that require the formation of an intermediary secondary cation were investigated (Figure S3).

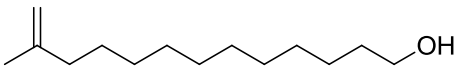

**15** **16**

**Figure S3.** Unreactive substrates.

Unfortunately, commercially available 4-penten-1-ol (**15**) and 4-hexen-1-ol (**16**) showed no conversion under standard reaction conditions.

Furthermore, the formation of a macrocyclic ether within the cavity was probed using hydroxy olefin **17**. When substrate **17** was subjected to the standard reaction conditions, no cyclic ether formation could be observed. However, the terminal double bond was slowly converted to the thermodynamically more stable trisubstituted double bond as indicated by GC and the $^{1}$H NMR spectrum of the reaction mixture. The synthesis of substrate **17** was performed as described below.

**12-Methyltridec-12-en-1-ol (17)**




**17**

$C_{14}H_{28}O$
212.38 g/mol

A mixture of 1-bromo-11-hydroxyundecane (600 mg, 2.39 mmol, 1.0 eq.), imidazole (488 mg, 7.17 mmol, 3.0 eq.) and *tert*-butyldimethylsilyl chloride (50% in toluene, 1.08 mL, 3.11 mmol, 1.3 eq.) in anhydrous THF (4.5 mL) was stirred at rt for 24 h. The solvent was subsequently removed under vacuum and the residue was diluted with water and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. Purification via flash column chromatography ($CH_2Cl_2$) afforded the TBS-protected alcohol (868 mg, 2.38 mmol, 99%) as a colorless oil. To a solution of the protected alcohol (365 mg, 1.00 mmol, 1.0 eq.) and anhydrous $FeCl_3$ (16.2 mg, 100 μmol, 0.1 eq.) in anhydrous THF (10 mL) was added dropwise a solution of isopropenylmagnesium bromide (0.5 M in THF, 4.00 mL, 2.00 mmol, 2.0 eq.) and tetramethylethylenediamine (0.28 mL, 1.90 mmol, 1.9 eq.) over the course of 45 min at 0 °C.

After stirring for 30 min at 0 °C, the reaction was carefully quenched with saturated aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The crude TBS-protected hydroxy olefin was then dissolved in anhydrous THF (14 mL) and cooled to 0 °C. After dropwise addition of tetrabutylammonium fluoride (1.0 M in THF, 1.50 mL, 1.50 mmol, 1.5 eq.), the reaction mixture was stirred for 4 h at rt. The reaction was quenched by the addition of water (50 mL). The crude product was subsequently extracted with EtOAc (3 × 30 mL) and washed with brine. The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under vacuum. After flash column chromatography (pentane/$Et_2O$ = 5/1), hydroxy olefin **17** (131 mg, 617 μmol, 62% over 2 steps) was obtained as a colorless oil containing about 14% of inseparable undec-10-en-1-ol.

**$^1$H NMR** (360 MHz, $CDCl_3$): $\delta$ [ppm] = 4.68 (s, 1H), 4.66 (s, 1H), 3.64 (t, $J$ = 6.6 Hz, 2H), 2.00 (t, $J$ = 7.7 Hz, 2H), 1.71 (s, 3H), 1.61 - 1.52 (m, 2H), 1.46 - 1.38 (m, 2H), 1.37 - 1.22 (m, 14H).

**$^{13}$C NMR** (91 MHz, $CDCl_3$): $\delta$ [ppm] = 146.5, 109.7, 63.3, 38.0, 33.0, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 27.8, 25.9, 22.5.

**HRMS** (ESI): calcd. for $C_{14}H_{29}O^+$ [$(M+H)^+$]: 213.2218, found: 213.2213.

**IR** (ATR): $\tilde{\nu}$ [$cm^{-1}$] = 3320, 3074, 2924, 2852, 1650, 1457, 1373, 1056, 908, 884, 721.

**TLC**: $R_f$ = 0.21 (pentane/$Et_2O$ = 5/1) [$KMnO_4$].

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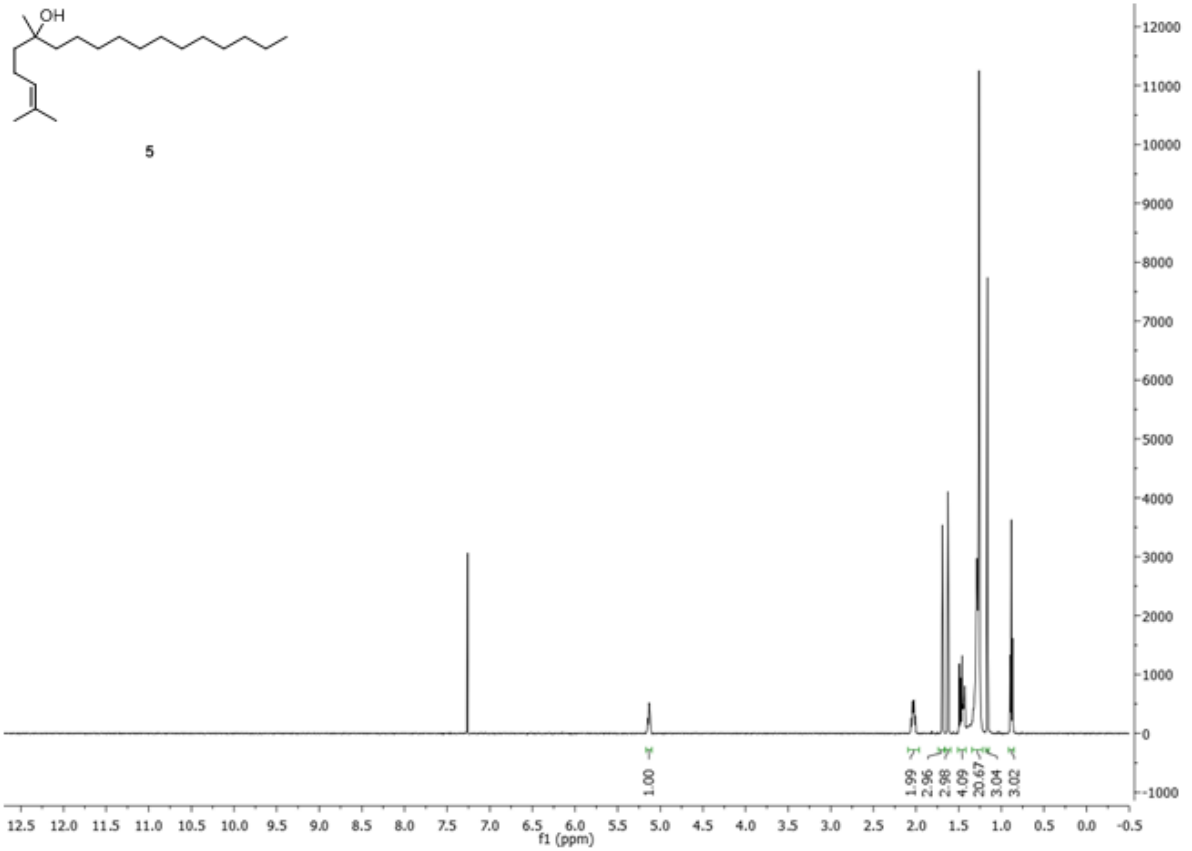
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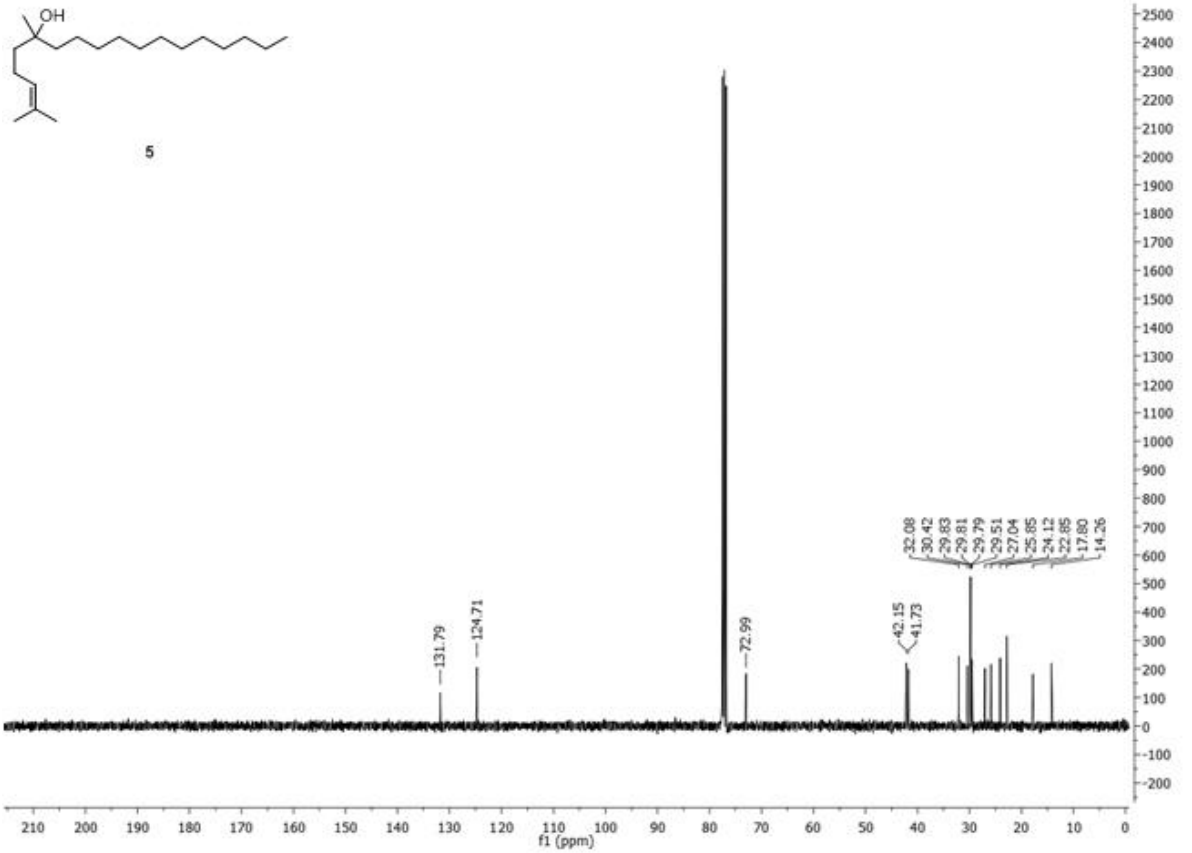
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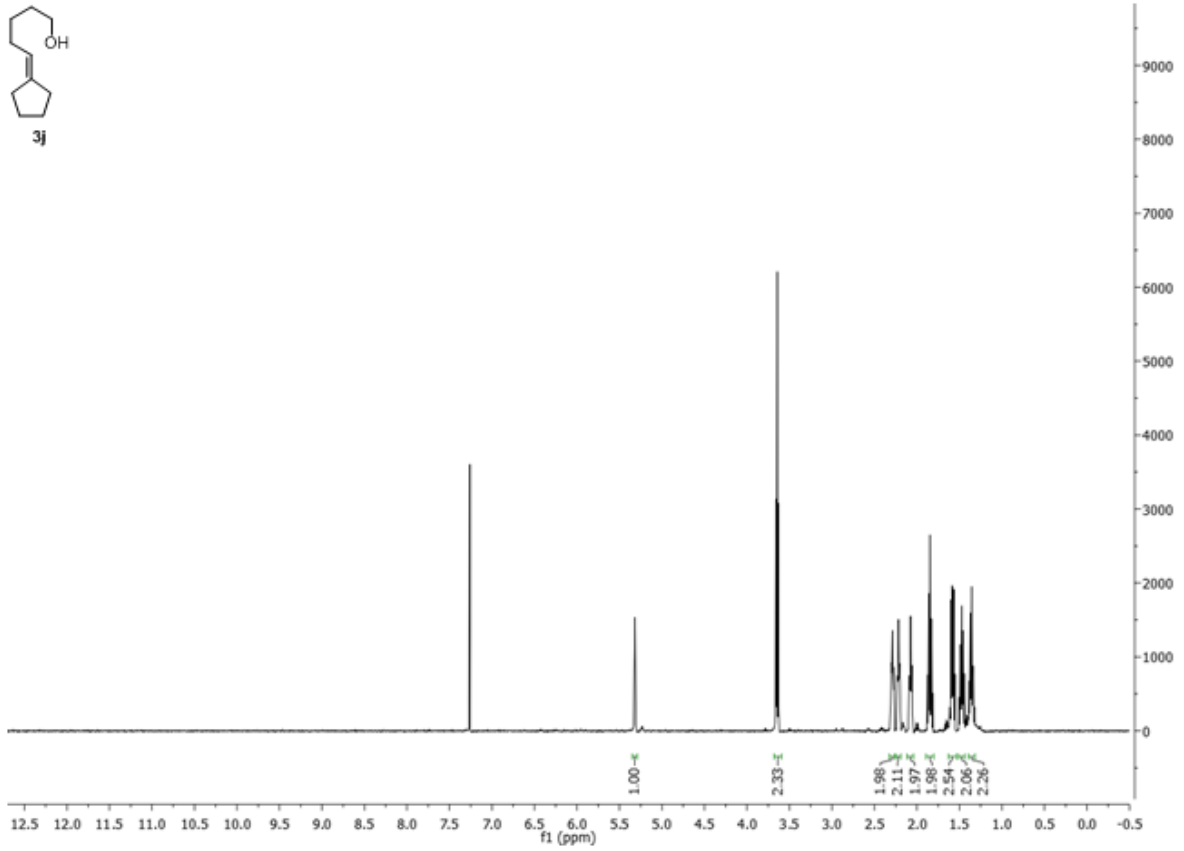
f1 (ppm)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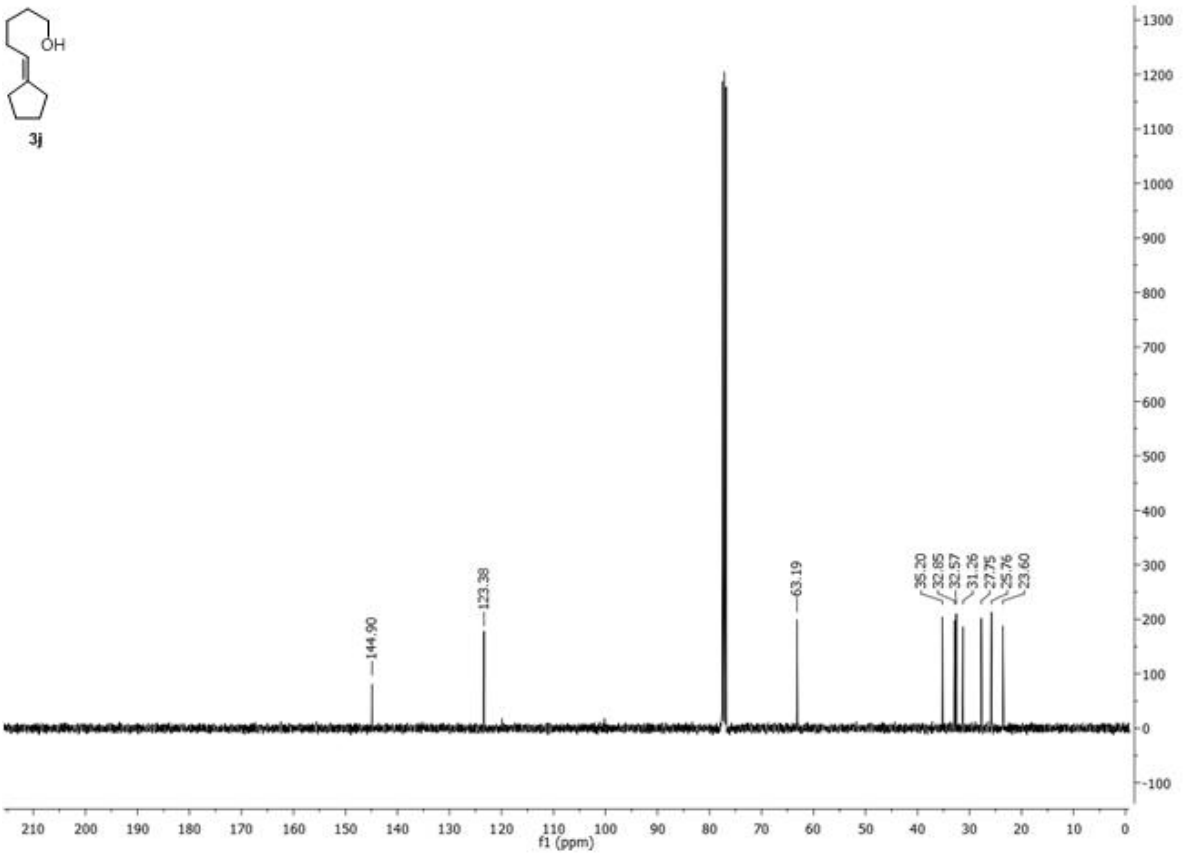
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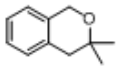

4g


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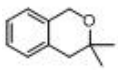
2.00
6.73
f1 (ppm)



4g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126.46
125.95
124.06
70.97
63.24
39.86
26.61
f1 (ppm)

4i


4000
3500
3000
2500
2000
1500
1000
500
0
2.00
8.57
6.01
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

4i


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2600
2400
2200
2000
1800
1600
1400
1200
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800
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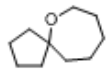
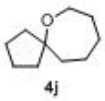
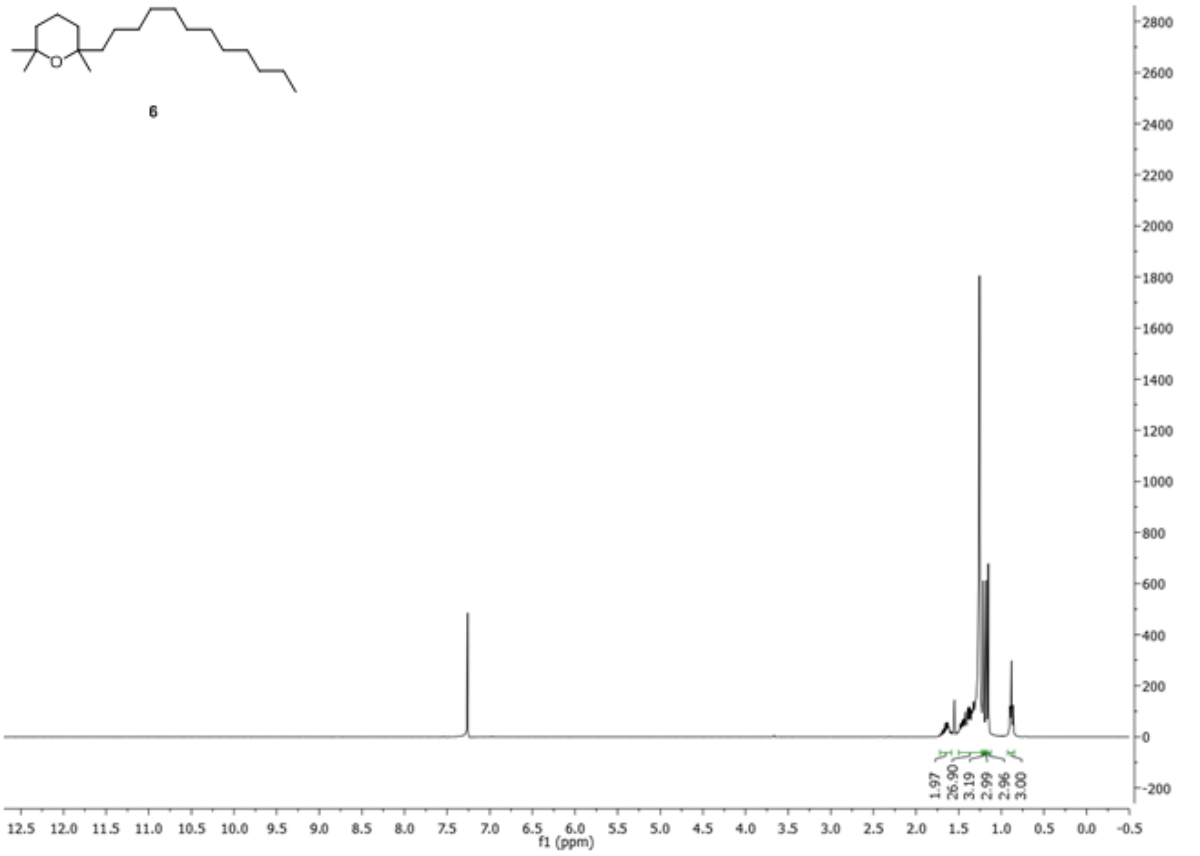


4j



4j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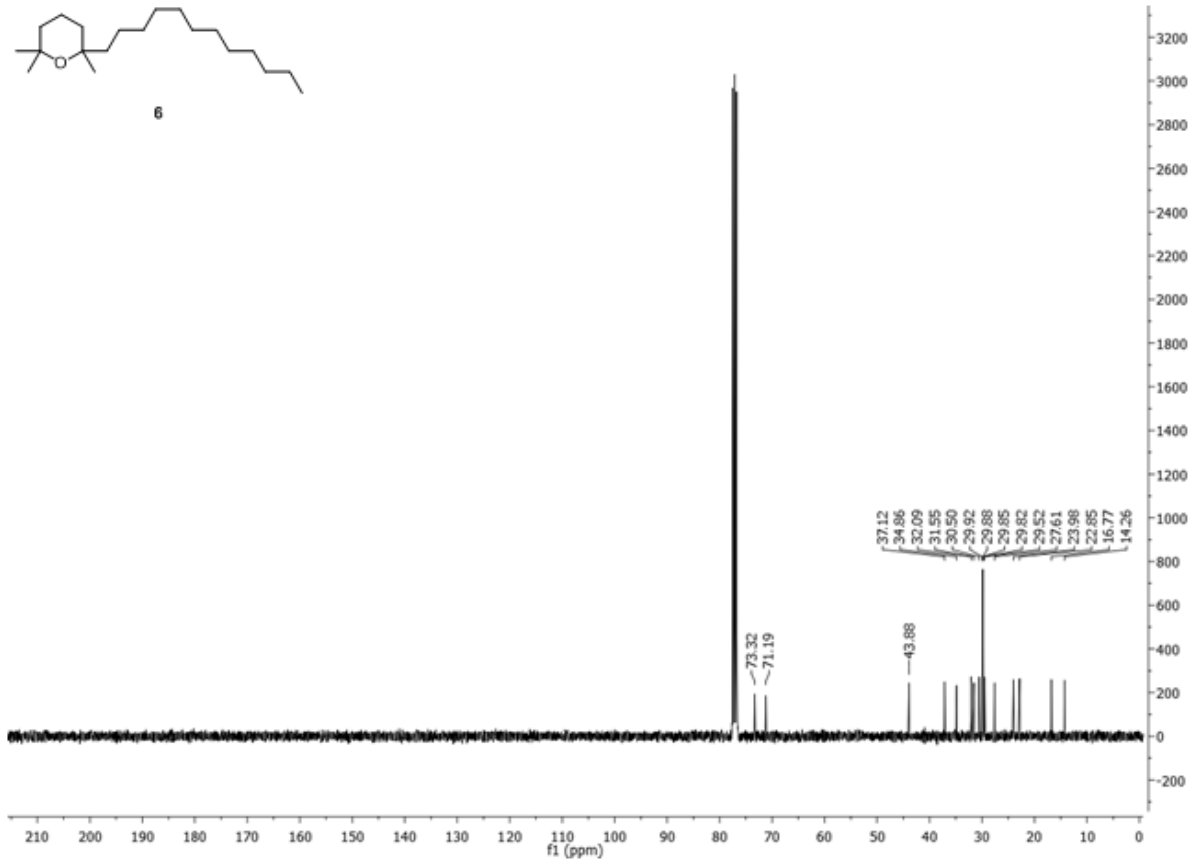
3.00
f1 (ppm)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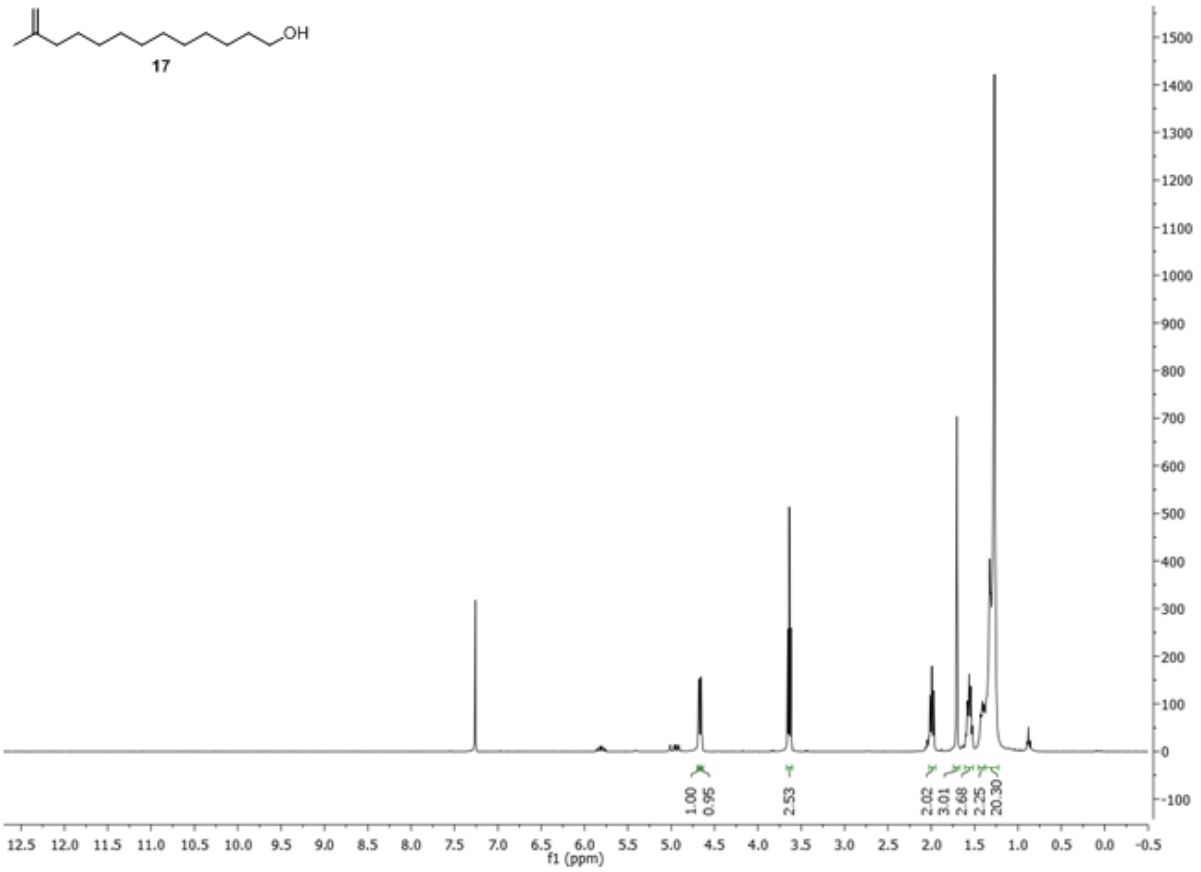
43.88
f1 (ppm)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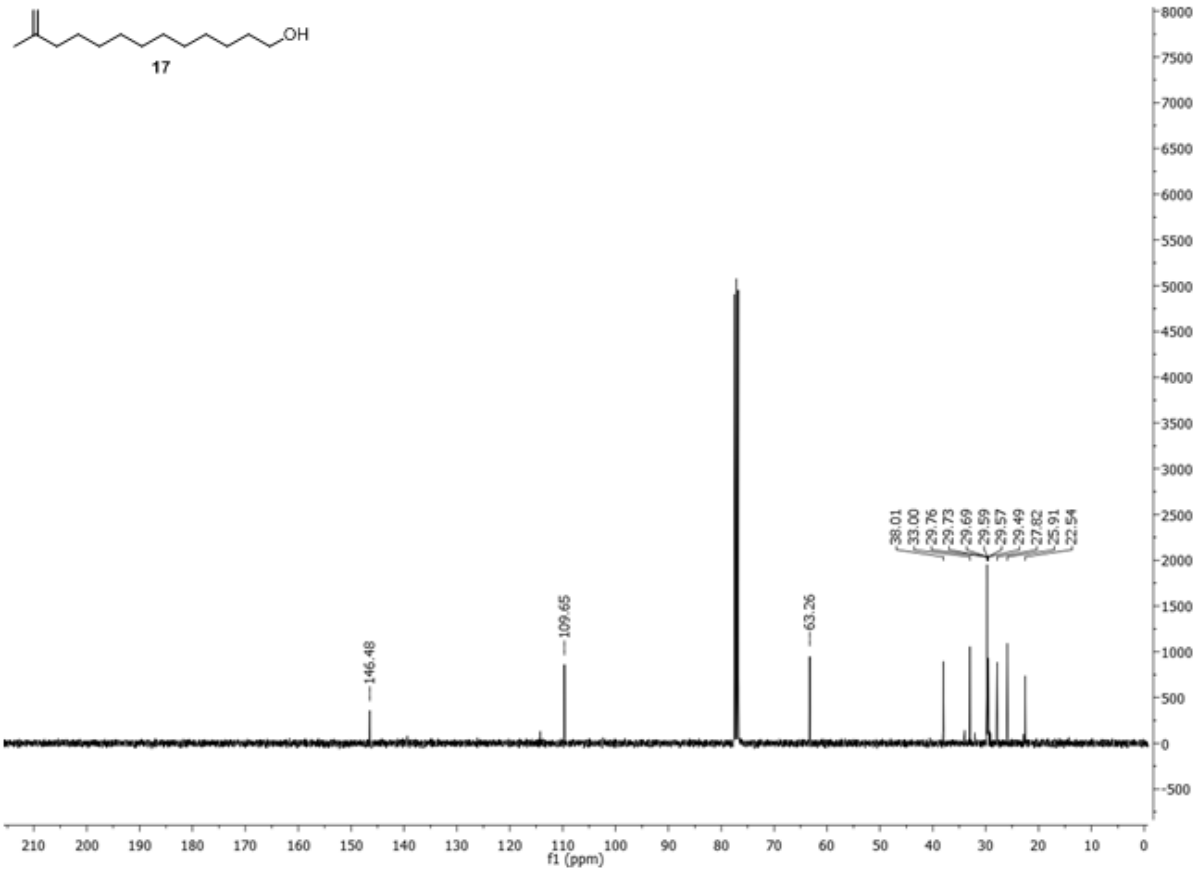
3.01
2.68
2.25
20.30
f1 (ppm)


OH
17
146.48
109.65
63.26
38.01
33.00
29.76
29.73
29.69
29.59
29.57
29.49
27.82
25.91
22.54
f1 (ppm)