Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Efficient Piancatelli rearrangement on large scale using Zippertex technology under subcritical water conditions

Guillaume Arcile, Jamal Ouazzani* and Jean-François Betzer*

Institut de Chimie des Substances Naturelles (ICSN), CNRS UPR 2301 - Université Paris-Saclay
1 avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France

Table of Contents

1. General information

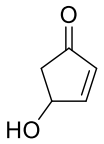
All non-aqueous reactions were run under an inert atmosphere (argon), by using standard techniques for manipulating air-sensitive compounds. Anhydrous THF was obtained by filtration through drying columns. All reagent-grade chemicals and other solvents were obtained from commercial suppliers and were used as received. Reactions were monitored by analytical thin-layer chromatography (TLC) on silica gel (60 F_{254}) plates (Merck) and visualized using UV light (254 and 312 nm) and developed by heating the plate after spraying with an aqueous solution of sulfomolybdic acid. Flash column chromatography was conducted on Merck silica gel 60 (40-63 µm) or on Combiflash Companion using Interchim silica columns. Proton magnetic resonance ^{1}H NMR spectra (500 MHz) and carbon magnetic resonance ^{13}C NMR spectra (125 MHz) were recorded on Bruker Avance spectrometer. Analyses were acquired in $CDCl_3$ (δ_H 7.26 ppm; δ_C 77.16 ppm), D_2O (δ_H 4.79 ppm) or acetone-*d*6 (δ_H 2.05 ppm; δ_C 29.84 and 206.66 ppm). The following abbreviations are used for the proton spectra multiplicities : s: singulet, d: doublet, t: triplet, q: quadruplet, m: multiplet. Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra (IR) were obtained on a Perkin-Elmer Spectrum 100 model instrument and are reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectra (HRMS) were recorded with a Micromass LCT Premier XE instrument (Waters) and were determined by electrospray ionization (ESI) coupled with a time of flight analyser (TOF).

2. Experimental Procedure and Characterization Data

General Procedure for reactions in Zippertex

A solution of furan derivative (12 - 50 mmol) in water or water/*t*-BuOH 5:1 (0.05 - 0.1 *M*) was placed in Zippertex® bowl, then nitrogen/air pressure (100 bars) was applied and the mixture was heated in 5-10 min to 100 or 150°C for 2 to 4.5 hours. After cooling to room temperature in 30-40 min, the cell was depressurized and the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (30 - 80% EtOAc/*n*-heptane) to give cyclopentanone derivatives.

Table 1, entry 3: HCP. 4-Hydroxycyclopent-2-en-1-one.



The title compound was obtained from furfuryl alcohol (5.0 g, 50 mmol) according to the general procedure in water at 150 °C for 4.5 h. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-heptane 50:50) to give pure **HCP** (3.25 g, 65% yield) as a dark yellow oil.

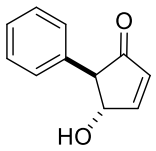
Scheme 5: synthesis HCP on 500 mmol scale

The title compound was obtained from furfuryl alcohol (49.1 g, 500 mmol) according to the general procedure in water at 150 °C for 4 h. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-heptane 50:50) to give pure **HCP** (24.0 g, 49% yield) as a dark yellow oil.

The spectra data are consistent to the previous described compound (CAS number 61305-27-9) in Literature (Curran, T. T. *et al. Tetrahedron* **1997**, *53*, 1983-2004).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 5.6, 2.3 Hz, 1H), 6.23 (dd, *J* = 5.6, 1.0 Hz, 1H), 5.07-5.05 (m, 1H), 2.78 (dd, *J* = 18.4, 5.9 Hz, 1H), 2.28 (dd, *J* = 18.4, 2.0 Hz, 1H).

Table 2, entry 3: *trans*-Ph-HCP. 4-Hydroxy-5-phenylcyclopent-2-en-1-one.

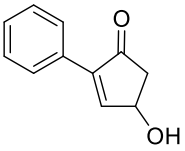


The title compound was obtained from α-phenylfurfuryl alcohol (2.6 g, 15 mmol) according to the general procedure in water at 100 °C for 3 h. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-heptane 40:60) to give ***trans*-Ph-HCP** (2.32 g, 89% yield, dr > 90:10) as a dark yellow oil.

The spectra data are consistent to the previous described compound (CAS number 70951-36-9) in Literature (Ulbrich, K. *et al. Synlett* **2010**, 2037-2040).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 5.7, 2.2 Hz, 1H), 7.41-7.27 (m, 3H), 7.15-7.12 (m, 2H), 6.34 (dd, *J* = 5.7, 1.2 Hz, 1H), 4.99 (s, 1H), 3.45 (d, *J* = 2.8 Hz, 1H), 2.38 (d, *J* = 6.0 Hz, 1H).

Table 2, entry 3: isomerized-Ph-HCP. 4-Hydroxy-2-phenylcyclopent-2-en-1-one.

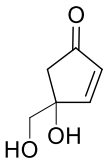


The title compound was obtained as the thermodynamic by-product during the above experiment for the formation of ***trans*-Ph-HCP**. This compound was separated by flash chromatography on silica gel (EtOAc/*n*-heptane 40:60) to give **isomerized-Ph-HCP** (230 mg, 9% yield) as a dark yellow oil.

The spectra data are consistent to the previous described compound (CAS number 62486-26-4) in Literature (Csákÿ, A. G. *et al. Tetrahedron Asym.* **2004**, 15, 647-652.)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.63 (m, 3H), 7.62 (bs, 1H), 7.41-7.35 (m, 2H), 5.06 (bs, 1H), 3.02 (dt, *J* = 18.5, 5.6 Hz, 1H), 2.54 (dd, *J* = 18.5, 5.6 Hz, 1H).

Table 3, entry 2: HHMCP. 4-Hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one.

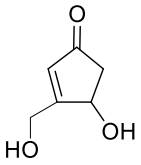


The title compound was obtained from furan-2,5-dicarbinol (6.4 g, 50 mmol) according to the general procedure in water at 150 °C for 4.5 h. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-heptane 60:40) to give pure **HHMCP** (2.95 g, 46% yield) as a pale yellow oil.

The spectra data are consistent to the previous described compound (CAS number 1606389-13-2) in Literature (Xu, Y.-J. *et al. Appl. Catal., A* **2017**, *543*, 266-273).

^{1}H NMR (500 MHz, D_2O) δ 7.70 (d, *J* = 5.7 Hz, 1H), 6.37 (d, *J* = 5.7 Hz, 1H), 3.77 (d, *J* = 11.5 Hz, 1H), 3.72 (d, *J* = 11.5 Hz, 1H), 2.72 (d, *J* = 18.4 Hz, 1H), 2.50 (d, *J* = 18.4 Hz, 1H).

Table 3, entry 2: isomerized-HHMCP. 4-Hydroxy-3-(hydroxymethyl)cyclopent-2-en-1-one.



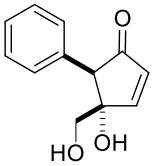
The title compound was obtained as the thermodynamic by-product during the above experiment for the formation of **HHMCP**. This compound was separated by flash chromatography on silica gel (EtOAc/*n*-heptane 60:40) to give pure **isomerized-HHMCP** (0.33 g, 5% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, D_2O) δ 6.28 (s, 1H), 5.04 (d, *J* = 6.0 Hz, 1H), 4.71 (d, *J* = 18.7 Hz, 1H), 4.57 (d, *J* = 18.7 Hz, 1H), 2.99 (dd, *J* = 18.7, 6.0 Hz, 1H), 2.43 (d, *J* = 18.7 Hz, 1H).
^{13}C NMR (125 MHz, D_2O) δ 209.9 (CO), 182.7 (C), 128.0 (CH), 69.2 (CH), 59.5 (CH_2), 44.5 (CH_2).

IR (neat) ν_{max}: 3387, 1683, 1626, 1438, 1270, 1138, 1055, 992 cm^{-1}.

HRMS (ESI): *m/z* calcd. for $C_6H_9O_3$ $[M+H]^+$ 129.0552 found 129.0545.

Table 4, entry 3: *trans*-Ph-HHMCP. 4-Hydroxy-4-(hydroxymethyl)-5-phenylcyclopent-2-en-1-one.

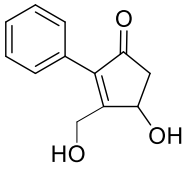


The title compound was obtained from α-phenylfuran-2,5-dicarbinol (2.45 g, 12 mmol) according to the general procedure in water/*t*-BuOH 5:1 at 100 °C for 2 h. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-heptane 60:40) to give ***trans*-Ph-HHMCP** (1.64 g, 67% yield, dr > 90:10) as a pale yellow oil.

The spectra data are consistent to the previous described compound (CAS number 2639810-33-4) in Literature (Cacheux, F. et al. *Org. Chem. Front.* **2021**, *8*, 2449-2455).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 5.9 Hz, 1H), 7.39-7.30 (m, 3H), 7.20-7.17 (m, 2H), 6.41 (d, *J* = 5.9 Hz, 1H), 3.85 (s, 1H), 3.42-3.35 (m, 2H).

Table 4, entry 2: isomerized-Ph-HHMCP. 4-Hydroxy-3-(hydroxymethyl)-2-phenylcyclopent-2-en-1-one.



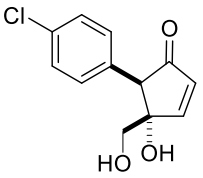
The title compound was obtained as the thermodynamic by-product during the above experiment for the formation of ***trans*-Ph-HHMCP**. This compound was separated by flash chromatography on silica gel (EtOAc/*n*-heptane 60:40) to give pure **isomerized-Ph-HHMCP** (0.07 g, 3% yield) as a beige solid; melting point: 91-93 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.34 (m, 3H), 7.26-7.24 (m, 2H), 5.26 (d, *J* = 5.9 Hz, 1H), 4.85 (d, *J* = 15.0 Hz, 1H), 4.75 (d, *J* = 15.0 Hz, 1H), 2.94 (dd, *J* = 18.5, 6.3 Hz, 1H), 2.52 (dd, *J* = 18.5, 2.0 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8 (CO), 168.2 (C), 140.4 (C), 130.0 (C), 129.1 (CH), 129.1 (CH), 128.8 (CH), 128.6 (CH), 128.6 (CH), 69.6 (CH), 60.3 (CH_2), 44.2 (CH_2).

IR (neat) ν_{max}: 3396, 1700, 1444, 1309, 1134, 1061, 769, 701 cm^{-1}.

HRMS (ESI): *m/z* calcd. for $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0865 found 205.0860.

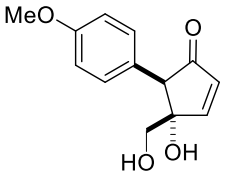
Scheme 4, line 1: *trans*-(4-Cl-C_6H_4)-HHMCP. 4-Hydroxy-4-(hydroxymethyl)-5-(4-chloro)cyclopent-2-en-1-one.



The title compound was obtained from α-(4-Cl-C_6H_4)furan-2,5-dicarbinol (2.8 g, 12 mmol) according to the general procedure in water/*t*-BuOH 5:1 at 100 °C for 2 h. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-heptane 80:20) to give ***trans*-(4-Cl-C_6H_4)-HHMCP** (2.08 g, 73% yield, dr > 80:20) as a pale yellow solid.

The spectra data are consistent to the previous described compound (CAS number 2639810-38-9) in Literature (Cacheux, F. et al. *Org. Chem. Front.* **2021**, *8*, 2449-2455).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 5.9 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.39 (d, *J* = 5.9 Hz, 1H), 3.82 (s, 1H), 3.34 (s, 2H), 3.27 (s, 1H).



Scheme 4, line 2: *trans*-(4-MeO-C_6H_4)-HHMCP. 4-Hydroxy-4-(hydroxymethyl)-5-(4-methoxyphenyl)cyclopent-2-en-1-one.

The title compound was obtained from α-(4-MeO-C_6H_4)furan-2,5-dicarbinol (2.8 g, 12 mmol) according to the general procedure in water/*t*-BuOH 5:1 at 100 °C for 2 h. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-heptane 80:20) to give ***trans*-(4-MeO-C_6H_4)-HHMCP** (2.28 g, 82% yield, dr > 90:10) as a beige solid.

The spectra data are consistent to the previous described compound (CAS number 2639810-45-8) in Literature (Cacheux, F. et al. *Org. Chem. Front.* **2021**, *8*, 2449-2455).

^{1}H NMR (500 MHz, acetone-d_6) δ 7.59 (d, *J* = 5.9 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.29 (d, *J* = 5.9 Hz, 1H), 4.67 (s, 1H), 3.78 (s, 3H), 3.73-3.71 (m, 1H), 3.70 (s, 1H), 3.29-3.16 (m, 2H).

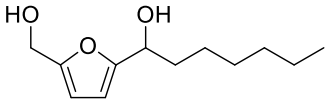


Table 5, preparation of α-(*n*-hexyl)furan-2,5-dicarbinol. 1-(5-(Hydroxymethyl)furan-2-yl)heptan-1-ol.

To a solution of 5-(hydroxymethyl)furfural (4.0 g, 31.7 mmol) in THF (50 mL) at 0 °C was added *n*-hexylmagnesium bromide (2.0 *M* in Et_2O, 35.0 mL, 70.0 mmol, 2.2 eq). The reaction mixture was allowed to warm to room temperature and stirred for 2h. The mixture was quenched with saturated NH_4Cl (20 mL), acidified at pH 5-6 with 0.5 *M* HCl and extracted with EtOAc (3x100 mL) The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-heptane 60:40) to give the pure title compound (5.25 g, 78% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, acetone-d_6) δ 6.16 (d, *J* = 3.1 Hz, 1H), 6.13 (d, *J* = 3.1 Hz, 1H), 4.59-4.54 (m, 1H), 4.46 (d, *J* = 5.7 Hz, 2H), 4.12-4.09 (m, 1H), 1.83-1.71 (m, 2H), 1.48-1.41 (m, 1H), 1.36-1.25 (m, 7H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6) δ 158.5 (C), 155.2 (C), 108.1 (CH), 106.4 (CH), 67.9 (CH), 57.4 (CH_2), 36.8 (CH_2), 32.6 (CH_2), 29.9 (CH_2), 26.3 (CH_2), 23.3 (CH_2), 14.3 (CH_3).

IR (neat) ν_{max}: 3317, 2928, 2857, 1459, 1190, 1013, 790 cm^{-1}.

HRMS (ESI): *m/z* calcd. for $C_{12}H_{20}O_3Na$ $[M+Na]^+$ 235.1310 found 235.1302.

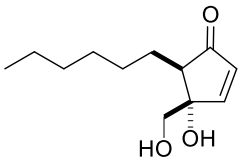


Table 5, line 3: *trans*-(*n*-C_6H_{13})-HHMCP. 5-*n*-Hexyl-4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one.

The title compound was obtained from α-(*n*-hexyl)furan-2,5-dicarbinol (2.5 g, 12 mmol) according to the general procedure in water/*t*-BuOH 5:1 at 150 °C for 4.5 h. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-heptane 80:20) to give ***trans*-(*n*-C_6H_{13})-HHMCP)** (0.58 g, 23% yield, dr > 95:5) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 5.9 Hz, 1H), 6.22 (d, *J* = 5.9 Hz, 1H), 3.84 (d, *J* = 10.7 Hz, 1H), 3.57 (d, *J* = 10.7 Hz, 1H), 2.83 (s, 1H), 2.41 (dd, *J* = 8.0, 5.9 Hz, 1H), 2.07 (s, 1H), 1.78-1.71 (m, 1H), 1.63-1.55 (m, 1H), 1.54-1.48 (m, 1H), 1.44-1.38 (m, 1H), 1.36-1.25 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6 (CO), 162.7 (CH), 133.6 (CH), 81.7 (C), 66.5 (CH_2), 57.5 (CH), 31.7 (CH_2), 29.6 (CH_2), 28.6 (CH_2), 24.4 (CH_2), 22.7 (CH_2), 14.2 (CH_3).

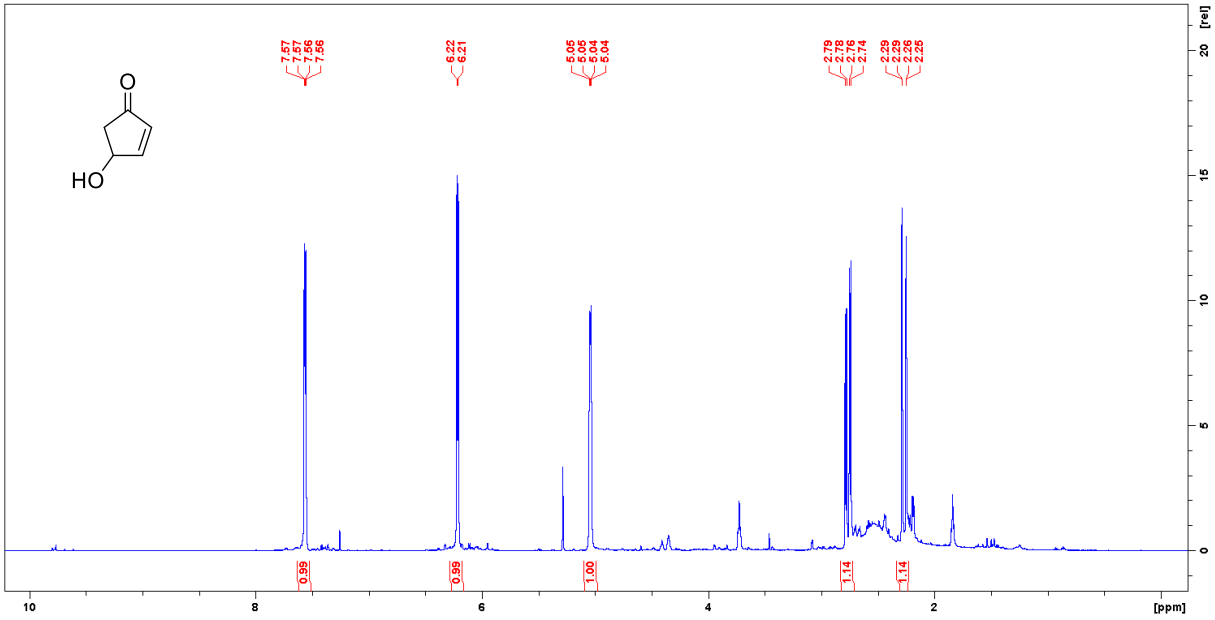
IR (neat) ν_{max}: 3394, 2928, 2857, 1699, 1115, 1044, 807 cm^{-1}.

HRMS (ESI): *m/z* calcd. for $C_{12}H_{21}O_3$ $[M+H]^+$ 213.1491 found 213.1485.

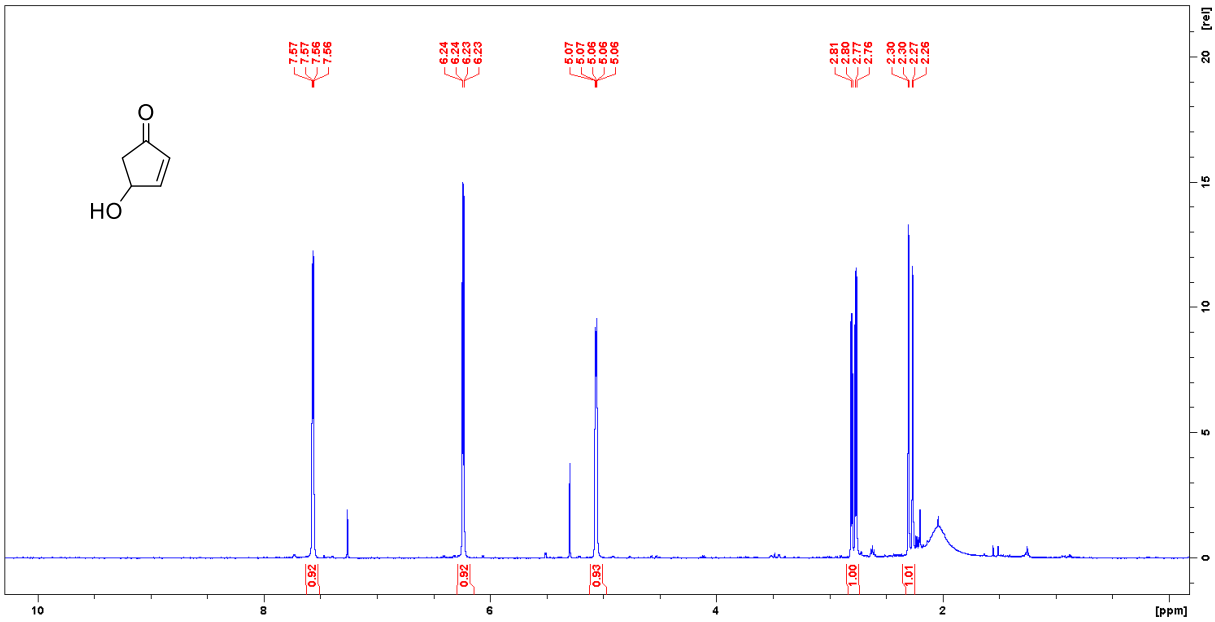
3. NMR Spectra

^{1}H NMR ($CDCl_3$, 500 MHz) of 4-hydroxycyclopent-2-en-1-one (HCP)

Crude mixture

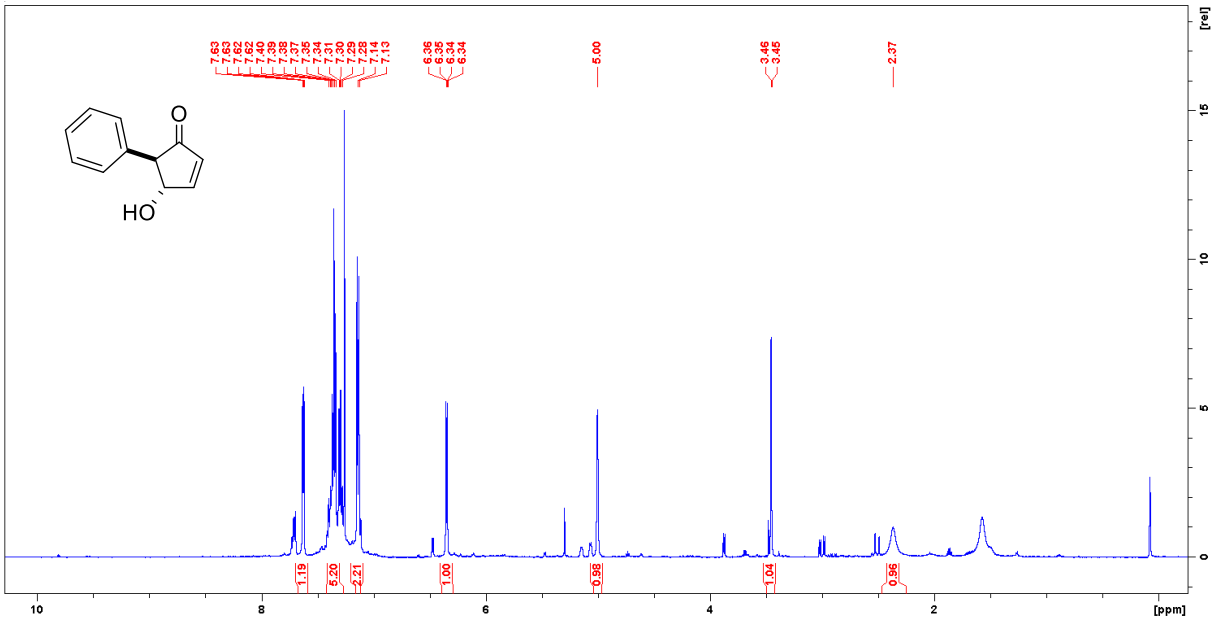


Purified HCP

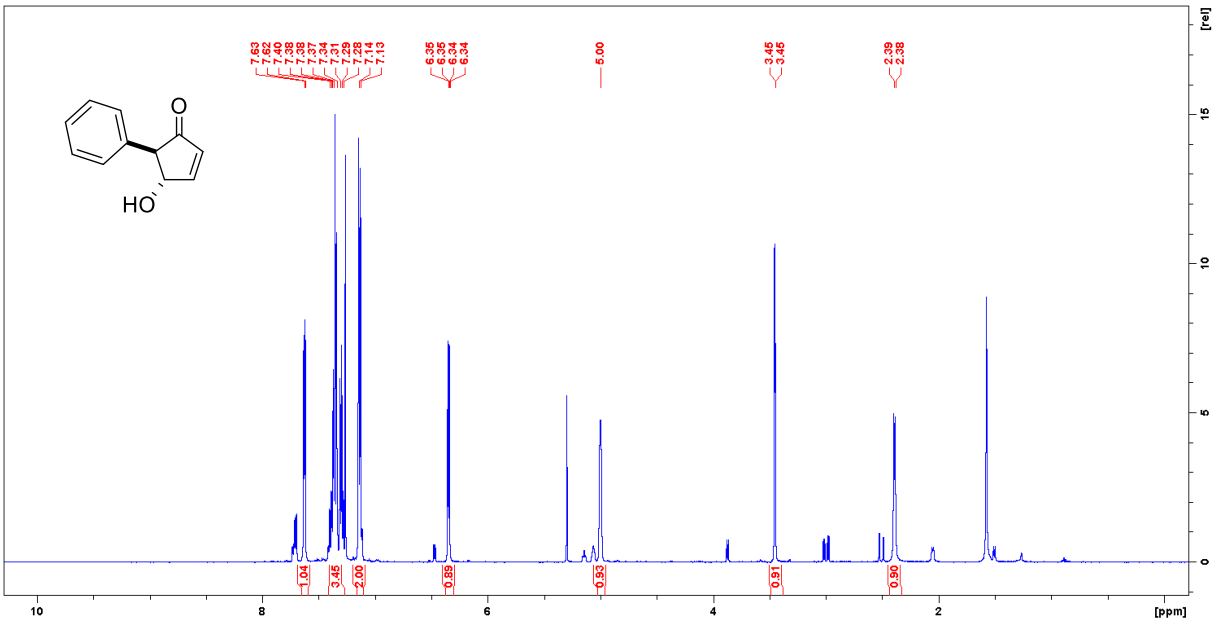


^{1}H NMR ($CDCl_3$, 500 MHz) of 4-hydroxy-5-phenylcyclopent-2-en-1-one (*trans*-Ph-HCP)

Crude mixture

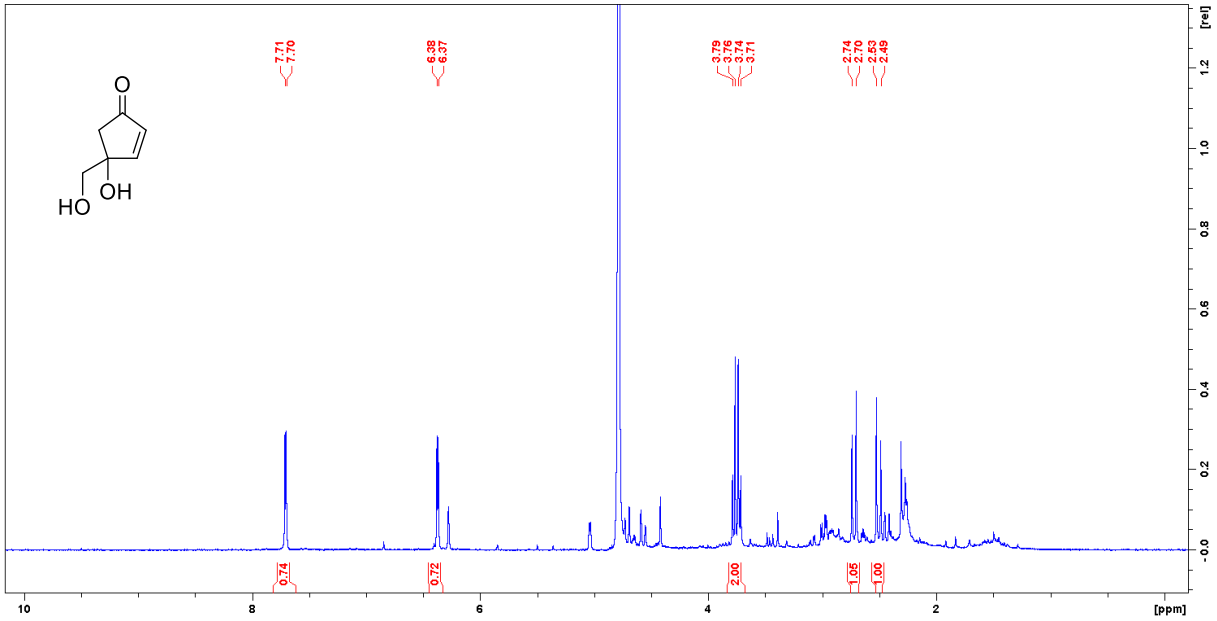


Purified *trans*-Ph-HCP

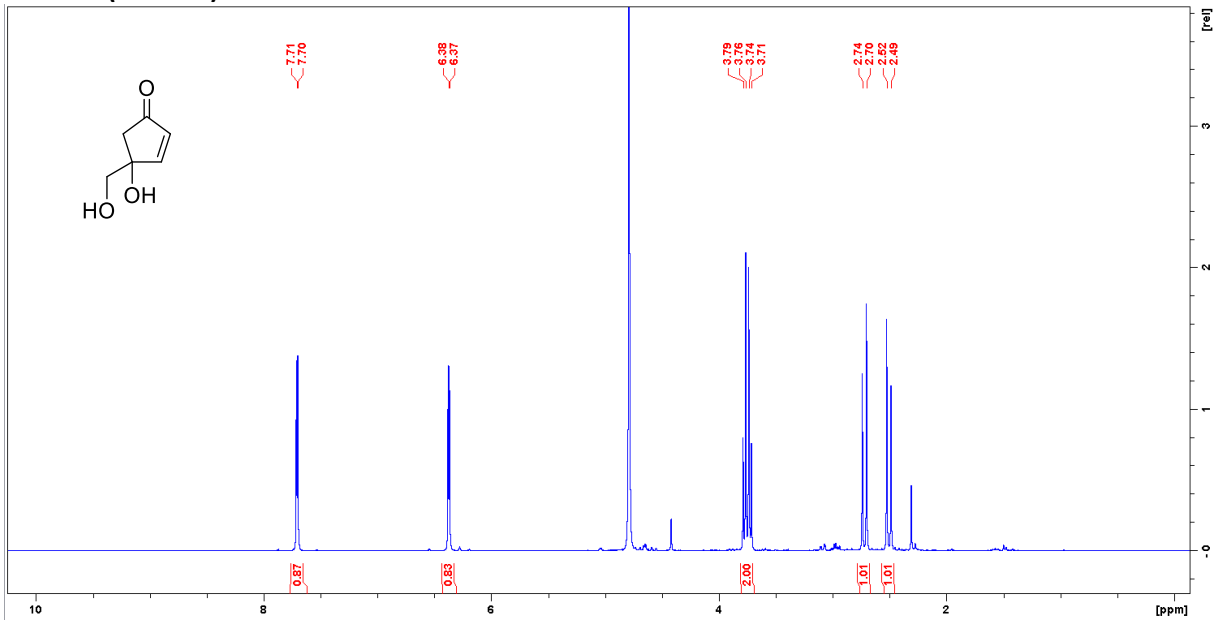


^{1}H NMR (D_2O, 500 MHz) of 4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (HHMCP)

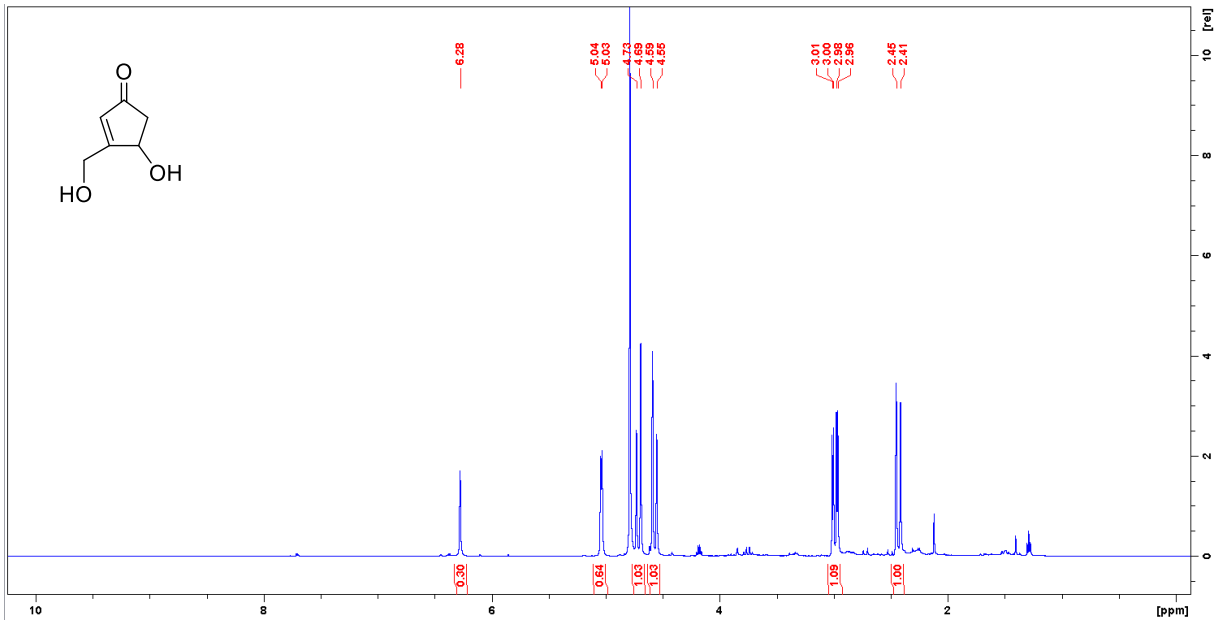
Crude mixture



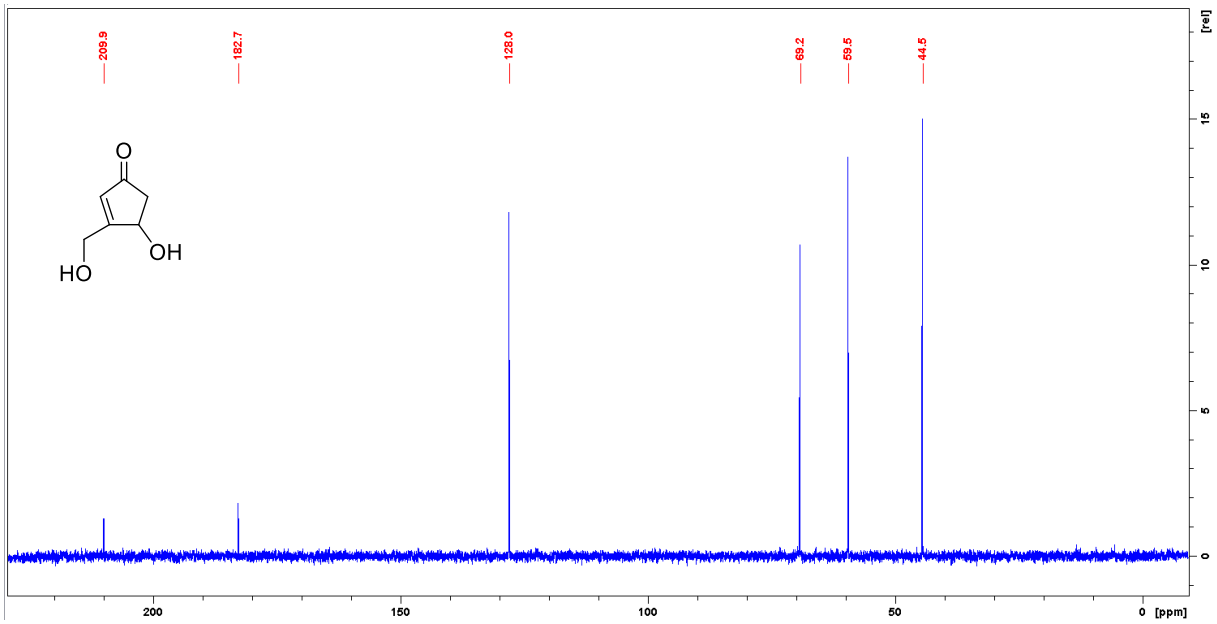
Purified (HHMCP)



^{1}H NMR (D_2O, 500 MHz) of 4-hydroxy-3-(hydroxymethyl)cyclopent-2-en-1-one (isomerized-HHMCP)

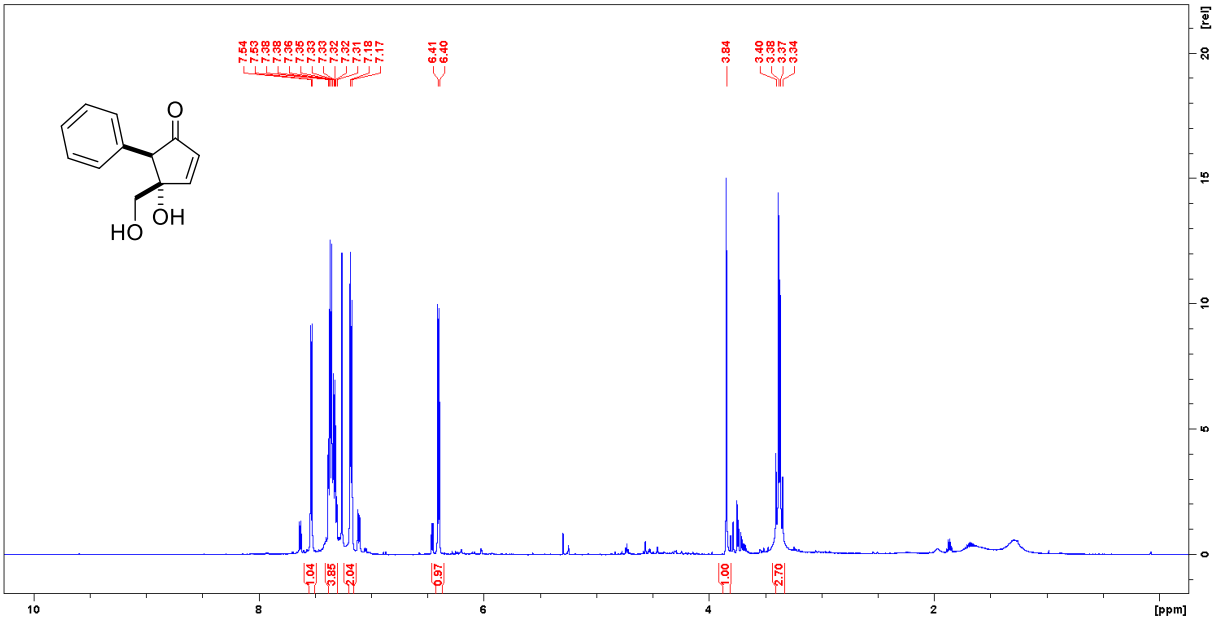


^{13}C NMR (D_2O, 125 MHz) of 4-hydroxy-3-(hydroxymethyl)cyclopent-2-en-1-one (isomerized-HHMCP)

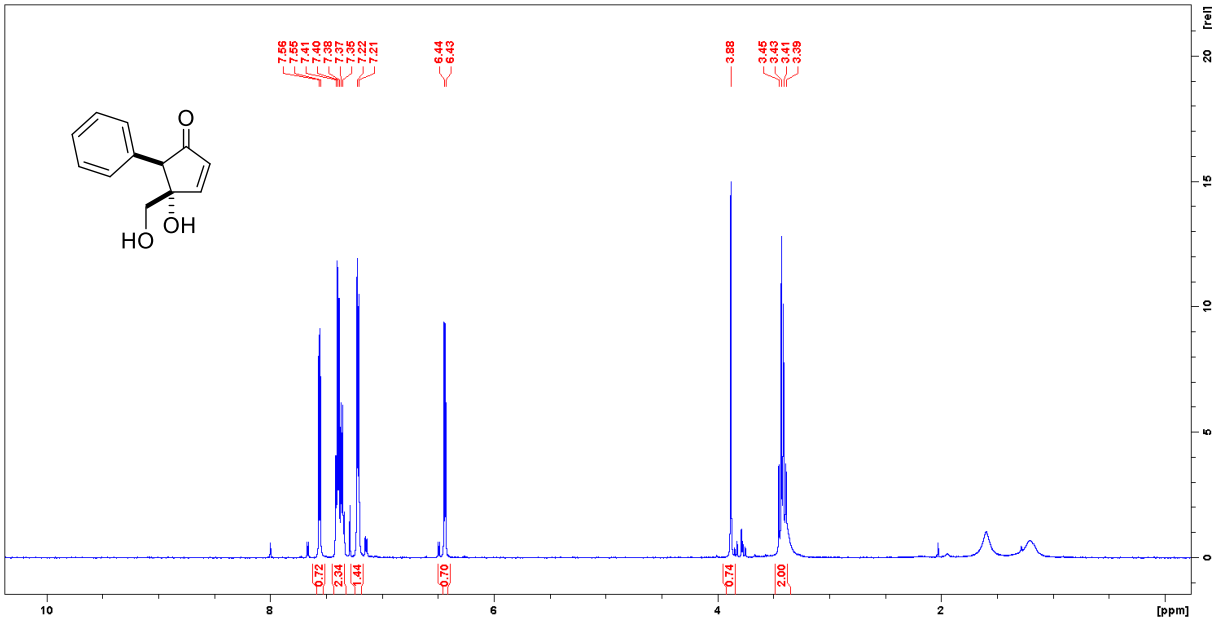


^{1}H NMR ($CDCl_3$, 500 MHz) of 4-hydroxy-4-(hydroxymethyl)-5-phenylcyclopent-2-en-1-one (*trans*-Ph-HHMCP)

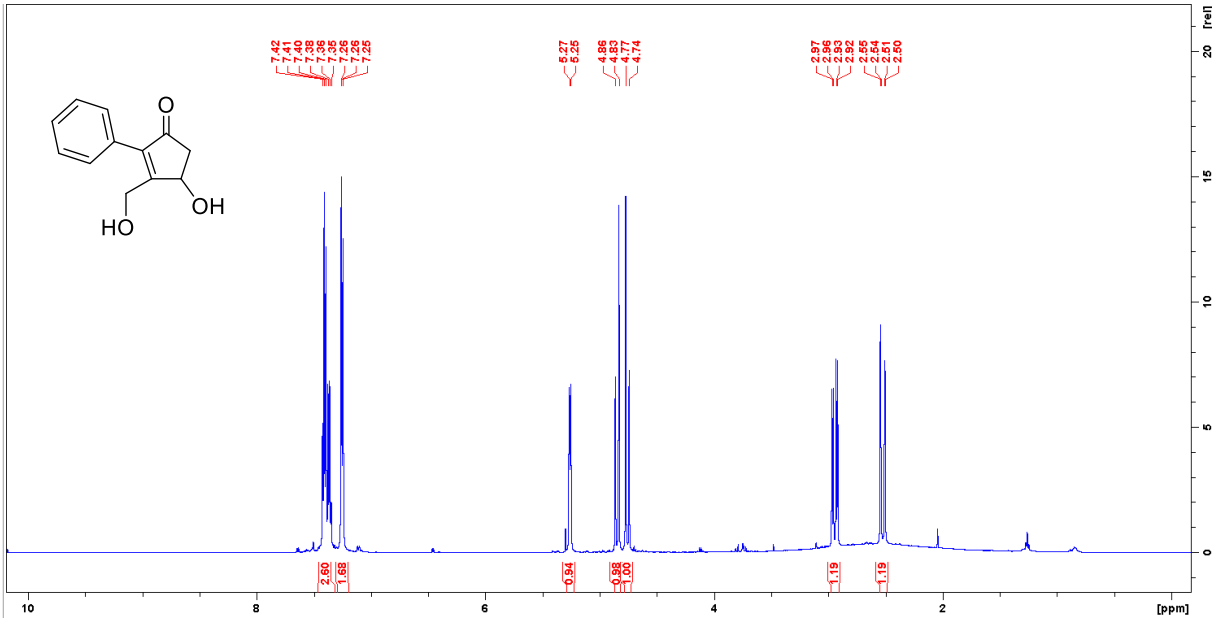
Crude mixture



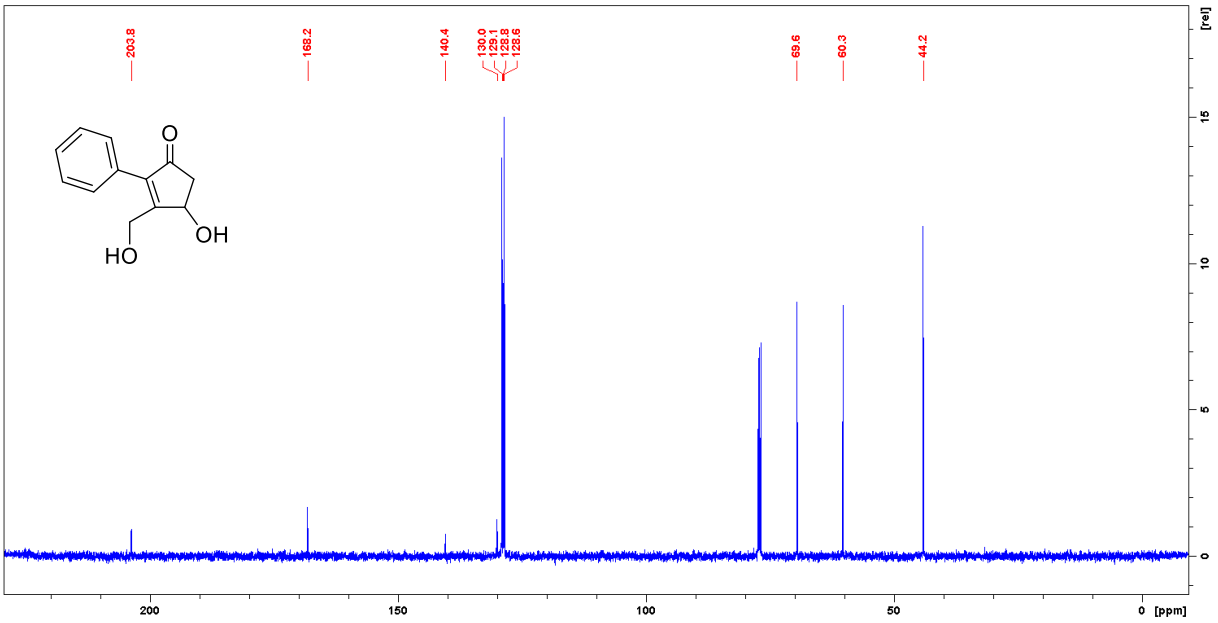
Purified *trans*-Ph-HHMCP



^{1}H NMR ($CDCl_3$, 500 MHz) of 4-hydroxy-3-(hydroxymethyl)-2-phenylcyclopent-2-en-1-one (isomerized-Ph-HHMCP)

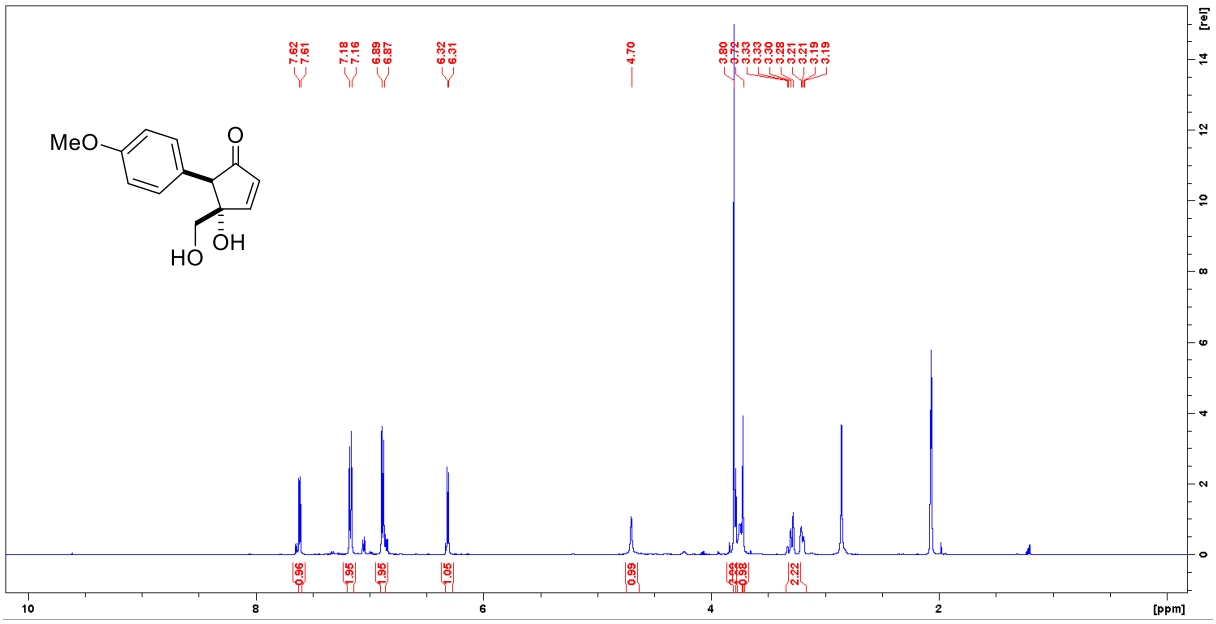


^{13}C NMR ($CDCl_3$, 125 MHz) of 4-hydroxy-3-(hydroxymethyl)-2-phenylcyclopent-2-en-1-one (isomerized-Ph-HHMCP)

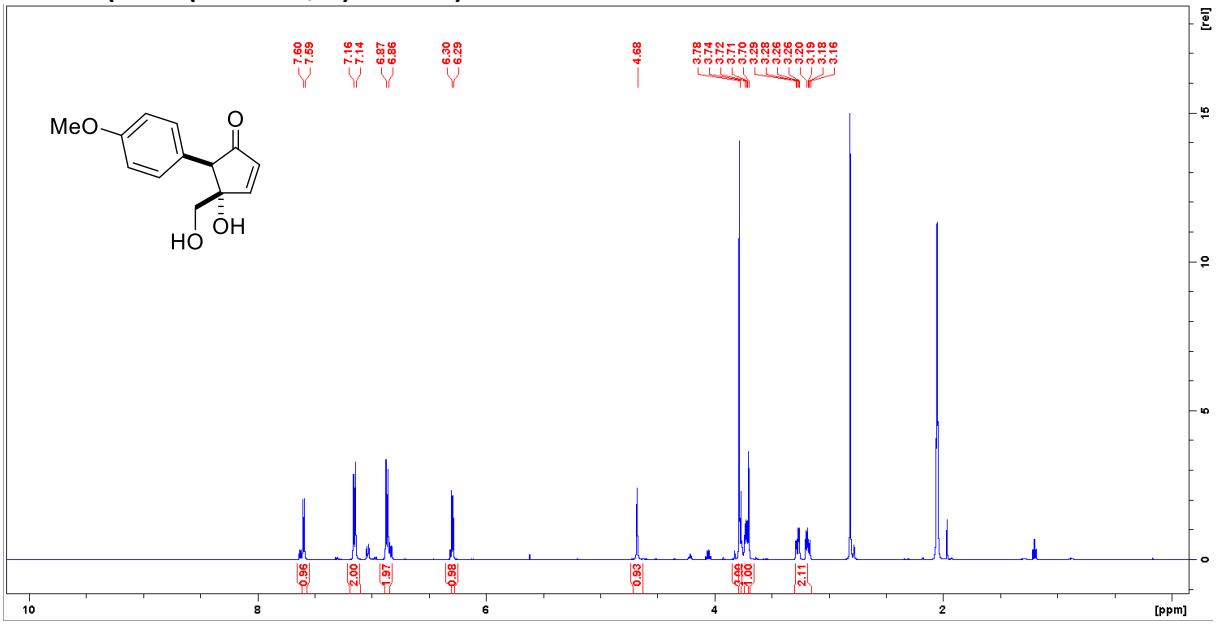


^{1}H NMR (acetone-d_6, 500 MHz) of 4-hydroxy-4-(hydroxymethyl)-5-(4-methoxyphenyl)cyclopent-2-en-1-one (*trans*-(4-MeO-C_6H_4)-HHMCP)

Crude mixture

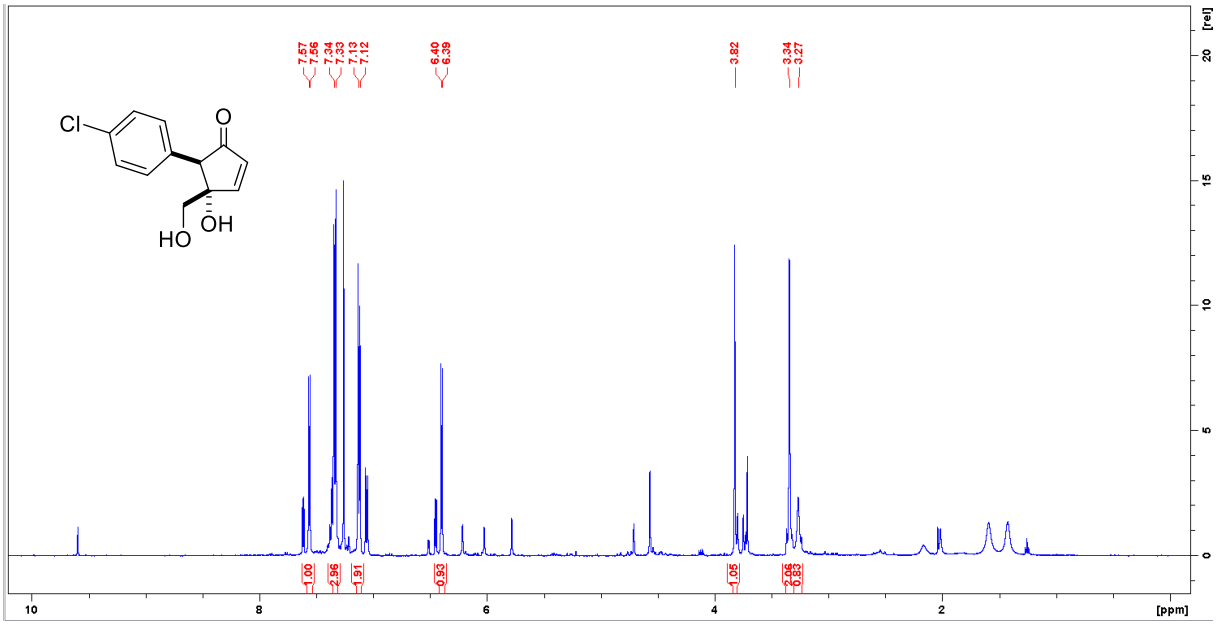


Purified (*trans*-(4-MeO-C_6H_4)-HHMCP)

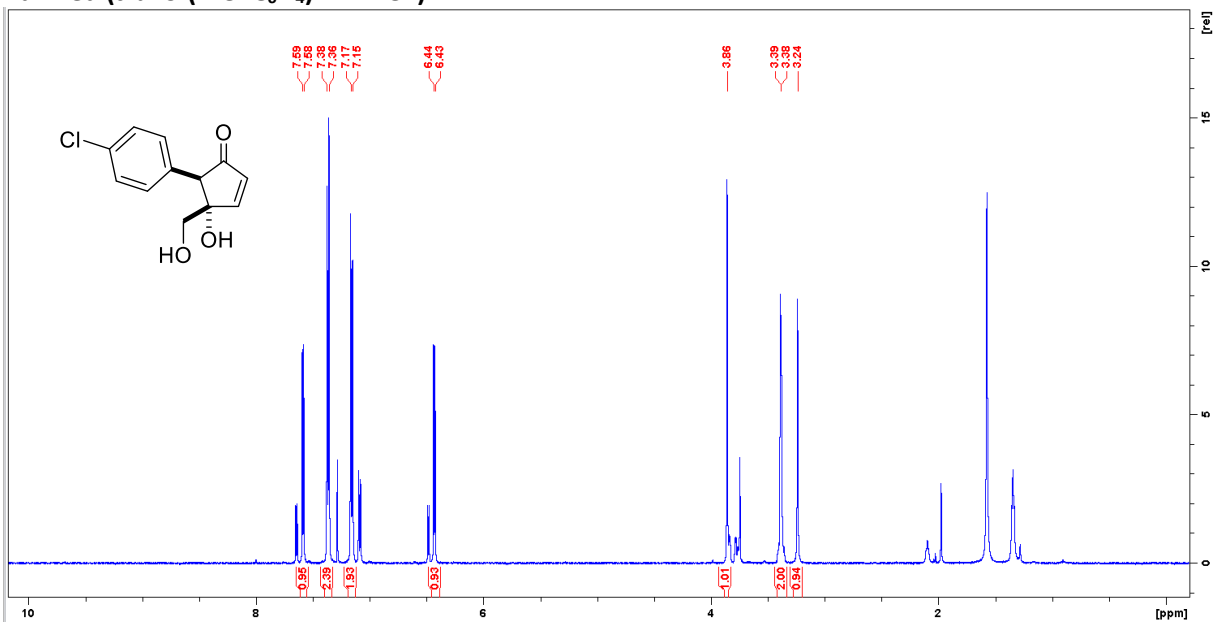


^{1}H NMR ($CDCl_3$, 500 MHz) of 5-(4-chlorophenyl)-4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (*trans*-(4-Cl-C_6H_4)-HHMCP)

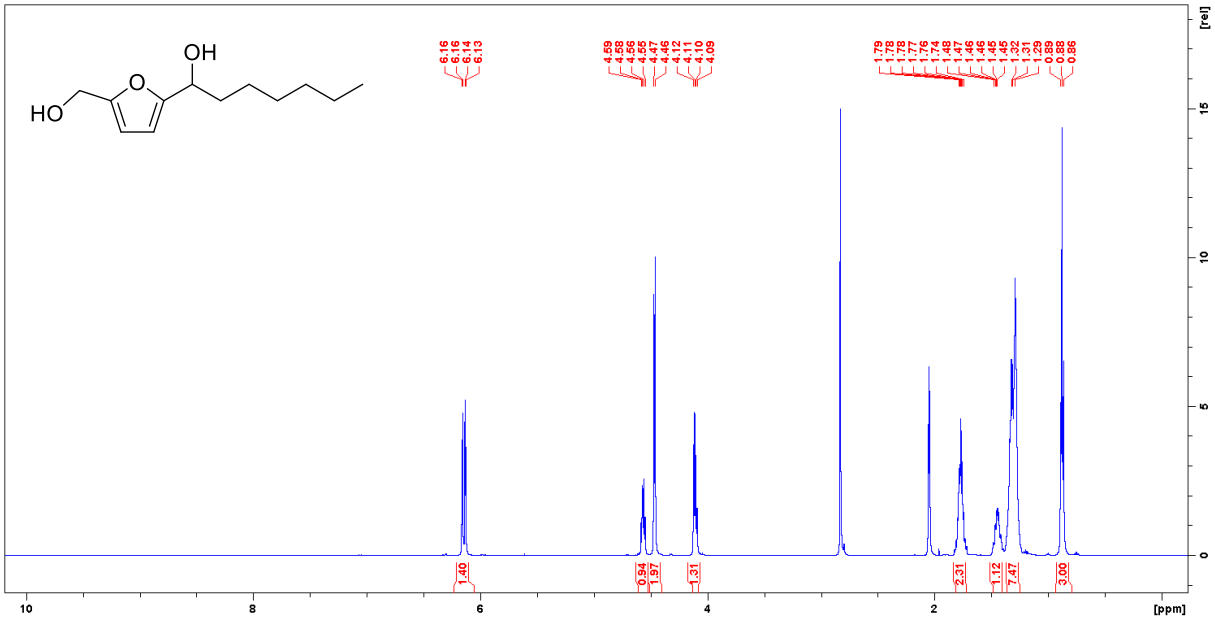
Crude mixture



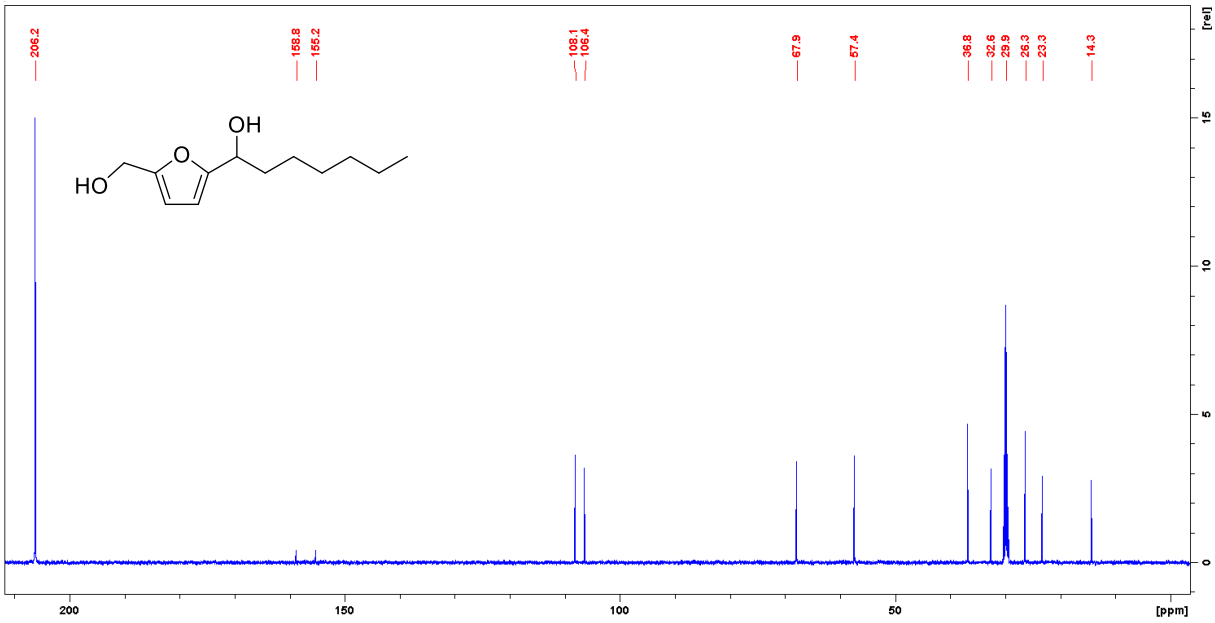
Purified (*trans*-(4-Cl-C_6H_4)-HHMCP)



^{1}H NMR (acetone-d_6, 500 MHz) of 1-(5-(hydroxymethyl)furan-2-yl)heptan-1-ol

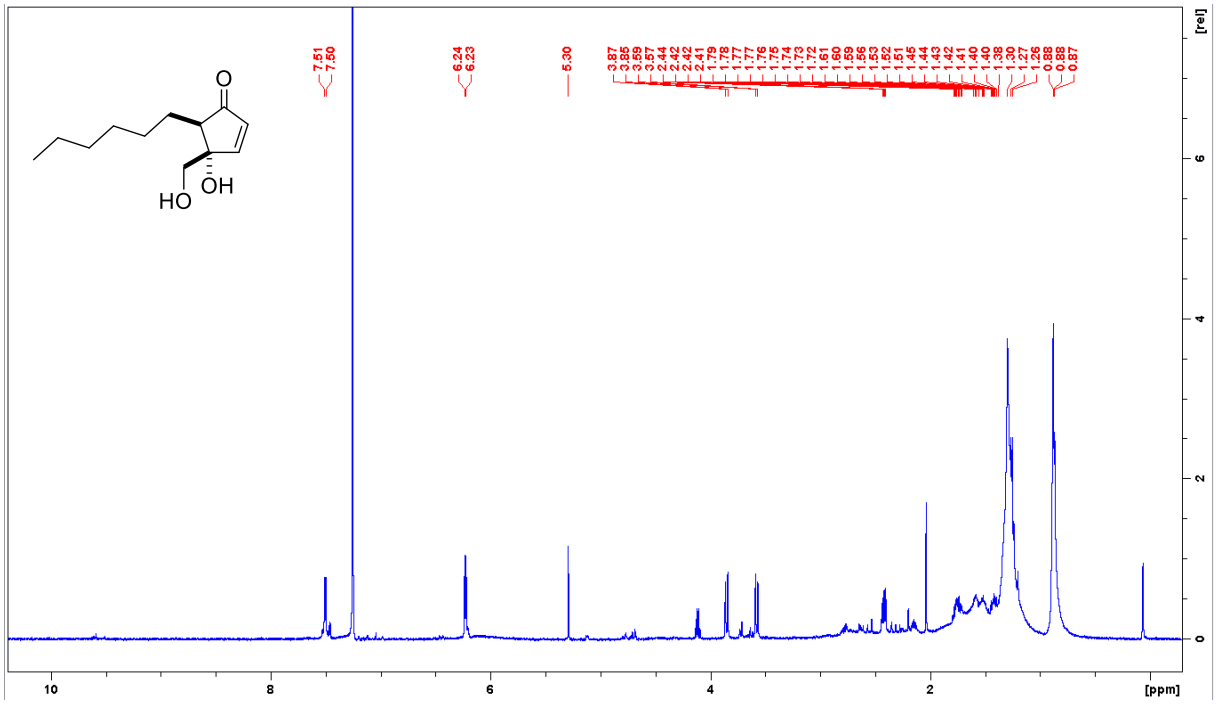


^{13}C NMR (acetone-d_6, 125 MHz) of 1-(5-(hydroxymethyl)furan-2-yl)heptan-1-ol

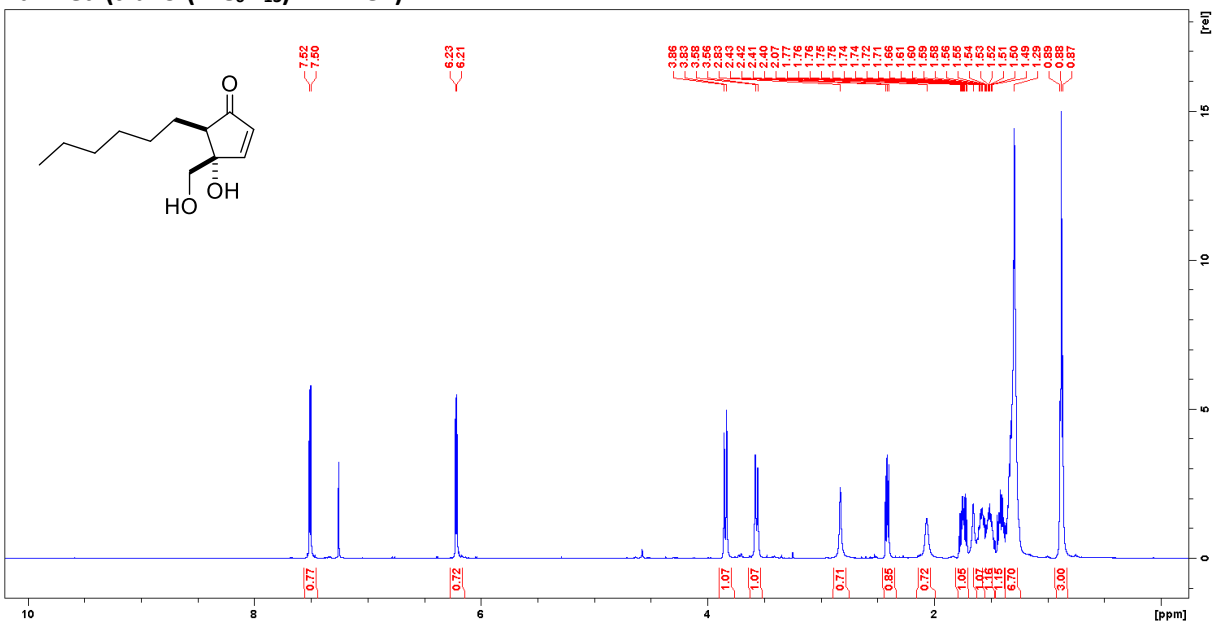


^{1}H NMR ($CDCl_3$, 500 MHz) of 5-hexyl-4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (*trans*-(*n*-C_6H_{13})-HHMCP)

Crude mixture



Purified (*trans*-(*n*-C_6H_{13})-HHMCP)



^{13}C NMR ($CDCl_3$, 125 MHz) of 5-hexyl-4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (*trans*-(*n*-C_6H_{13})-HHMCP