Oxidative Cyclization of β -Hydroxyenones with Palladium (II): a Novel Entry to 2,3 dihydro-4*H*-pyran-4-ones

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Supporting Information

General Information:

Infrared spectra were recorded on a Paragon 1000 FT-IR spectrometer and only peaks of interest are reported. ^1H NMR spectra were recorded on Bruker DQX 400 and DPX 400 spectrometers, at a frequency of 400 MHz. Chemical shifts are reported in ppm and coupling constants (J) are given in hertz (Hz). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on a Bruker DQX 400 spectrometer at a frequency of 100 MHz. The chemical shifts are reported in ppm. Mass spectra (m/z) were recorded on Micromass GCT in Chemical Ionisation (NH_3 , CI^+) or on a AutoSpec-oaTof instruments (CI^+).

Analytical thin layer chromatography (TLC) was performed on Merck Silica gel 60 F₂₅₄ plates. All reactions were carried out under an argon or oxygen atmosphere respectively in dried glassware with magnetic stirring. Tetrahydrofuran (THF) was distilled from sodium and benzophenone and both 1,2-dimethoxy-ethane (DME) and diisopropylamine were distilled from calcium hydride. All other commercially obtained reagents were used as received.

Copies of ^1H NMR and ^{13}C NMR spectra for all relevant compounds are provided.

General Procedure A: Preparation of β -hydroxyenones

To a precooled (0 °C) solution of diisopropylamine (1.7 equivalents) in anhydrous THF was added n-butyl lithium (2.3 M solution in hexane, 1.5 equivalents). The resulting solution was stirred at 0 °C for 30 min and then cooled down to -78 °C, before adding the ketone substrate (1.5 equivalents) in anhydrous THF dropwise *via* cannula. The reaction mixture was stirred for a further 15 min at this temperature, before the aldehyde component (1 equivalent) in anhydrous THF was added *via* cannula. The resulting solution was stirred at -78 °C for a further 15 minutes and then quenched by the addition of saturated ammonium chloride solution. The resulting reaction mixture was allowed to warm to room temperature and the two layers separated. The

aqueous layer was further extracted with ethyl acetate (3 × 50 ml) and the combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude residue which was further purified by flash column chromatography.

General Procedure B: Preparation of β -hydroxyenones

To a solution of the Weinreb amide in THF at – 40 °C, was added dropwise *via* cannula the respective Grignard reagent (3 to 7 equivalents) in THF. The reaction mixture was allowed to stir at 0 °C until completion as judged by TLC. The reaction mixture was then quenched at - 40 °C by the addition of saturated ammonium chloride solution. The reaction mixture was allowed to warm to room temperature and the two layers separated. The neutral aqueous layer was extracted with ethyl acetate (3 × 50 ml) and the combined organic layers were then dried (MgSO₄), filtered and concentrated *in vacuo* to a give residue which was further purified by flash column chromatography.

General Procedure C: Palladium (II) catalyzed cyclization reaction

A 25 ml Schlenk tube was charged with a palladium source (5-10 mol%), a co-oxidant (10 mol%) and an additive (10-200 mol%) and then evacuated and back-filled with oxygen (3x, balloon). The substrate, in DME (2-3 ml), was then added *via* cannula to the Schlenk tube. The resulting reaction mixture was heated to 50 °C and stirred at this temperature until completion. The reaction mixture was then allowed to cool down to room temperature, diluted with Et₂O and filtered through a sinter funnel. The filtrate was concentrated *in vacuo* to give a crude residue which was further purified by flash column chromatography.

(E)-6-hydroxy-8-phenyl-2-octen-4-one (1a): General procedure A was followed, employing 1.1 g of pent-3-en-2-one (11.2 mmol), 1.3 g of diisopropylamine (12.6 mmol), 4.86 ml of n-butyl lithium (11.2 mmol) and 1 g of 3-phenylpropionaldehyde (7.5 mmol). Purification by flash column chromatography on silica (1:3 EtOAc/hexane) afforded the title compound as a yellow oil (1.2 g, 74%). IR (film): 3438, 1661, 1630 cm⁻¹; ¹H NMR (CDCl₃) δ 1.69-1.77 (m, 1 H), 1.82-1.90 (m, 1 H), 1.92 (dd, ³J = 6.8, 1.5 Hz, 3 H), 2.65 (dd, ³J = 17.4, 8.8 Hz, 1 H), 2.68-2.78 (m, 1 H), 2.75 (dd, ³J = 17.4, 2.8 Hz, 1 H), 2.82-2.89 (m, 1 H), 3.34 (d, ³J = 3.3 Hz, 1 H), 4.07-4.14 (m, 1 H), 6.12 (dq, ³J = 15.7, 1.5 Hz, 1 H), 6.88 (dq, ³J = 15.7, 6.8 Hz, 1 H), 7.18-7.32 (m, 5 H), ¹³C NMR (CDCl₃) δ 18.34, 31.79, 38.12, 45.87, 67.01, 125.81, 128.37,

128.47, 132.16, 141.93, 144.12, 202.25; HRMS m/z calcd for $C_{14}H_{19}O_2$: 219.1385; found: 219.1391.

(Z)-6-hydroxy-8-phenyl-2-octen-4-one (1a): General procedure B was followed, employing 0.25 g of β -hydroxy-N-methoxy-N-methyl-benzenepentanamide (1.05 mmol) and 14.6 ml of 1-propenylmagnesium bromide (0.5 M in THF, 7.3 mmol, 7 equivalents) in dry THF (15 ml). The reaction was stirred at 0 °C for 4 hours. Purification by flash column chromatography on silica (1/3: EtOAc/hexane) afforded (*E*)-6-hydroxy-8-phenyl-2-octen-4-one (0.137g, 60%) and (*Z*)-6-hydroxy-8-phenyl-2-octen-4-one (0.066 g, 29%). For (*Z*)-6-hydroxy-8-phenyl-2-octen-4-one: IR (film): 3438, 1661, 1630 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.69-1.77 (m, 1H), 1.82-1.89 (m, 1 H), 2.14 (dd, $^3J = 7.3$, 1.7 Hz, 3 H), 2.60 (dd, $^3J = 18.1$, 8.1 Hz, 1 H), 2.65-2.75 (m, 2 H), 2.84 (m, 1 H), 3.34 (bs, 1 H), 4.07-4.14 (m, 1 H), 6.13 (dq, $^3J = 11.4$, 1.7 Hz, 1 H), 6.26 (dq, $^3J = 11.4$, 7.3 Hz, 1 H), 7.18-7.32 (m, 5 H), ^{13}C NMR ($CDCl_3$) δ 16.09, 31.75, 38.05, 50.21, 67.01, 125.81, 127.54, 128.37, 128.47, 141.93, 144.43, 202.25.

5-hydroxy-2-methyl-7-phenyl-1-hepten-3-one (1b): General procedure B was followed, employing 0.36 g of β -hydroxy-N-methyl-N-methoxy-benzenepentanamide (1.47 mmol) and 11.0 ml of isopropenylmagnesium bromide (1 M in THF, 11.0 mmol, 7 equivalents) in dry THF (12 ml). The reaction was stirred at 0 °C for 2 ½ hours. Purification by flash column chromatography on silica (1/3: EtOAc/hexane) afforded 5-hydroxy-2-methyl-7-phenyl-1-hepten-3-one (0.18 g, 55%). IR (film): 3430, 1670 and 1630 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.70-1.78 (m, 1 H), 1.85-1.92 (m, 1 H), 1.88 (t, $^3J = 1.1$ Hz, 3 H), 2.69-2.97 (m, 4 H), 3.25 (d, $^3J = 2.8$ Hz, 1 H), 4.07-4.14 (m, 1 H), 5.82 (q, $^3J = 1.5$ Hz, 1 H), 5.97 (s, 1 H), 7.18-7.32 (m, 5 H), ^{13}C NMR ($CDCl_3$) δ 17.26, 31.80, 38.09, 43.86, 67.08, 125.78, 125.82, 128.37, 128.46, 141.92, 144.54, 202.59; HRMS m/z calcd for $C_{14}H_{19}O_2$: 219.1385, found: 219.1392.

3-hydroxy-1-phenyl-dec-6-en-5-one (1c): General procedure A was followed, employing 0.73 ml of 3-hepten-2-one (5.6 mmol), 0.65 g of diisopropylamine (6.5 mmol), 2.43 ml of *n*-butyl lithium (5.6 mmol) and 0.5 g of 3-phenylpropionaldehyde (3.7 mmol). Purification by flash column chromatography (1:4 EtOAc/hexane) gave the title compound as a yellow oil (98%). 1H NMR ($CDCl_3$) δ 0.96 (t, $^3J =$

7.3 Hz, 3 H), 1.51 (q, $^3J = 7.3$ Hz, 2 H), 1.80 (m, 2 H), 2.21 (qd, $^3J = 7.3, 1.5$ Hz, 2 H), 2.60-2.90 (m, 4 H), 3.32 (d, $^3J = 3.03$ Hz, 1 H), 4.07-4.14 (m, 1 H), 6.09 (dt, $^3J = 15.9, 1.5$ Hz, 1 H), 6.82 (dt, $^3J = 15.9, 6.8$ Hz, 1 H), 7.17-7.30 (m, 5 H), ^{13}C NMR (CDCl_3) δ 13.69, 21.25, 31.79, 34.50, 38.11, 45.92, 67.00, 125.81, 128.37, 128.47, 130.66, 141.94, 148.85, 201.19.

6-hydroxy-6-phenyl-2-hexen-4-one (1d)⁴: General procedure A was followed, employing 0.65 ml of pent-3-en-2-one (5.6 mmol), 0.9 ml of diisopropylamine (6.4 mmol), 2.54 ml of n-butyl lithium (5.6 mmol) and 0.38 ml of benzaldehyde (3.7 mmol). Purification by flash column chromatography on silica (1:4 EtOAc/hexane) afforded the title compound as a colourless oil (0.48 g, 68 %). IR (film): 3450, 1736, 1661 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.92 (d, $^3J = 6.8$ Hz, 3 H), 2.95 (d, $^3J = 3.0$ Hz, 1 H), 2.96 (d, $^3J = 3.0$ Hz, 1 H), 3.60 (t, $^3J = 2.8$ Hz, 1 H), 5.18-5.23 (m, 1 H), 6.15 (dq, $^3J = 15.7, 1.5$ Hz, 1 H), 6.89 (dq, $^3J = 15.7, 6.8$ Hz, 1 H), 7.26-7.41 (m, 5 H), ^{13}C NMR (CDCl_3) δ 18.38, 48.05, 70.01, 125.67, 127.56, 127.60, 128.48, 132.09, 142.94, 144.50, 200.19; HRMS m/z calcd for $\text{C}_{12}\text{H}_{12}\text{O}$: 173.0966; found: 173.0958.

5-hydroxy-1-phenyl-hept-1-en-3-one (1e)⁵: General procedure A was followed, employing 1.63 g of trans-4-phenyl-but-3-en-2-one (11.2 mmol), 0.53 ml of propanal (7.45 mmol), 1.79 ml of diisopropylamine (12.7 mmol) and 4.85 ml of n-butyl lithium (2.3 M in hexane, 11.2 mmol). The reaction mixture was left to stir at -78 °C for 2 ½ hours. Purification by flash column chromatography on silica (1:4 EtOAc/hexane) gave the title compound as a yellow oil (57%). IR (film): 3451, 1652, 1608 cm^{-1} , ^1H NMR (CDCl_3) δ 1.00 (t, $^3J = 7.5$ Hz, 3 H), 1.40-1.65 (m, 2 H), 2.75 (dd, $^3J = 17.3, 9.1$ Hz, 1 H), 2.90 (dd, $^3J = 17.3, 2.7$ Hz, 1 H), 3.27 (d, $^3J = 3.3$ Hz, 1 H), 4.02-4.11 (m, 1 H), 6.72 (d, $^3J = 16.4$ Hz, 1 H), 7.40-7.44 (m, 3 H), 7.54-7.58 (m, 2 H), 7.59 (d, $^3J = 16.4$ Hz, 1 H), ^{13}C NMR (CDCl_3) δ 9.92, 29.39, 46.41, 69.20, 126.34, 128.39, 129.00, 130.76, 134.19, 143.51, 201.00; LRMS m/z for $\text{C}_{13}\text{H}_{17}\text{O}_2$: 205.17.

7-benzyloxy-6-hydroxy-hept-2-en-4-one (1f): General procedure was followed, employing 0.47 ml of benzyloxyacetaldehyde (3.3 mmol), 0.58 ml of pent-3-en-2-one (5.0 mmol), 0.80 ml of diisopropylamine (5.7 mmol) and 2.17 ml of n-butyl lithium (2.3 M in hexane, 5.0 mmol). Purification by flash column chromatography on silica (1:3 EtOAc/hexane) afforded the title compound (0.53g, 68%). IR (film): 3446, 1662 and 1629 cm^{-1} ;

^1H NMR (CDCl_3) δ 1.92 (dd, $^3J = 6.8, 1.5$ Hz, 3 H), 2.78 (d, $^3J = 6.1$ Hz, 2 H), 3.16 (d, $^3J = 3.8$ Hz, 1 H), 3.50 (dd, $^3J = 8.8, 5.6$ Hz, 1 H), 3.52 (dd, $^3J = 8.8, 4.8$ Hz, 1 H), 4.31 (m, 1 H), 4.56 (d, $^3J = 12.1$ Hz, 1 H), 4.59 (d, $^3J = 12.1$ Hz, 1 H), 6.14 (dq, $^3J = 15.7, 1.5$ Hz, 1 H), 6.90 (dq, $^3J = 15.7, 6.8$ Hz, 1 H), 7.28-7.39 (m, 5 H); ^{13}C NMR (CDCl_3) δ 18.31, 42.71, 67.05, 73.26, 73.40, 127.73, 128.41, 132.19, 137.96, 144.04, 198.84; HRMS m/z calcd for $\text{C}_{14}\text{H}_{19}\text{O}_3$: 235.1334; found: 235.1337.

5-hydroxy-7-phenyl-1-hepten-3-one (1g): General procedure B was followed, employing 0.25 g of β -hydroxy-N-methyl-N-methoxy-benzenepentanamide (1.05 mmol) and 3.16 ml of vinylmagnesium bromide (1 M in THF, 3.16 mmol, 3 equivalents) in dry THF (15 ml). The reaction mixture was left to stir at 0 °C for five hours. Purification by flash column chromatography on silica (1/3: EtOAc/hexane) afforded 5-hydroxy-7-phenyl-hept-3-one (0.148 g, 69%) as a pale yellow oil. IR (film): 3435, 1678 and 1613 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.70-1.78 (m, 1 H), 1.83-1.93 (m, 1 H), 2.69-2.79 (m, 2 H), 2.84 (dd, $^3J = 9.3, 4.0$ Hz, 1 H), 2.87 (dd, $^3J = 9.3, 5.2$ Hz, 1 H), 3.18 (bs, 1 H), 4.09-4.16 (m, 1 H), 5.91 (dd, $^3J = 10.4, 1.0$ Hz, 1 H), 6.24 (d, $^3J = 17.7$ Hz, 1 H), 6.47 (dd, $^3J = 17.7, 10.4$ Hz, 1 H), 7.19-7.33 (m, 5 H); ^{13}C NMR (CDCl_3) δ 31.77, 38.07, 45.87, 66.82, 125.86, 128.40, 128.46, 129.31, 136.66, 141.83, 201.33; HRMS m/z calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2$: 205.1228, found: 205.1230.

6-hydroxy-oct-2-en-4-one (1h): General procedure A was followed, employing 1.1 g of pent-3-en-2-one (11.2 mmol), 1.3 g of diisopropylamine (12.6 mmol), 4.86 ml of n-butyl lithium (11.2 mmol) and 0.43 g propanal (7.5 mmol). Purification by flash column chromatography on silica (2:3 Et_2O /Pentane) afforded the title compound as a yellow oil (71%). IR (film): 3428, 1667, 1629 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.95 (t, $^3J = 7.2$ Hz, 3 H), 1.50 (m, 2 H), 1.91 (dd, $^3J = 6.8, 1.7$ Hz, 3 H), 2.59 (dd, $^3J = 17.4, 9.2$ Hz, 1 H), 2.74 (dd, $^3J = 17.4, 2.7$ Hz, 1 H), 3.22 (bs, 1 H), 3.98 (m, 1 H), 6.12 (dq, $^3J = 15.7, 1.7$ Hz, 1 H), 6.89 (dq, $^3J = 15.7, 6.8$ Hz, 1 H); ^{13}C NMR (CDCl_3) δ 9.85, 18.30, 29.32, 45.45, 69.09, 132.23, 143.90, 201.04; HRMS m/z calcd for $\text{C}_8\text{H}_{15}\text{O}_2$: 143.1072; found 143.1067.

6-methyl-2-phenylethyl-2,3-dihydro-4H-pyran-4-one (2a):

General procedure C was followed, employing 0.25 g of (*E*)-6-hydroxy-8-phenyl-2-octen-4-one (1.14 mmol), 20.3 mg of PdCl₂ (0.1 mmol, 10 mol%), 11.28 mg of CuCl (0.11 mmol, 10 mol%) and 16.18 mg of di-sodium hydrogen phosphate (0.1 mmol, 10 mol%) in DME (4 ml). The reaction mixture was stirred at 50 °C for 5 hours. Purification by flash column chromatography on silica (1:4 EtOAc/hexane) afforded the title compound as a yellow oil (0.2 g, 79%). For (*Z*)-6-hydroxy-8-phenyl-2-octen-4-one, the same general procedure was followed and 20 hours of stirring at 50 °C also led to the formation of the title compound (0.15g, 59%, unoptimized yield). IR (film): 1674, 1615 cm⁻¹; ¹H NMR (CDCl₃) δ 1.97 (dddd, ³*J* = 16.5, 9.4, 7.1, 4.6 Hz, 1 H), 2.02 (s, 3 H), 2.14 (dtd, ³*J* = 17.1, 8.8, 5.8 Hz, 1 H), 2.38 (ddd, ³*J* = 16.7, 4.0, 1.1 Hz, 1 H), 2.45 (dd, ³*J* = 16.7, 12.8 Hz, 1 H), 2.72-2.90 (m, 2 H), 4.35 (m, 1 H), 5.31 (s, 1 H), 7.18-7.32 (m, 5 H); ¹³C NMR (CDCl₃) δ 21.06, 31.07, 36.03, 40.78, 78.16, 104.88, 126.19, 128.38, 128.54, 140.78, 174.22, 192.70; HRMS *m/z* calcd for C₁₄H₁₇O₂·, found 217.1229; found 217.1232.

2-phenylethyl-6-propyl-2,3-dihydro-4H-pyran-4-one (2c):

General procedure C was followed, employing 0.15 g of 3-hydroxy-1-phenyl-dec-6-en-5-one (0.61 mmol), 10.1 mg of PdCl₂ (0.061 mmol, 10 mol%), 6.03 mg of CuCl (0.061 mmol, 10 mol%) and 8.84 mg of di-sodium hydrogen phosphate (0.061 mmol, 10 mol%). The reaction mixture was stirred at 50 °C for 20 hours. Purification by flash column chromatography on silica (1:3 EtOAc/hexane) afforded the title compound as a pale yellow oil (76%). IR (film): 1665, 1604 cm⁻¹; ¹H NMR (CDCl₃) δ 0.98 (t, ³*J* = 7.3 Hz, 3 H), 1.61 (q, ³*J* = 7.3 Hz, 2 H), 1.91-2.20 (m, 2 H), 2.20-2.35 (m, 2 H), 2.35-2.51 (m, 2 H), 2.70-2.88 (m, 2 H), 4.33 (qq, ³*J* = 4.3 Hz, 1 H), 5.32 (s, 1 H), 7.18-7.35 (m, 5 H); ¹³C NMR (CDCl₃) δ 13.59, 19.75, 31.09, 36.04, 36.70, 41.03, 78.04, 104.23, 126.18, 128.37, 128.53, 140.78, 177.46, 148.85, 192.92; HRMS *m/z* calcd for C₁₆H₂₁O₂·, found 245.1542; found 245.1544.

6-methyl-2-phenyl-2,3-dihydro-4H-pyran-4-one (2d)¹:

General procedure C was followed, employing 0.19 g of 6-hydroxy-6-phenyl-2-hexen-4-one (1 mmol), 17.73 mg of PdCl₂ (0.1 mmol, 10 mol%), 9.89 mg of CuCl (0.1 mmol, 10 mol%) and 14.2 mg of di-sodium hydrogen phosphate (0.1 mmol, 10 mol%). The reaction mixture was stirred at 50 °C for 8 hours. Purification by flash column chromatography on silica (1:4 EtOAc/hexane) afforded the title compound as a yellow oil (0.16 g, 86%). IR (film): 1660, 1607 cm⁻¹; ¹H NMR (CDCl₃) δ 2.01 (s, 3 H), 2.59 (dt, ³J = 16.8 and 2.3 Hz, 1 H), 2.81 (ddd, ³J = 16.8 Hz, 14.4 and 2.0 Hz, 1 H), 5.39 (ddd, ³J = 14.4, 3.5 and 2.0 Hz, 1 H), 5.44 (s, 1 H), 7.36-7.44 (m, 5 H); ¹³C NMR (CDCl₃) δ 21.06, 42.36, 80.85, 105.21, 126.16, 128.80, 138.19, 174.28, 192.29; HRMS *m/z* calcd for C₁₂H₁₃O₂: 189.0916, found: 189.0914.

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2-ethyl-6-phenyl-2,3-dihydro-4H-pyran-4-one (2e):

General Procedure C was followed, employing 0.146 g of 5-hydroxy-1-phenyl-hept-1-en-3-one (0.71 mmol), 12.67 mg of PdCl₂ (0.07 mmol, 10 mol%), 7.07 mg of CuCl (0.07 mmol, 10 mol%) and 10.14 mg (0.07 mmol, 10 mol%) of di-sodium hydrogen phosphate. The reaction reached completion after stirring for 9 days at 50 °C. Purification by flash column chromatography (1:3 EtOAc/hexanes) gave the title compound as a yellow oil (43%). IR (film): 1660 and 1602 cm⁻¹; ¹H NMR (CDCl₃) δ 1.12 (t, ³J = 7.5 Hz, 3 H), 1.82 (qd, ³J = 7.5, 2.4 Hz, 1 H), 1.94-2.02 (m, 1 H), 2.50 (ddd, ³J = 16.7, 14.1, 0.7 Hz, 1 H), 2.57 (dd, ³J = 16.7, 12.6 Hz, 1 H), 4.45-4.53 (m, 1 H), 6.01 (s, 1 H), 7.42-7.51 (m, 3 H), 7.73-7.77 (m, 2 H); ¹³C NMR (CDCl₃) δ 9.55, 27.65, 41.01, 80.72, 101.96, 126.49, 128.64, 131.58, 132.87, 170.25, 193.61; HRMS *m/z* calcd for C₁₃H₁₅O₂: 203.1072; found 203.1072.

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2-benzyloxymethyl-6-methyl-2,3-dihydro-4H-pyran-4-one

(2f): General Procedure C was followed, employing 0.25 g of 7-benzyloxy-6-hydroxy-hept-2-en-4-one (1.07 mmol), 18.92 mg of PdCl₂ (0.11 mmol, 10 mol%), 10.56 mg of CuCl (0.11 mmol, 10 mol%) and 15.05 mg (0.11 mmol, 10 mol%) of di-sodium hydrogen phosphate (0.11 mmol, 10

mol%). The reaction mixture was stirred at 50 °C for 6 hours. Purification by flash column chromatography on silica (1:3 EtOAc/hexane) afforded the title compound as a pale yellow oil (0.19 g, 75%). IR (film): 1660 and 1606 cm⁻¹; ¹H NMR (CDCl₃) δ 2.04 (s, 3 H), 2.34 (ddd, ³J = 16.7, 3.8, 1.0 Hz, 1 H), 2.64 (dd, ³J = 16.7, 13.9 Hz, 1 H), 3.69 (dd, ³J = 10.9, 4.0 Hz, 1 H), 3.72 (dd, ³J = 10.9, 5.2 Hz, 1 H), 4.51-4.59 (m, 1 H), 4.60 (d, ³J = 12.1 Hz, 1 H), 4.65 (d, ³J = 12.1 Hz, 1 H), 5.33 (s, 1 H), 7.30-7.40 (m, 5 H); ¹³C NMR (CDCl₃) δ 21.02, 37.36, 70.71, 73.52, 78.09, 104.95, 127.70, 128.49, 137.53, 137.53, 174.03, 192.26; HRMS *m/z* calcd for C₁₄H₁₇O₃: 233.1178, found: 233.1180.

2-phenylethyl-2,3-dihydro-4H-pyran-4-one (2g)⁶: General procedure C

was followed, employing 50 mg of 5-hydroxy-7-phenyl-1-hepten-3-one (0.25 mmol), 4.4 mg of PdCl₂ (0.025, 10 mol%), 2.5 mg of CuCl (0.025, 10 mol%) and 3.5 mg of di-sodium hydrogen phosphate (0.025 mmol, 10 mol%). The reaction mixture was stirred at 50 °C for 6 hours. Purification by column chromatography on silica (2:3 EtOAc/hexane) gave a inseparable mixture of 2-phenylethyl-2,3-dihydro-4H-pyran-4-one and 5-hydroxy-7-phenyl-heptan-3-one (65 mg, 0.30 mmol) in 60 % yield, containing 70 % of the cyclic product and 30 % of the reduced by-product respectively. For 2-phenylethyl-2,3-dihydro-4H-pyran-4-one: IR (film): 1660 and 1593 cm⁻¹; ¹H NMR (CDCl₃) δ 1.99 (dddd, ³J = 16.5, 9.4, 7.1, 4.6 Hz, 1 H), 2.11 (dtd, ³J = 17.1, 8.8, 5.8 Hz, 1 H), 2.40 (ddd, ³J = 16.7, 4.0, 1.1 Hz, 1 H), 2.51 (dd, ³J = 16.7, 13.2 Hz, 1 H), 2.65-2.90 (m, 2 H), 4.35 (m, 1 H), 5.42 (dd, ³J = 6.0, 1.1 Hz, 1 H), 7.10-7.21 (m, 3 H), 7.22-7.34 (m, 2 H), 7.40 (d, ³J = 6.0 Hz, 1 H); ¹³C NMR (CDCl₃) δ 30.95, 36.04, 41.85, 78.44, 107.08, 126.25, 128.38, 128.58, 140.65, 163.19, 192.49; HRMS *m/z* calcd for C₁₃H₁₅O₂: 203.1072; found: 203.1064 and for the reduced by-product 5-hydroxy-7-phenyl-heptan-3-one: ¹H NMR (CDCl₃) δ 1.06 (t, ³J = 7.3 Hz, 3 H), 1.70 (m, 1 H), 1.82 (m, 1 H), 2.45 (q, ³J = 7.3 Hz, 2 H), 2.50-2.60 (m, 2 H), 2.65-2.90 (m, 2 H), 4.06 (m, 1 H), 7.10-7.21 (m, 3 H), 7.22-7.34 (m, 2 H), ¹³C NMR (CDCl₃) δ 7.52, 31.74, 36.75, 38.04, 48.54, 60.87, 125.85, 128.38, 128.58, 141.85, 212.50; HRMS *m/z* calcd for C₁₃H₁₉O₂: 207.1385, found: 207.1402.

2-ethyl-6-methyl-2,3-dihydro-pyran-4-one (2h)³: General procedure C was

followed, employing 160 mg of 6-hydroxy-oct-2-en-4-one (1.1 mmol), 20.1 mg of PdCl₂ (0.1 mmol, 10 mol%), 11.32 mg of CuCl (0.11 mmol, 10 mol%) and 16.07 mg of di-sodium hydrogen

phosphate (0.1 mmol, 10 mol%). The reaction reached was stirred at 50 °C for 10 hours. Purification by flash column chromatography on silica (2:3 Et₂O/pentane) afforded the title compound as a yellow oil (0.081g, 52%). IR (film): 1668 and 1615 cm⁻¹; ¹H NMR (CDCl₃) δ 1.03 (t, ³J = 7.4 Hz, 3 H), 1.72 (m, 1 H), 1.82 (m, 1 H), 2.05 (s, 3 H), 2.35 (dd, ³J = 16.6, 4.8 Hz, 1 H), 2.41 (dd, ³J = 16.6, 12.1 Hz, 1 H), 4.29 (ddt, ³J = 12.1, 6.8 and 5 Hz, 1 H), 5.27 (s, 1 H); ¹³C NMR (CDCl₃) δ 9.21, 21.02, 27.48, 40.33, 80.38, 104.72, 177.4, 201.74; HRMS *m/z* calcd for C₈H₁₃O₂: 141.0916; found 141.0916.

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