

Supporting Information

**Synthesis and Assignment of Absolute Stereochemistry of (–)-Oleocanthal: A Potent,
Naturally Occurring Non-Steroidal Anti-Inflammatory and Anti-Oxidant Agent Derived
from Extra Virgin Olive Oils**

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Materials and Methods. Reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. *n*-Butyllithium and *t*-butyllithium were purchased from Aldrich. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040 – 0.062 mm) supplied by Silicycle and Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Infrared spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. Proton and carbon-13 NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26), methanol (δ 3.31), acetonitrile (δ 1.94), DMSO (δ 2.50), or benzene (δ 7.15) for ¹H NMR and either chloroform (δ 77.0), methanol (δ 49.2), acetonitrile (δ 118.7), DMSO (δ 39.5), or benzene (δ 128.0) for ¹³C NMR. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center.

Cyclopentenone (–)-14. To a 500 mL round-bottom flask was added the first generation Grubbs catalyst (650 mg, 1 mol %) and a solution of diene (–)-**13** (14.9 g, 80 mmol) in 200 mL CH₂Cl₂. The reaction was stirred at room temperature for 4 h and PCC (35 g, 2.0 equiv.) was added. After 12 h, the reaction mixture was diluted with 200 mL ether and Florisil gel (20 g) was added. The reaction was filtered through a short plug of Florisil gel and concentrated *in vacuo*. A short plug of silica using 30 % ethyl acetate/hexanes as eluant to remove baseline material afforded (–)-**14** (10.5 g, 87% yield) as white crystals. *R_f* 0.46 (40% ethyl acetate/hexanes); [α]_D²⁰ –69.4 (*c* = 0.60, CHCl₃); mp = 69–70 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.62 (dd, *J* = 2.4, 6.0 Hz, 1H), 6.22 (d, *J* = 6.0 Hz, 1H), 5.28 (dd, *J* = 2.4, 5.6 Hz, 1H), 4.47 (d, *J* = 5.6 Hz, 1H), 1.42 (s, 3H), 1.41 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 203.2, 159.6, 134.5, 115.5, 78.7, 76.5, 27.5, 26.2; IR (neat) 2987.4, 2935.9, 1730.4, 1591.2, 1378.5, 1222.3, 1084.5, 852.1 cm^{–1}; HRMS (CI) calcd for C₈H₁₀O₃ 154.0630, found 154.0645. For (+)-**14**, same procedure from (+)-**13**, [α]_D²⁰ +69.5 (*c* = 0.85, CHCl₃), all other data the same.

Cyclopentanone (–)-10. A mixture of (–)-**14** (1.00 g, 6.32 mmol) and 10% Pd/C (100 mg, 10 wt %) in ethyl acetate (100 mL) was flushed with hydrogen at room temperature. The reaction was stirred under a hydrogen atmosphere (maintained with a balloon) overnight. The flask was then flushed with air and the mixture filtered through a Celite cake and concentrated *in vacuo* to afford (–)-**10** (0.94 g, 95% yield) as white crystals. *R_f* 0.46 (40% ethyl acetate/hexanes); [α]_D²⁰ –251.7 (*c* = 0.58, CHCl₃); mp = 51–52 °C; ¹H NMR (500 MHz, CDCl₃) δ 4.82 (app t, *J* = 4.7 Hz, 1H), 4.16 (d, *J* = 5.1 Hz, 1H), 2.60 (m, 1H), 2.27 (m, 2H), 2.05 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 214.6, 111.7, 78.8, 77.3, 32.8, 26.6, 24.7, 23.2; IR (neat) 2987.9, 2937.9, 1750.8, 1374.5, 1215.3, 1084.5, 864.4 cm^{–1}; HRMS (CI) calcd for C₈H₁₂O₃ 156.0786, found 156.0779. For (+)-**10**, same procedure from (+)-**14**, [α]_D²⁰ +271.1 (*c* = 0.87, CHCl₃), all other data the same.

Methyl ester (–)-16. A solution of LHMDs (1M in THF, 4.07 mL, 1.1 equiv) in THF (20 mL) was cooled to –78 °C and a solution of enone (–)-**10** (580 mg, 3.7 mmol) in THF (15 mL) at –78 °C was slowly added via cannula. After 40 min, HMPA (1.93 mL, 3.0 equiv) was added followed by Me₂Zn (2M in toluene, 1.85

mL, 1.0 equiv). After 20 min, methyl bromoacetate (1.05 mL, 3.0 equiv) was added dropwise and the reaction was allowed to warm to $-45\text{ }^{\circ}\text{C}$. After 4 h at $-45\text{ }^{\circ}\text{C}$, the solution was quenched with saturated aq. NH_4Cl . The mixture was extracted twice with ether, and the combined extracts were washed with water, brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Flash chromatography, using 15% ethyl acetate/hexanes as eluant, gave 477 mg (57% yield) of ester (–)-**16** as an amber oil. R_f 0.39 (40% ethyl acetate/hexanes); $[\alpha]_D^{20} -136.8$ ($c = 1.30$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 4.81 (app t, $J = 4.9$ Hz, 1H), 4.31 (d, $J = 5.3$ Hz, 1H), 3.67 (s, 3H), 2.88 (m, 1H), 2.69 (d, $J = 5.3$ Hz, 2H), 2.37 (dd, $J = 9.1$, 14.2 Hz, 1H), 1.88 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 214.2, 172.1, 112.1, 78.9, 76.0, 51.9, 39.6, 33.3, 29.8, 26.8, 24.8; IR (neat) 2988.4, 2953.3, 1732.9, 1438.8, 1373.4, 1198.7, 1074.2, 850.6 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{16}\text{O}_5\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 251.0895, found 251.0893. For (+)-**16**, same procedure from (+)-**10**, $[\alpha]_D^{20} +137.5$ ($c = 1.25$, CHCl_3), all other data the same.

Alkene (–)-17. A suspension of ethyl triphenylphosphonium bromide (1.50 g, 4.0 mmol) in THF (2.0 mL) at $0\text{ }^{\circ}\text{C}$ was added LDA (2M in THF, 2 mL, 4.0 mmol). The resulting red solution was stirred at $0\text{ }^{\circ}\text{C}$ for 30 min and then at room temperature for 1 h. The reaction was cooled to $-45\text{ }^{\circ}\text{C}$, and a $-45\text{ }^{\circ}\text{C}$ solution of (–)-**16** (228 mg, 1.0 mmol) in THF (2.0 mL) was slowly added via cannula. After 2 h at $-45\text{ }^{\circ}\text{C}$, the reaction was quenched with saturated aq. NH_4Cl . The mixture was extracted twice with ether, and the combined extracts were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. A short plug of silica to remove the baseline material was followed by flash chromatography using 10% ethyl acetate/hexanes as eluant, to afford 102 mg (42% yield, >10:1 E:Z ratio) of alkene (–)-**17** as an amber oil. R_f 0.73 (40% ethyl acetate/hexanes); $[\alpha]_D^{20} -128.4$ ($c = 0.75$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 5.71 (q, $J = 7.1$ Hz, 1H), 4.79 (d, $J = 5.6$ Hz, 1H), 4.62 (m, 1H), 3.68 (s, 3H), 3.36 (br s, 1H), 2.60 (dd, $J = 4.7$, 15.4 Hz, 1H), 2.29 (dd, $J = 9.6$, 15.4 Hz, 1H), 2.11 (m, 1H), 1.82 (m, 1H), 1.71 (d, $J = 7.1$ Hz, 3H), 1.44 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.5, 143.4, 125.3, 111.2, 82.8, 79.2, 51.5, 38.8, 36.7, 36.0, 27.6, 25.6, 14.2; IR (neat) 2932.6, 1735.5, 1437.6, 1370.1, 1209.4, 1162.4, 1075.7 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{20}\text{O}_4\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 263.1259, found 263.1270. For (+)-**17**, same procedure from (+)-**16**, $[\alpha]_D^{20} +134.2$ ($c = 1.10$, CHCl_3), all other data the same.

Acid (–)-18. A solution of methyl ester (–)-17 (60 mg, 0.25 mmol) in a 1:1 mixture of THF/MeOH (2 mL) at room temperature was added a freshly prepared aq. LiOH solution (1.0 M, 1 mL). After 2 h, the reaction was diluted with water, extracted three times with ether, and the combined extracts were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to furnish an amber oil (56 mg, quantitative yield). *R*_f 0.21 (40% ethyl acetate/hexanes); [α]_D²⁰ –53.6 (*c* = 1.10, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.73 (q, *J* = 7.1 Hz, 1H), 4.79 (d, *J* = 5.1 Hz, 1H), 4.62 (m, 1H), 3.31 (br s, 1H), 2.66 (dd, *J* = 4.5, 15.7 Hz, 1H), 2.33 (dd, *J* = 9.7, 15.7 Hz, 1H), 2.15 (m, 1H), 1.82 (m, 1H), 1.71 (d, *J* = 7.1 Hz, 3H) 1.44 (s, 3H), 1.32 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 177.4, 143.3, 123.7, 111.2, 82.9, 79.2, 38.7, 36.7, 35.8, 27.6, 25.6, 14.3; IR (neat) 3330.0, 2933.8, 1709.9, 1379.9, 1210.8, 1154.4, 1059.7 cm^{–1}. For (+)-18, same procedure from (+)-17, [α]_D²⁰ +59.0 (*c* = 0.90, CHCl₃), all other data the same.

Phenol (–)-19. A solution of (–)-18 (23 mg, 0.10 mmol), 4-hydroxyphenethyl alcohol (14 mg, 1.0 equiv) and triphenylphosphine (105 mg, 4.0 equiv) in THF (3 mL) at 0 °C was added diethylazodicarboxylate (63 μ L, 4.0 equiv). The reaction was stirred at room temperature overnight. Concentration *in vacuo* followed by flash chromatography with 30% ethyl acetate/hexanes afforded (–)-19 (32 mg, 92% yield) as a colorless oil. *R*_f 0.46 (40% ethyl acetate/hexanes); [α]_D²⁰ –73.8 (*c* = 1.00, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.05 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 5.70 (q, *J* = 7.1 Hz, 1H), 5.48 (br s, 1H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.62 (app dt, *J* = 5.6, 3.8 Hz, 1H), 4.23 (t, *J* = 7.1 Hz, 2H), 3.30 (br s, 1H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.55 (dd, *J* = 4.7, 15.3 Hz, 1H), 2.23 (dd, *J* = 9.7, 15.3 Hz, 1H), 2.05 (m, 1H), 1.83 (m, 1H), 1.77 (d, *J* = 7.1, 3H) 1.44 (s, 3H), 1.31 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 154.5, 143.2, 129.9, 123.5, 115.4, 111.2, 82.8, 79.2, 65.1, 39.0, 36.6, 36.0, 34.2, 27.6, 25.6, 14.2; IR (neat) 3393.9, 2925.5, 2854.7, 1732.3, 1516.5, 1271.0, 1158.8, 1075.5 cm^{–1}; HRMS (ESI) calcd for C₂₀H₂₆O₅Na (M + Na)⁺ 369.1678, found 369.1827. For (+)-19, same procedure from (+)-18, [α]_D²⁰ +82.5 (*c* = 0.75, CHCl₃), all other data the same.

Oleocanthal (–)-1. A solution of (–)-19 (31 mg, 0.09 mmol) in CH₃CN (1 mL) was added 4N HCl (0.5 mL) and the solution was stirred at room temperature for 1 h. The reaction was diluted with water and

extracted with ethyl acetate three times, and the combined extracts were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. A solution of the resulting diol in CH_2Cl_2 (1.5 mL) at 0 °C was added dropwise to an aqueous solution of NaIO_4 (28 mg, 1.4 equiv in 1 mL water). After 40 min at room temperature, the reaction mixture was diluted with water, and extracted twice with CH_2Cl_2 . The combined extracts were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. A short plug of silica with 30% ethyl acetate/hexanes afforded (–)-**1** (20 mg, 75% yield for two steps) as a colorless oil. R_f 0.52 (60% ethyl acetate/hexanes); $[\alpha]_D^{20}$ –0.78 ($c = 0.90$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 9.64 (s, 1H), 9.24 (d, $J = 2.0$ Hz, 1H), 7.04 (d, $J = 8.3$ Hz, 2H), 6.74 (d, $J = 8.5$ Hz, 2H), 6.64 (q, $J = 7.1$ Hz, 1H), 4.19 (m, 2H), 3.65 (m, 1H), 2.90 (m, 1H), 2.78 (t, $J = 7.0$ Hz, 2H), 2.72 (m, 2H), 2.65 (m, 1H), 2.08 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 200.4, 195.1, 171.9, 154.3, 154.2, 143.4, 129.5, 130.1, 115.4, 65.2, 46.3, 36.9, 34.2, 27.3 15.2; IR (neat) 3351.2, 2924.2, 1723.6, 1675.1, 1516.1, 1226.6 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{O}_5\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 327.1208, found 327.1217. For unnatural (+)-**1**, same procedure from (+)-**19**, $[\alpha]_D^{20}$ +0.73 ($c = 0.55$, CHCl_3), all other data the same.