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Synthesis of (±)-oleocanthal via a tandem intramolecular Michael cyclization–HWE olefination

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ABSTRACT

A synthesis of racemic oleocanthal has been accomplished in 11 steps from 1,3 propanediol by a key tandem intramolecular Michael cyclization–Horner–Wadsworth–Emmons olefination.

The secoiridoids are a class of plant-derived monoterpenes containing the substituted pyran core of secologanin (**1**). This class of natural products arises in biological systems from the oxidative cleavage of the loganin skeleton (**2**) by the cytochrome P450 enzyme secologanin synthase (Fig. 1).[1] Secologanin then undergoes various modifications to produce a wide array of structures displaying diverse biological activities including analgesic[2], anti-inflammatory[3], anti-arthritic[4], anti-allergenic[5], antibacterial[6], and antiviral[7] activities. Coupling of the simple secoiridoids with tryptamine gives rise to a large class (>250 examples) of indole and oxindole alkaloids including geissoschizine, strychnine, reserpene, ajmaline, and the Vinca alkaloids with highly varied carbon frameworks and biological profiles.

We reasoned that, given the structural similarities of the secologanin-derived natural products, synthetic access to the more complex secoiridoid and secologanin tryptamine alkaloids could be obtained through a single strategically functionalized intermediate. As a test case for our strategy, our attention focused on the secoiridoid oleocanthal (**3**) for both its relative structural simplicity that retains the compact arrangement of functionality of the secoiridoids and its demonstrated potency as an inhibitor of the COX-1 and COX-2 enzymes[3,8], making it an ideal entry point into the synthesis of this class of natural products. Important to our retrosynthetic analysis was proceeding through an intermediate with functionalities that could be independently manipulated allowing for future adaptation of this synthesis to produce a diverse selection of natural product targets. Lactone **5** appeared ideal for this purpose as it contained the requisite carbon backbone as well as properly situated synthetic handles with orthogonal reactivities.

We envisioned the dialdehyde moiety of **3** arising from the reduction and oxidation of lactone **5** whose carbon framework could be assembled through a key tandem Michael cyclization and Horner–Wadsworth–Emmons (HWE) olefination[9] of phosphonoacetic ester **6** (Scheme 1). This allows for the simultaneous assembly of the desired lactone core, the addition of the two-carbon olefin sidechain, and the introduction of a stereogenic center. Studies to control the absolute configuration of this new stereogenic center through the introduction of chiral auxiliaries are currently underway.

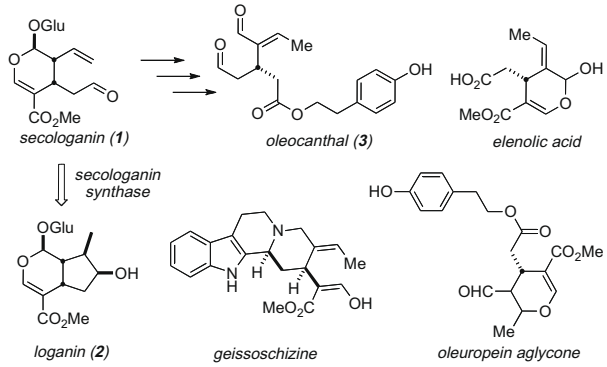
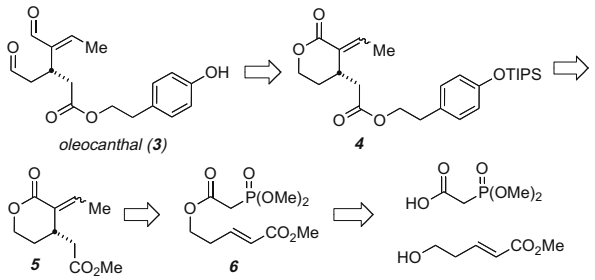


Figure 1. Structures of several secologanin derivatives.



Scheme 1. Retrosynthetic analysis.

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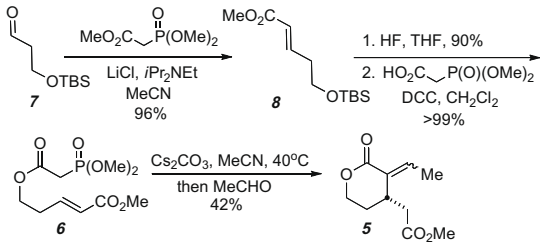


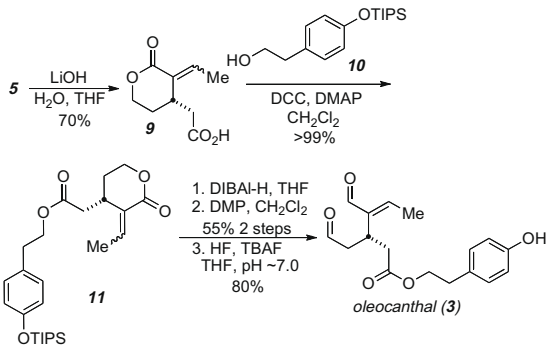
Scheme 2. Synthesis of lactone **5**.

Assembly of lactone **5** began with the synthesis of aldehyde **7** from 1,3-propanediol utilizing the method reported by Schaus and coworkers.[10] Reaction of **7** with commercially available trimethyl acetophosphonate under Masamune-Roush conditions produced the unsaturated ester **8** as a single isomer and in good yield (Scheme 2). Deprotection and subsequent esterification gave the desired substrate **6**, which upon treatment with Cs_2CO_3 and acetaldehyde in warm acetonitrile underwent sequential intramolecular Michael cyclization and HWE olefination to yield lactone **5** as an inconsequential 1.6:1 mixture of *E*/*Z* isomers.

Selective hydrolysis of the methyl ester of **5** yielded acid **9** that was esterified with protected tyrosol **10** affording lactone **11**, which upon reduction and Dess–Martin oxidation gave the dialdehyde precursor to oleocanthal as a single isomer (Scheme 3). This sensitive dialdehyde rapidly decomposed when treated with standard deprotection conditions (HF, HF-pyr, and TBAF) but underwent clean deprotection to furnish (±)-oleocanthal when the neutral conditions described in the literature by Smith et al. were employed (HF, TBAF aqueous THF at pH 7).[2]

We have demonstrated a short and scalable synthesis of (±)-oleocanthal, which can be readily adapted to allow access to a diverse selection of secoiridoid natural products. Current efforts are underway both to control the absolute stereochemistry of the key intramolecular Michael cyclization step of this approach and then to employ this method to synthesize several secoiridoids and secologanin tryptamine alkaloids.

Synthesis of ester **8**: To a flame dried 2 L round-bottomed flask (RBF) charged with 20.98 mL (121.3 mmol, 1.1 equiv) methyl 2-(dimethoxyphosphoryl)acetate dissolved in 1000 mL dry MeCN were added 6.170 g (145.5 mmol, 1.2 equiv) LiCl and then 21.12 mL (121.3 mmol, 1.2 equiv) *i*Pr_2NEt. The reaction was stirred at ambient temperature for 15 min and then 22.84 g (121.3 mmol, 1 equiv) aldehyde **7** dissolved in a minimum of MeCN was added. After stirring for 4 h the reaction was concentrated to approximately 50% volume, added to brine, and extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel chromatography eluting with 4:1 hex./EtOAc to yield 28.56 g (96%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (dt, J = 15.6, 7.2 Hz, 1H), 5.87 (dt, J = 15.9, 1.5 Hz, 1H), 3.71 (s, 3H), 3.70 (m, 2H), 2.40 (qd, J = 6.6, 1.8 Hz, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 167.1, 146.4, 122.7, 61.7, 51.6, 35.9, 26.0, 18.5, −5.2; IR (NaCl, film): 1729, 1660 cm^{-1}; HRMS (+TOF): $[M+H]^+$ 245.1568 calcd for $C_{12}H_{25}O_3Si$, found: 245.1571; R_f = 0.40 (9:1 hex./EtOAc).



Scheme 3. Synthesis of (±)-oleocanthal.

Synthesis of phosphonate **6**: To a 1 L HDPE bottle was added 24.85 g (101.7 mmol, 1 equiv) (*E*)-methyl 5-(*tert*-butyldimethylsilyloxy)pent-2-enoate (**8**) dissolved in 500 mL dry THF followed by 53 mL HF as a 48% solution in H_2O. The reaction was stirred for 6 h at ambient temperature, then slowly added to $NaHCO_{3(satd)}$, and extracted twice with EtOAc. Combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue was dissolved in 1:1 hex./EtOAc and filtered through a short silica gel plug. Concentration yielded 11.90 g (90%) of the desired alcohol as a pale yellow oil.

An oven-dried 100 mL RBF was charged with 2.940 g (22.58 mmol, 1 equiv) of the above alcohol, 4.560 g (27.11 mmol, 1.2 equiv) 2-(dimethoxyphosphoryl)acetic acid, and 45 mL dry CH_2Cl_2. To this was added 5.590 g (27.11 mmol, 1.2 equiv) DCC dissolved in a minimum volume of CH_2Cl_2. The reaction was stirred for 45 min at ambient temperature before being filtered through a Celite pad and concentrated. Purification by flash chromatography eluting with EtOAc yielded 6.310 g (>99%) of **6** as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (dt, J = 15.6, 6.9 Hz, 1H), 5.83 (dt, J = 15.9, 1.5 Hz, 1H), 4.18 (t, J = 6.3 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 2.91 (d, J_{HP} = 21.6 Hz, 2H), 2.49 (qd, J = 6.6, 1.5 Hz, 2H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 166.6, 165.7, 144.1, 123.5, 63.6, 53.4, 51.7, 34.3, 32.5, 31.4; IR (NaCl, film): 1724, 1660; HRMS (+TOF) calcd for $C_{10}H_{18}O_7P$ $[M+H]^+$ 281.0785, found 281.0788; R_f = 0.18 (EtOAc).

Synthesis of lactone **5**: To 179 mg (0.639 mmol, 1 equiv) (*E*)-methyl 5-(2-(diethoxyphosphoryl)acetoxy)pent-2-enoate (**6**) dissolved in 3 mL dry MeCN in an oven-dried 25 mL RBF was added 416 mg (1.28 mmol, 2 equiv) Cs_2CO_3. The reaction was heated to reflux for 1.5 h, cooled to 0 °C, and 107 μL (1.92 mmol, 3 equiv) freshly distilled acetaldehyde was added in a single portion. The reaction was vigorously stirred for 16 h at ambient temperature and was then acidified with 1 N HCl. This mixture was extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography eluting with 2:1 to 1:1 hex./EtOAc to yield 53.0 mg (42%) of **5** (1.6:1 *E*/*Z*) as a yellow oil.

Synthesis of lactone **11**: To 69.0 mg (0.345 mmol, 1 equiv) crude lactone **5** dissolved in 2 mL 3:1 THF:H_2O in a 10 mL RBF was added 25.0 mg (1.03 mmol, 3 equiv) LiOH. The reaction was stirred at ambient temperature for 2 h and then acidified with 1 N HCl. This mixture was extracted thrice with EtOAc, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel flash chromatography eluting with 1:1:0.01 to 0:1:0 hex./EtOAc/HOAc to yield 44.0 mg (70%) of the desired acid as an inseparable mixture (1.6:1 *E*/*Z*) of *E*/*Z* isomers as a pale yellow oil.

To 36.0 mg (0.193 mmol, 1 equiv) of the above acid dissolved in 2 mL dry CH_2Cl_2 in an oven-dried 10 mL RBF and cooled to 0 °C was added 85.0 mg (0.290 mmol, 1.5 equiv) 2-(4-(triisopropylsilyloxy)phenyl)ethanol (**10**) followed by 60.0 mg (0.290 mmol, 1.5 equiv) DCC and a spatula tip of DMAP. The reaction was stirred for 16 h at ambient temperature, filtered through Celite, concentrated, and purified by silica gel flash chromatography eluting with 2:1 hex./EtOAc to yield 89.0 mg (>99%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *Z*-isomer δ 7.05 (m, 2H), 6.82 (m, 2H), 6.19 (qd, J = 7.2, 1.5 Hz, 1H), 4.26 (t, J = 6.9 Hz, 2H), 4.11 (td, J = 9.0, 3.6 Hz, 1H), 3.81 (m, 1H), 3.09 (m, 1H), 2.84 (dt, J = 17.1, 6.9 Hz, 3H), 2.44 (ddd, J = 15.6, 8.9, 6.3 Hz, 2H), 2.04 (dd, J = 7.2, 1.2 Hz, 3H), 1.24 (m, 3H), 1.10 (s, 18H), *E*-isomer δ

7.01–7.09 (m, 3H), 6.79 (m, 2H), 4.24–4.38 (m, 3H), 4.16 (m, 1H) 3.32 (m, 1H), 2.85 (t, J = 7.2 Hz, 2H), 2.41 (m, 2H), 1.83 (d, J = 7.5 Hz, 3H), 1.70 (m, 2H), 1.22 (m, 3H), 1.07 (m, 18H); ^{13}CNMR (75 MHz, $CDCl_3$) mixture of isomers δ 172.4, 171.4, 166.5, 154.9, 142.1, 139.6, 133.8, 130.2, 129.9, 129.8, 120.1, 120.1, 68.2, 65.5, 38.0, 34.4, 34.1, 29.6, 27.4, 27.0, 25.8, 25.2, 18.3, 14.4, 12.8; IR (NaCl, film) 1732, 1511 cm^{-1}; HRMS (+TOF) calcd for $C_{26}H_{41}O_5Si$ $[M+H]^+$ 461.2728, found 461.2722; R_f = 0.24 (2:1 hex./EtOAc).

*Synthesis of oleocanthal (**3**)*: To 47.0 mg (0.102 mmol, 1 equiv) (*S*)-4-(triisopropylsilyloxy)phenethyl 2-(3-ethylidene-2-oxotetrahydro-2*H*-pyran-4-yl)acetate (**11**) dissolved in 1 mL dry THF in a 10 mL flame-dried RBF at −78 °C was slowly added 102 μL of a 1 M solution of DIBAL in toluene. After stirring the reaction for 1 h at −78 °C 100 μL dry MeOH was added, the reaction was allowed to warm to ambient temperature, and 5 mL saturated Rochelle's salt solution was added. After stirring for 30 min this mixture was extracted thrice with EtOAc, dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography eluting with 4:1 hex./EtOAc to yield 48 mg of the desired alcohol as a colorless oil.

This residue was dissolved in 1 mL dry CH_2Cl_2, charged to a 10 mL oven-dried RBF, and cooled to 0 °C. To this solution was added 65.0 mg (0.153 mmol, 1.5 equiv) Dess–Martin periodinane and the reaction was stirred for 3 h at ambient temperature before the addition of 5 mL 5:1 $Na_2S_2O_{3(satd)}$:$NaHCO_{3(satd)}$ solution. This mixture was stirred for 15 min before being extracted thrice with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography eluting with 4:1 hex./EtOAc yielded 26.0 mg (55%) of the desired dialdehyde as a colorless oil.

To 7.0 mg of the above dialdehyde dissolved in 250 μL dry THF at 0 °C was added 50 μL of a solution prepared by the addition of 40% $HF_{(aq)}$ to a 1 M THF solution of TBAF until the pH of the resulting solution reached 7 as evidenced by pH paper. The reaction was stirred for 2 h at 0 °C, added to brine, and extracted thrice with EtOAc. Combined organic layers were dried over Na_2SO_4, concentrated, and taken up in 1:2 hex./EtOAc. This solution was filtered through a short plug of silica gel and concentrated to yield 3.7 mg (80%) of (±)-oleocanthal as a colorless film. All spectral properties matched data reported in the literature.[8]

Acknowledgments

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