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Syntheses of (−)-Oleocanthal, a Natural NSAID Found in Extra Virgin Olive Oil, the (−)-Deacetoxy-Oleuropein Aglycone, and Related Analogues

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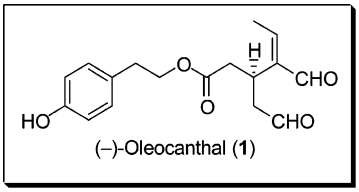
Received May 30, 2007



Phenolic compounds extracted from extra virgin olive oil have attracted considerable recent attention. One of the components, (−)-oleocanthal (**1**), an inhibitor of the COX-1 and COX-2 enzymes, possesses similar potency as the NSAID ibuprofen. In this, a full account, we disclose the first- and now second-generation syntheses of both enantiomers of the oleocanthals, as well as the first synthesis of the closely related (−)-deacetoxy-oleuropein aglycone and a series of related analogues for structure activity studies. To demonstrate the utility of the second-generation synthesis, multigram quantities of (−)-oleocanthal were prepared in 10 steps (14% overall yield) from commercially available D-lyxose.

Introduction

Extra virgin olive oil, the principle source of fat in the Mediterranean diet, has long been associated with health benefits.[1] For example, both cardiovascular mortality[2] and the incidents of breast and colon cancers[3] are remarkably low in the Mediterranean area, compared to other geographical regions such as the United States. Until recently, oleic acid, a monounsaturated fatty acid, was believed to be responsible for the majority of the cardioprotective attributes. Minor phenolic compounds, however, have recently been shown to have antioxidant, anti-inflammatory, and anti-thrombotic activities[4] and, as such, have been suggested to reduce a variety of disorders, including cognitive decline due to neurodegeneration (cf. Alzheimer's disease).[5] In most extra virgin olive oil, the phenolic compounds are usually present at concentrations ranging from 100 to 300 mg/kg,[6] although concentrations as high as 500−1000 mg/kg have been observed.[7]

In the early 1990s, Montedoro and co-workers described a number of phenolic compounds in olive oil belonging to the secoiridoid family, including tyrosol (**2**) and hydroxytyrosol (**3**),

(1) Visioli, F.; Caruso, D.; Grande, S.; Bosisio, R.; Villa, M.; Galli, G.; Sirotri, C.; Galli, C. *Eur. J. Nutr.* **2005**, *44*, 121−127.

(2) (a) Keys, A. *Am. J. Clin. Nutr.* **1995**, *61*, 995−999. (b) Ruano, J.; Lopez-Miranda, J.; Fuentes, F.; Moreno, J. A.; Bellido, C.; Perez-Martinez, P.; Lozano, A.; Gomez, P.; Jimenez, Y.; Perez Jimenez, F. *J. Am. Coll. Cardiol.* **2005**, *46*, 1864−1868.

(3) Visioli, F.; Poli, A.; Galli, C. *Med. Res. Rev.* **2002**, *22*, 65−75.

(4) (a) Visioli, F.; Bellomo, G.; Montedoro, G.; Galli, C. *Atherosclerosis* **1995**, *117*, 25−32. (b) Visioli, F.; Bellomo, G.; Galli, C. *Biochem. Biophys. Res. Commun.* **1998**, *247*, 60−64. (c) Visioli, F.; Caruso, D.; Plasmati, E. *Free Radical Res. Commun.* **2001**, *34*, 301−305. (d) Carluccio, M. A.; Siculella, L.; Ancora, M. A.; Massaor, M.; Scoditti, E.; Storelli, C.; Visioli, F.; Distante, A.; De Caterina, R. *Atheroscl. Thromb. Vasc. Biol.* **2003**, *23*, 622−629. (e) Owen, R. W.; Mier, W.; Giacosa, A.; Hull, W. E.; Spiegelhalder, B.; Bartsch, H. *Food Chem. Toxicol.* **2000**, *38*, 647−659. (f) Owen, R. W.; Giacosa, A.; Hull, W. E.; Haubner, R.; Spiegelhalder, B.; Bartsch, H. *Eur. J. Cancer* **2000**, *36*, 1235−1247. (g) Baldioli, M.; Servili, M.; Perretti, G.; Montedoro, G. F. *J. Am. Oil Chem. Soc.* **1996**, *73*, 1589−1593. (h) Manna, C.; D' Angelo, S.; Migliardi, V.; Loffredi, E.; Mazzoni, O.; Morrica, P.; Galletti, P.; Zappia, V. *J. Agric. Food Chem.* **2002**, *50*, 6521−6526. (i) Impellizzeri, J.; Lin, J. *J. Agric. Food Chem.* **2006**, *54*, 3204−3208.

(5) (a) Yan, Q.; Zhang, J.; Liu, H.; Babu-Khan, S.; Vassar, R.; Biere, A.; Citron, M.; Landreth, G. *J. Neurosci.* **2003**, *23*, 7504−7509. (b) Zhou, Y.; Su, Y.; Li, B.; Liu, F.; Ryder, J.; Wu, X.; Gonzalez-DeWhitt, P.; Gelfanova, V.; Hale, J.; May, P.; Paul, S.; Ni, B. *Science* **2003**, *302*, 1215−1217. (c) Weggen, S.; Eriksen, J.; Da, P.; Sagi, S.; Wang, R.; Pietrzik, C.; Findlay, K.; Smith, T.; Murphy, M.; Bulter, T.; Kang, D.; Marquez-Sterling, N.; Golde, T.; Koo, E. *Nature* **2001**, *414*, 212−216. (d) Pasinetti, G. *J. Alzheimers Dis.* **2002**, *4*, 435−445. (e) Solfrizzi, V.; Panza, F.; Torres, F.; Masroianni, F.; Del Parigi, A.; Venezia, A.; Capurso, A. *Neurology* **1999**, *52*, 1563−1569. (f) Solfrizzi, V.; Panza, F.; Capurso, A. *J. Neural Trans.* **2003**, *110*, 95−110.

(6) (a) Montedoro, G. M.; Servili, M.; Baldioli, R.; Selvaggini, E.; Macchioni, A. *J. Agric. Food Chem.* **1993**, *41*, 2228−2234. (b) Visioli, F.; Galli, C. *Nutr. Metab. Cardiovas.* **1995**, *5*, 306−314.

(7) Monti, S. M.; Ritieni, A.; Sacchi, R.; Skog, K.; Borgen, E.; Fogliano, V. *J. Agric. Food Chem.* **2001**, *49*, 3969−3975.

10.1021/jo071146k CCC: $37.00
Published on Web 08/08/2007

as well as larger, more complex phenols including ligstroside (**4**), ligstroside aglycone (**5**), and deacetoxy-ligstroside aglycone (**1**) (a.k.a. oleocanthal).[6a] Catechols, such as oleuropein (**6**), oleuropein aglycone (**7**), and deacetoxy-oleuropein aglycone (**8**), were also identified (Figure 1). Many of these compounds have been implicated in the bitterness, pungency, and astringency of extra virgin olive oil.[8]

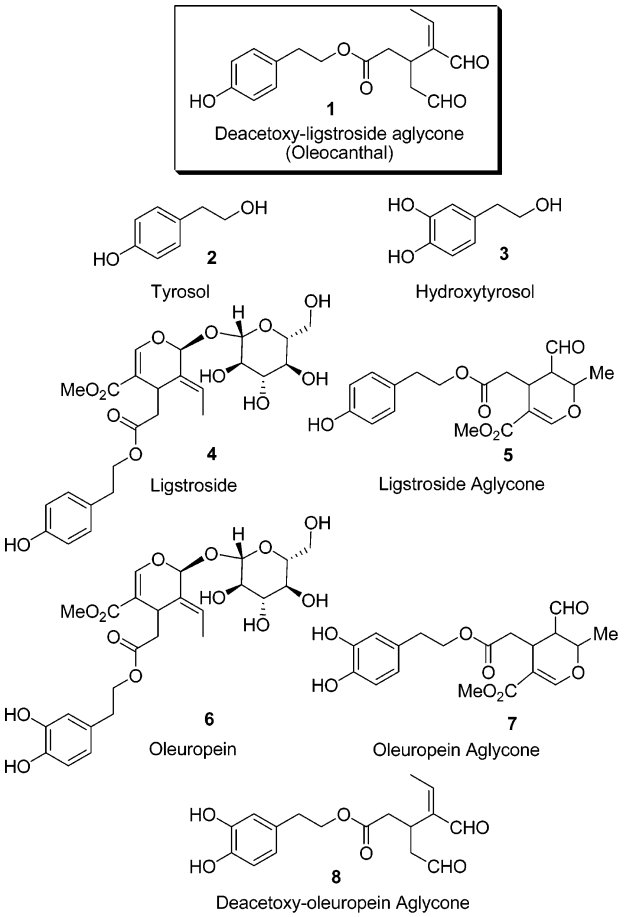


FIGURE 1. Minor phenolic compounds isolated from extra virgin olive oil.

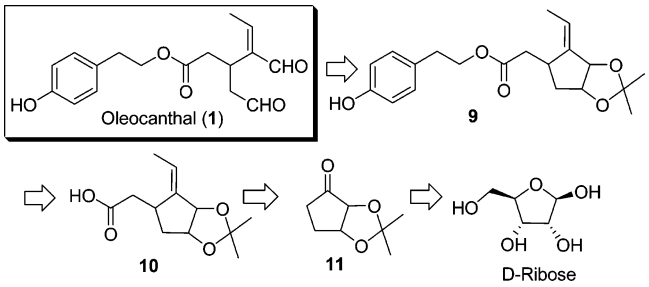
More recently (2003), Busch and co-workers at Unilever identified oleocanthal (**1**), employing extensive 1D and 2D NMR experiments, as the principle contributor to the back of the throat astringency commonly associated with high quality extra virgin olive oil.[8] Complementary work at the Monell Chemical Senses Center, Firmenich, Inc., and the University of Pennsylvania, recognizing the possibility of pharmacological activity of the irritant, confirmed the structure and activity of oleocanthal by total synthesis of both enantiomers.[9,10] The syntheses, in addition to permitting assignment of the absolute configuration of (−)-oleocanthal (**1**), provided material for biological study, specifically discovery of the COX-1 and COX-2 inhibitory activities similar in potency to the NSAID ibuprofen.[9]

In this, a full account, we outline the first- and now second-generation syntheses of (−)-oleocanthal (**1**) that not only permit rapid access to large quantities (>1 g), but also define a strategy for the first synthesis of the closely related (−)-deacetoxy-oleuropein aglycone (**8**), as well as a series of oleocanthal analogues for further biological evaluation.

Results and Discussion

The First-Generation Synthesis of (−)-Oleocanthal. From the outset, we envisioned that (+)- and (−)-oleocanthals could arise from the enantiomers of **11**, exploiting two stereoselective reactions: alkylation with methyl bromoacetate, followed by Wittig ethylenation (Scheme 1). Subsequent ester hydrolysis, esterification with tyrosol (**2**), removal of the acetonide, and oxidative cleavage of the resultant diol would complete the synthesis. Importantly, both enantiomers of **11** were envisioned to arise from commercially available, inexpensive D-(−)-ribose.

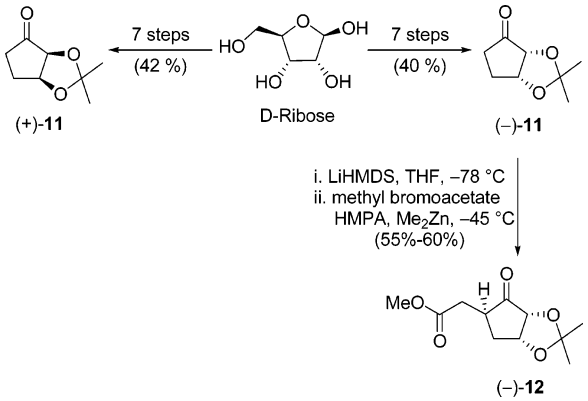
SCHEME 1. A First-Generation Retrosynthetic Analysis of Oleocanthal (1)



We began this synthetic venture by exploring a number of known routes to cyclopentanones (+)- and (−)-**11** (Scheme 2).[11] Although effective on modest scales (cf. 10−100 mg), access to significant quantities of the enantiomers of **11** proved difficult. As a result, routes beginning with D-(−)-ribose that pulled together a number of known steps were optimized to produce multigram quantities of (+)- and (−)-**11**. The overall yields for these seven-step sequences were 40 and 42%, respectively.

Alkylation of (−)-**11** proceeded from the less hindered face of the bicyclic framework to install the requisite two-carbon side chain in (−)-**12** (see Supporting Information for experimental procedures).[10] The next step, Wittig ethylenation of keto

SCHEME 2. Synthesis of Cyclopentanones (+)- and (−)-11 and Alkylation to Generate (−)-12



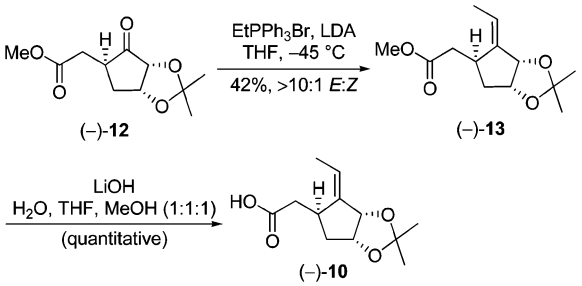
ester (−)-**12**, was particularly challenging.[12] Initially, use of (ethyl)triphenylphosphonium bromide and lithium diisopropylamide (LDA) at −45 °C (Scheme 3) proceeded with high *E*

(8) Andrewes, P.; Busch, J.; de Joode, T.; Groenewegen, A.; Alexandre, H. *J. Agric. Food Chem.* **2003**, *51*, 1415−1420 and references therein.

(9) Beauchamp, G.; Keast, R.; Morel, D.; Liu, J.; Pika, J.; Han, Q.; Lee, C.; Smith, A. B., III; Breslin, P. *Nature* **2005**, *437*, 45−46.

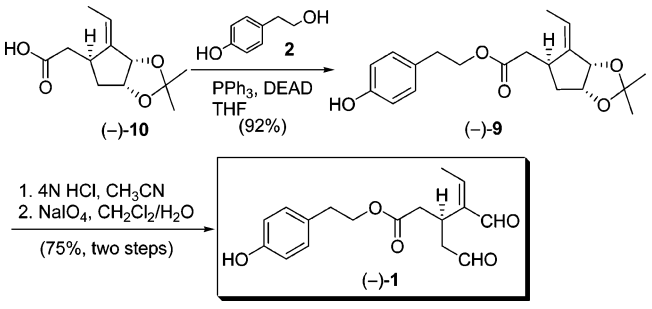
(10) Smith, A. B., III; Han, Q.; Breslin, P. A. S.; Beauchamp, G. K. *Org. Lett.* **2005**, *7*, 5075−5078.

SCHEME 3. Wittig Ethylenation of (−)-12



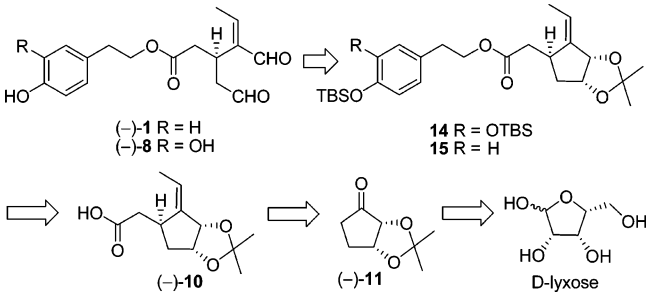
selectivity (>10:1, confirmed by NMR NOE analysis). However, the yield at best was modest (cf. 42%). More importantly, the transformation was not conducive to large-scale production of (−)-**13**. We also discovered that the *E*:*Z* selectivity depended critically on the reaction temperature. At 0 °C, the selectivity was 3.3:1 (*E*:*Z*), while at room temperature, the ratio eroded to 1.6:1. Use of the related strong base NaHMDS provided the desired *E* isomer with a 3.5:1 selectivity at −45 °C, while KHMDS provided predominantly the *Z* olefin (3:1)! Although advancement of material using the LDA/−45 °C protocol was difficult, sufficient quantities of (−)-**10** were prepared to complete a first-generation synthesis of (−)-oleocanthal (Scheme 4). To this end, chemoselective Mitsunobu[13] union of (−)-**10** with 4-hydroxyphenethyl alcohol (tyrosol) **2**, followed by liberation of the vicinal diol and oxidative cleavage with $NaIO_4$, completed construction of (−)-**1**, which proved identical in all respects to an authentic sample of natural (−)-oleocanthal, including chiroptic [e.g., ^{1}H NMR, ^{13}C NMR, IR, HR-MS; $[\alpha]^{20}_D$ −0.90 (*c* = 2.0, $CHCl_3$)] and human organoleptic properties.[9] The absolute stereochemistry of natural (−)-oleocanthal was thus assigned as 3*S*,4*E*. In a similar fashion, the (+)-enantiomer of oleocanthal was also constructed.

SCHEME 4. Completion of the First-Generation Synthesis



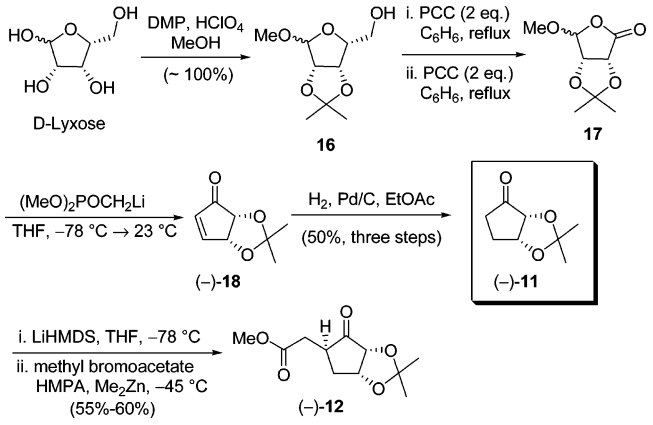
A Second-Generation Synthesis of (−)-Oleocanthal (1). To facilitate large-scale production of (−)-oleocanthal (**1**), in conjunction with the design and synthesis of analogues for further biological evaluation, three issues vis-à-vis the first-generation synthesis demanded attention. First, an alternative route to cyclopentanone (−)-**11** was required to reduce both the number of steps and overall cost. Second, a more effective Wittig olefination protocol was needed to increase both the yield and *E*:*Z* selectivity. Finally, an alternative esterification procedure was required to avoid the tedious removal of the Mitsunobu byproducts. With these considerations in mind, we devised a second-generation strategy as outlined in Scheme 5 to both (−)-oleocanthal (**1**) and the (−)-deacetoxy-oleuropein aglycone (**8**). Highlights of the strategy would entail use of D-lyxose as the starting material for production of cyclopentanone (−)-**11**, an improved esterification protocol, and a protecting group strategy for the phenolic hydroxyl group(s). Importantly, this strategy held the promise of ready access to a series of oleocanthal analogues for a detailed structure activity study (vide infra).

SCHEME 5. A Second-Generation Retrosynthetic Analysis of (−)-Oleocanthal (1) and (−)-Deacetoxy-oleuropein Aglycone (8)



To convert D-lyxose to acetal **16**, we began by adopting a protocol developed by Borchardt[14] et al. (Scheme 6). Exhaustive oxidation of **16** employing pyridinium chlorochromate (PCC) (4 equiv) provided lactone **17** in 62% yield. This transformation involves both oxidation of the primary alcohol and cleavage of a C−C bond. Treatment of the resultant lactone (**17**) with the lithium anion derived from dimethyl methylphosphate produced enone (−)-**18**, which upon hydrogenolysis furnished ketone (−)-**11**. The overall yield of (−)-**11** from D-lyxose was reproducibly 50% on a 10 gram scale. Although D-lyxose is more expensive (ca. 3 times) than D-ribose, the starting material utilized in the first-generation synthesis, this sequence eliminates three steps, reduces the use of several expensive reagents, and is scalable. Equally important, only a single chromatographic separation is required after hydrogenolysis. Alkylation as achieved in the first-generation synthesis then afforded (−)-**12** in 55−60% yield.

SCHEME 6. Synthesis of Ketone (−)-11



Turning to the Wittig ethylenation of (−)-**12**, the first-generation conditions (cf. $EtPPh_3Br$ and LDA) proved inefficient for the large-scale production of (−)-**13**. We attributed the modest yield (42%) to the ease of enolization of ketone (−)-

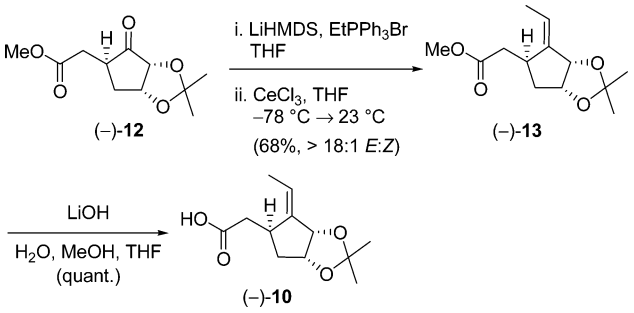
(11) For other synthetic approaches, see: (a) Moon, H.; Choi, W.; Kim, H.; Jeong, L. *Tetrahedron: Asymmetry* **2002**, *13*, 1189−1193. (b) Jin, Y.; Liu, P.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. *J. Org. Chem.* **2003**, *68*, 9012−9018. (c) Yang, M.; Wei, Y.; Schneller, S. *J. Org. Chem.* **2004**, *69*, 3993−3996. (d) Palmer, A.; Jager, V. *Eur. J. Org. Chem.* **2001**, *66*, 1293−1308. (e) Paquette, L.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849−7856.

(12) Wittig, G.; Geissler, G. *Ann.* **1953**, *580*, 44−57.

(13) Mitsunobu, O. *Synthesis* **1981**, 1−28.

12.[15] To circumvent this issue, we employed anhydrous cerium(III) chloride, an additive known to facilitate anion reactions with readily enolizable, sterically encumbered ketones, presumably by reducing the basicity of the nucleophile.[16] Optimal conditions entailed deprotonation of ethyl(triphenylphosphonium) bromide with LHMDS, treatment of the corresponding ylide with anhydrous $CeCl_3$, followed by addition of ketone (−)-**12** in THF at −78 °C. Typical yields ranged from 66 to 68%. Pleasingly, the reaction could be carried out at −78 °C, resulting in an increase in selectivity (ca. >18:1). Equally important, this transformation could be routinely carried out on multigram scale (Scheme 7).

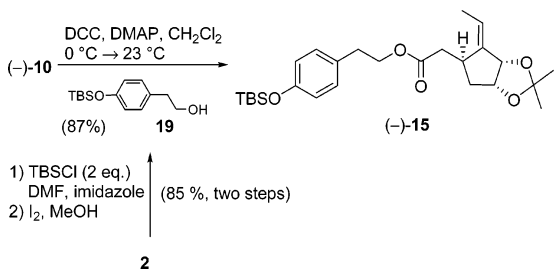
SCHEME 7. Cerium(III) Chloride Mediated Wittig Reaction of (−)-12



Having achieved two of the requisite three process improvements, we turned to the esterification protocol. Hydrolysis of ester (−)-**13** proceeded in high yield to furnish acid (−)-**10**. Although on small scale Mitsunobu coupling of acid (−)-**10** with tyrosol (**2**) was both efficient and high yielding, removal of the Mitsunobu byproducts on scale up proved difficult. Attempts to substitute diisopropyl azodicarboxylate (DIAD) or di-*tert*-butyl azodicarboxylate (DBAD), although again high-yielding, also required chromatography to obtain pure (−)-**9**.[17]

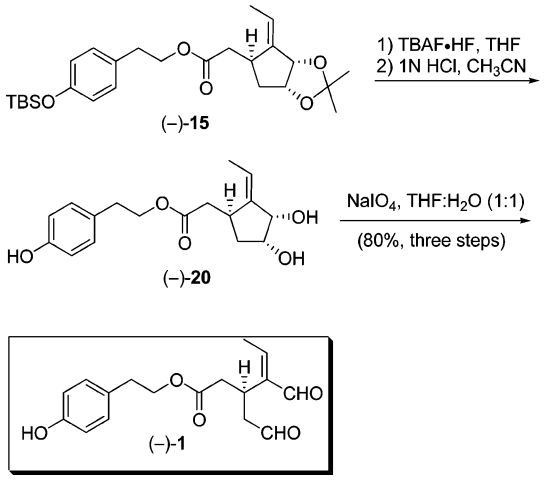
To circumvent this issue, we examined a series of alternative esterifications. The optimal protocol proved to entail DCC coupling with DMAP employing the TBS-protected phenol **19** (Scheme 8), the latter readily prepared in two high-yielding steps (85%) from tyrosol (**2**). Although TBS protection increased the longest linear sequence by one step, the additional cost of this sequence was offset by the time and expense required to remove the Mitsunobu byproducts. Indeed, union of (−)-**10** with **19**, performed at 0 °C, furnished (−)-**15** in 87% yield requiring only filtration through a short plug of silica gel to effect purification.

SCHEME 8. New Esterification Protocol of (−)-10



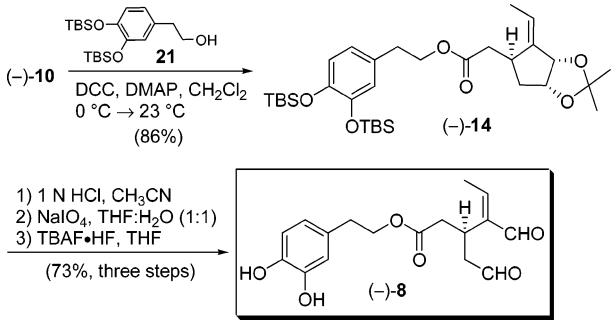
Completion of the second-generation synthesis was now envisioned to be achieved in "one-flask" via removal of the acetonide and TBS moieties (Scheme 9). Unfortunately, the strong acidic conditions required to remove the TBS ether led to substantial decomposition. A two-step sequence was thus developed involving treatment of (−)-**15** with TBAF, buffered with hydrofluoric acid, to remove the TBS group, followed by exposure to 1 N HCl in acetonitrile; near quantitative yield of the diol (−)-**20** resulted. Oxidative cleavage with $NaIO_4$ then completed our second-generation synthesis of (−)-oleocanthal. The final three steps proceeded in 80% overall yield. To demonstrate the utility of the second-generation synthesis, 2.3 g of (−)-oleocanthal (**1**) were prepared in 10 steps (14% overall yield) from commercially available D-lyxose.

SCHEME 9. Three-Step Conversion of (−)-15 to (−)-1



Synthesis of (−)-Deacetoxy-Oleuropein Aglycone (8). Having achieved an effective second-generation synthesis of (−)-oleocanthal, we turned to the closely related (−)-deacetoxy-oleuropein aglycone (**8**). Employing the same coupling strategy (Scheme 10), union of acid (−)-**10** with the bis-TBS-protected catechol **21** furnished (−)-**14** in 86% yield. To avoid possible oxidation of the catechol during the late-stage periodate cleavage, the acetonide was first selectively removed with dilute acid and the resultant diol then subjected to periodate oxidation, followed by removal of the TBS group as described for (−)-oleocanthal (**1**). This three-step sequence, proceeding in 73% yield, completed the first total synthesis of (−)-deacetoxy-oleuropein aglycone (**8**), which proved identical in all respects to an authentic sample of natural (−)-deacetoxy-oleuropein aglycone, including chiroptic properties [e.g., ^{1}H NMR, ^{13}C NMR, IR, HR-MS; $[\alpha]^{20}_D$ −67.0 (c = 0.05, $CHCl_3$)].[18]

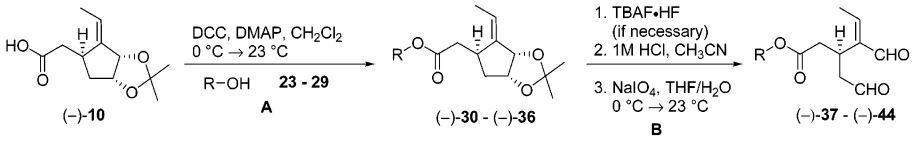
SCHEME 10. Synthesis of (−)-8

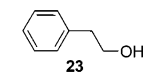
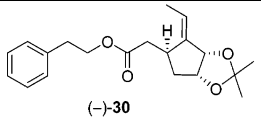
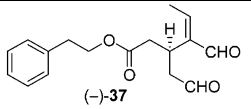
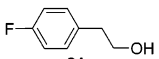
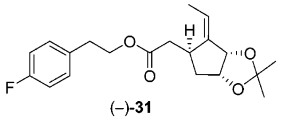
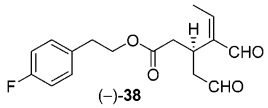
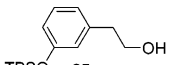
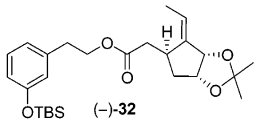
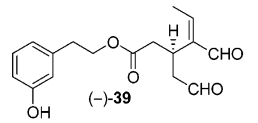
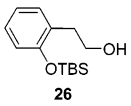
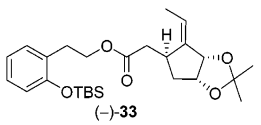
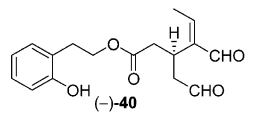
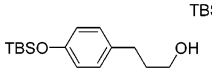
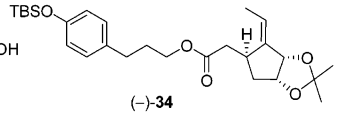
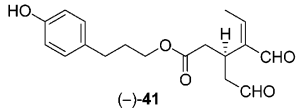
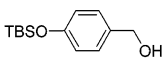
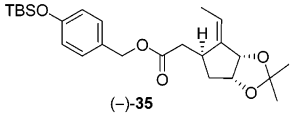
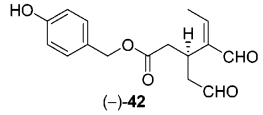
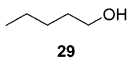
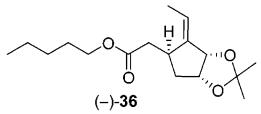
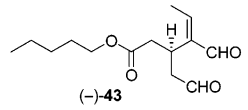
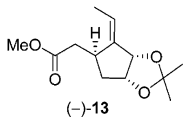
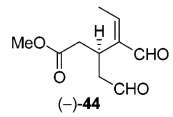


(14) Ali, S. M.; Ramesh, K.; Borchardt, R. T. *Tetrahedron Lett.* **1990**, *31*, 1509−1512.

(15) El Fakih, H.; Pautet, F.; Fillion, H.; Luche, J. *Tetrahedron Lett.* **1992**, *33*, 4909−4910.

TABLE 1. Synthesis of (−)-Oleocanthal Analogues



Entry	Alcohol	Ester	% Yield **A**	Dialdehyde	% Yield **B**
1	 **23**	 (−)-**30**	87	 (−)-**37**	82
2	 **24**	 (−)-**31**	89	 (−)-**38**	80
3	 **25**	 (−)-**32**	82	 (−)-**39**	78
4	 **26**	 (−)-**33**	87	 (−)-**40**	82
5	 **27**	 (−)-**34**	78	 (−)-**41**	81
6	 **28**	 (−)-**35**	85	 (−)-**42**	81
7	 **29**	 (−)-**36**	80	 (−)-**43**	75
8	N/A	 (−)-**13**	N/A	 (−)-**44**	78

(−)-Oleocanthal Analogues. To explore the biological properties of the oleocanthals, we initiated a structure activity study. Analysis of the oleocanthal skeleton suggested three regions for structural modification: the phenol, the alkyl linker, and the unsaturated dialdehyde functionality (Figure 2). Critical to this venture was the ready availability of acid (−)-**10**. Turning

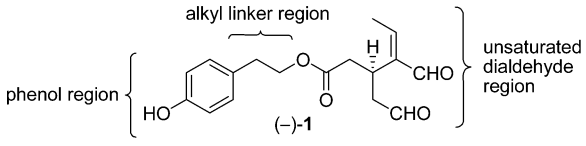


FIGURE 2. Design of (−)-oleocanthal analogues.

to the phenol region, union of (−)-**10** with a series of aromatic alcohols (**23**−**26**) readily provided esters (−)-**30**−**33** (Table 1, entries 1−4). Exposure of (−)-**30** and (−)-**31** to dilute acid, followed by periodate oxidation, led to oleocanthal analogues (−)-**37** and (−)-**38**. Alternatively, exposure of (−)-**32** and (−)-**33** to buffered TBAF to remove the TBS groups, followed in turn by dilute acid treatment and periodate oxidation, furnished (−)-**39** and (−)-**40**. Yields in general were excellent.

To explore the length of the alkyl linker, union of (−)-**10** with alcohols **27** and **28** led to esters (−)-**34** and (−)-**35**, respectively. The now standard three-step deprotection/oxidative cleavage sequence provided (−)-**41** and (−)-**42** (Table 1, entries 5 and 6). We also prepared two analogues that did not possess the phenolic moiety. The first, the straight-chain alkyl ester (−)-**43**, was constructed exploiting an analogous DCC union with *n*-pentanol to generate ester (−)-**36**. Conversion to the dialdehyde again proved efficient to provide (−)-**43**. Methyl ester (−)-**44** also proved readily accessible from (−)-**13** in two steps; acetonide removal and periodate cleavage proceeded in

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(17) Dembinski, R. *Eur. J. Org. Chem.* **2004**, *13*, 2763−2772.

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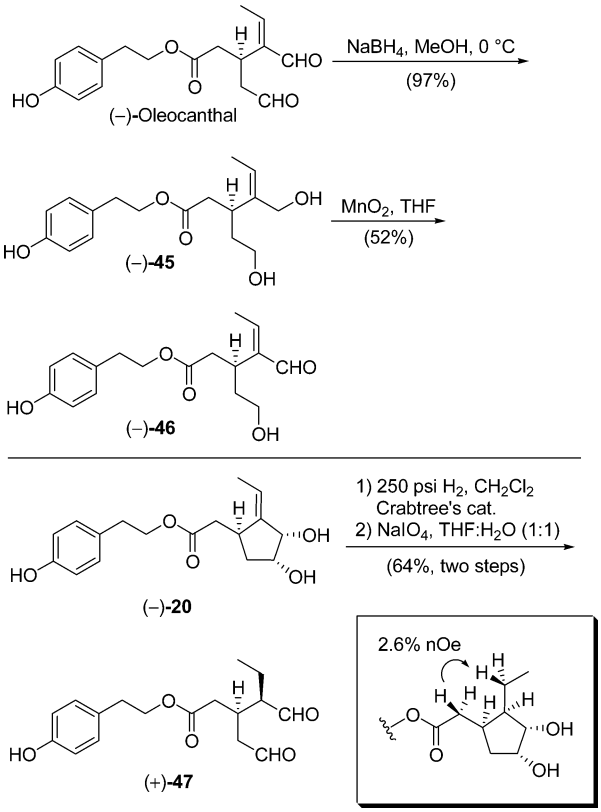
SCHEME 11. (−)-Oleocanthal Analogues



78% yield (Table 1, entries 7−8). The third series of analogues entailed variations in the region of the unsaturated dialdehyde. Reduction of (−)-oleocanthal (**1**) with $NaBH_4$ furnished the corresponding (−)-oleocanthal diol (−)-**45**. Selective oxidation of the allylic hydroxyl with MnO_2 then provided the monoaldehyde (−)-**46**. Finally, stereoselective reduction of the α,β-unsaturation on route to (+)-**47** was achieved by removing the TBS and acetonide groups to expose the vicinal diol functionality [i.e., (−)-**20**]. Hydroxyl-directed reduction of the alkene employing the Crabtree catalyst[19] (H_2/250 psi), followed by oxidative cleavage of the diol, then led to (+)-**47** (Scheme 11). The resultant stereochemical assignment was based on the observed ^{1}H NMR NOE data (see inset), in conjunction with literature precedent.[20]

In summary, an efficient scalable second-generation, stereocontrolled strategy for the multigram production of (−)-oleocanthal (**1**), a naturally occurring NSAID found in extra virgin olive oil, has been achieved in 12 steps, with a longest linear sequence of 10 steps and an overall yield of 14%. To demonstrate the utility of the second-generation sequence, multigram quantities have been prepared. A highlight of the second-generation synthesis entailed the first use of a $CeCl_3$-mediated Wittig olefination. In addition, the first total synthesis of (−)-deacetoxy-oleuropein aglycone (**8**), a closely related congener of (−)-oleocanthal, was achieved, in conjunction with the design and synthesis of a series of oleocanthal analogues. Further biological evaluation of (−)-oleocanthal (**1**), (−)-deacetoxy-oleuropein aglycone (**8**), and the related analogues, currently ongoing, will be reported in due course.

(19) (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205−215. (b) Nell, P. G. *Synlett* **2001**, 160.

(20) Simpson, A. F.; Bodkin, C. D.; Butts, C. P.; Armitage, M. A.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, *18*, 3047−3054.

Experimental Section

Second-Generation Synthesis of (−)-18. D-Lyxose (5.0 g, 33.3 mmol) was dissolved in 40 mL of acetone and 10 mL of 2,2-dimethoxypropane. The solution was cooled to 0 °C, and a 60% solution of perchloric acid (2.33 mL) was added dropwise. After addition, the reaction was stirred for 30 min then slowly warmed to 23 °C over 30 min. The reaction was stirred for 2 h at this temperature, then cooled to 0 °C. Na_2CO_3 (1.6 g in 5 mL of H_2O) was added slowly. When the bubbling ceased, the reaction was filtered through Celite and concentrated. The remaining mixture was taken up in 100 mL of Et_2O and 50 mL of H_2O. The aqueous layer was extracted three times with 100 mL portions of Et_2O. The combined organics were washed with brine, dried over Na_2SO_4, and concentrated to provide 6.8 g (quantitative) of **16** as a colorless oil that was taken forward without purification.

A solution of **16** (2.04 g, 10 mmol) in 200 mL of benzene in a 1 L three-neck flask was fitted with a Dean−Stark trap, reflux condenser, and a mechanical stirrer. With vigorous stirring, the solution was brought to reflux, and PCC (4.31 g, 20 mmol) was added in five equal portions over 2.5 h. The solution was refluxed an additional 8 h. The solution was allowed to cool to room temperature, and 100 g of Celite was added. The suspension was stirred for 30 min, then filtered. The filter cake was washed with 50 mL of benzene, and the combined organics were concentrated to about 50 mL. An additional 200 mL of benzene was added, and the same reflux apparatus was constructed. The solution was again brought to reflux, and an additional amount of PCC (4.31 g, 20 mmol) was added in five equal portions over 2.5 h. The suspension was refluxed for an additional 12 h. The reaction was cooled to room temperature, and Celite (100 g) was added. The suspension was stirred for 30 min, filtered, and the filter cake washed. The organics were concentrated to provide a yellow oil that was dissolved in a 1:1 hexanes/ethyl acetate mixture (ca. 150 mL) and passed through a short plug of silica gel to remove baseline material. The now colorless oil **17** (1.16 g, 62% yield from D-lyxose) was taken forward without purification.

A solution of dimethyl methylphosphate (779 mg, 6.17 mmol, 0.673 mL) in 40 mL of THF was cooled to −78 °C, and *n*-BuLi (2.68 mL, 6.17 mmol, 2.3 M in hexanes) was added dropwise. The reaction was stirred at this temperature for 30 min, and a solution of **17** in 4 mL of THF was added in one portion. The reaction was stirred for 2.5 h at −78 °C, then at 23 °C for 30 min. Et_2O was added (5 mL) followed by H_2O (5 mL). The reaction was poured into a separatory funnel containing 100 mL of Et_2O and 50 mL of H_2O. The organics were separated, and the aqueous layer was extracted three times with Et_2O. The combined organics were washed with brine, dried over Na_2SO_4, and concentrated to give 807 mg (85%) of (−)-**18** as a white solid with spectral data matching our known samples.

(3a*S*,4*E*,5*S*,6a*R*)-4-Ethylidenetetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-5-acetic acid methyl ester, (−)-13. To a flame-dried V-shaped flask under argon were added ethyl triphenylphosphonium bromide (3.04 g, 8.19 mmol, 1.7 equiv) and 10 mL of THF. Next, 7.24 mL (1.5 equiv) of a 1 M LHMDS solution in THF was added dropwise and the resulting red solution stirred at room temperature for 30 min. After 30 min, the solution was transferred dropwise via cannula to a suspension of anhydrous $CeCl_3$ (1.78 g, 7.24 mmol) in 20 mL of THF at −78 °C. The resulting yellow solution was stirred at −78 °C for 30 min, and a solution of (−)-**12** (1.1 g, 4.82 mmol) in 10 mL of THF was added over a period of 30 min via syringe down the side of the flask. The reaction was stirred for 30 min at −78 °C. Once complete, the reaction was warmed to room temperature and stirred for an additional 2 h. The suspension was diluted with an equal volume of hexanes and filtered through a short plug of silica gel. The silica gel plug was washed with an additional 50 mL of a 10% ethyl acetate/hexanes solution, and the extracts were concentrated to yield 790 mg (68%) of the desired alkene (ratio *E*:*Z* >18:1): $R_f = 0.73$ (40% ethyl acetate/

hexanes); $[\alpha]^{20}_D$ −128.4 (*c* = 0.75, $CHCl_3$); ^{1}H 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, 1735, 1437, 1370, 1209, 1162, 1075 cm^{-1}; HRMS (ES+) *m*/*z* 263.1270 [(M + Na)$^+$; calcd for $C_{13}H_{20}O_4Na$ 263.1259]. For (+)-**13**: $[\alpha]^{20}_D$ +134.2 (*c* = 1.10, $CHCl_3$); all other data were the same.

(3a*S*,4*E*,5*S*,6a*R*)-4-Ethylidenetetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-5-acetic acid, (−)-10. To a solution of ester (−)-**13** (1.0 equiv, 4.17 mmol, 1.0 g) were added 8.55 mL of THF and 8.55 mL of MeOH. The solution was cooled to 0 °C, and a solution of LiOH (4.0 equiv, 16.67 mmol, 431 mg) in 9.71 mL of water was added dropwise over 30 min. The reaction was stirred at room temperature for 1 h. Ethyl acetate (50 mL) was added and the reaction vigorously stirred. A 1 N HCl solution was slowly added to the aqueous phase until the pH of the phase became ∼3.5−4 by testing with pH indicator paper (noticeable color change in both the aqueous and organic phases). The organic phase was extracted twice with ethyl acetate, and the combined organics washed with brine, dried over $MgSO_4$, and concentrated. The acid can be used in the next step without purification: R_f = 0.21 (40% ethyl acetate/hexanes); $[\alpha]^{20}_D$ −53.6 (*c* = 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *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); ^{13}C NMR (125 MHz, $CDCl_3$) *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, 2933, 1709, 1379, 1210, 1154, 1059 cm^{-1}; HRMS (ES+) *m*/*z* 227.1274 [(M + H)$^+$; calcd for $C_{12}H_{19}O_4$ 227.1283]. For (+)-**10**: same procedure from (+)-**13**; $[\alpha]^{20}_D$ +59.0 (*c* = 0.90, $CHCl_3$); all other data were the same.

2-[4-(*tert*-Butyldimethylsilanyloxy)phenyl]ethanol, (19). To a solution of TBSCl (2.5 equiv, 90.5 mmol, 13.6 g) and imidazole (2.5 equiv, 90.5 mmol, 6.16 g) in 50 mL of anhydrous DMF was added 4-hydroxyphenethyl alcohol (1.0 equiv, 36.2 mmol, 5.0 g) in one portion (on larger scales, the 4-hydroxyphenethyl alcohol should be added in 2−5 g portions). After stirring overnight at room temperature, the solution was partitioned between 100 mL of water and 200 mL of hexanes. The water layer was washed twice with 100 mL portions of hexanes. The combined organics were washed with 50 mL of water and 50 mL of brine, dried over Na_2SO_4, and concentrated. The unpurified material (∼11 g) was taken forward to the next step.

A small portion of the unpurified material (3.67 g) was dissolved in 36 mL of MeOH, and I_2 (0.1 equiv by mass, 0.367 g) was added. The reaction was monitored by TLC but was generally complete after 2 h. The reaction was quenched by the addition of 15 mL of a 10% $Na_2S_2O_4$ solution and the MeOH evaporated under reduced pressure. The residue was taken up in 200 mL of Et_2O and washed with 50 mL portions of water and brine. The organics were dried over $MgSO_4$, concentrated, and purified by column chromatography (30% ethyl acetate/hexanes) to give 2.18 g (85%) of the desired product (**19**) as colorless oil: R_f = 0.69 (40% ethyl acetate/hexanes); IR (neat) 3348, 2929, 2884, 2858, 1609, 1510, 1257 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.07 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 3.81 (m, 2H), 2.80 (t, *J* = 6.5 Hz, 2H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 154.3, 131.0, 130.0, 120.1, 63.8, 38.3, 25.7, 18.2, −4.4; HRMS (ES+) *m*/*z* 253.1615 [(M + H)$^+$; calcd for $C_{14}H_{24}O_2Si$ 253.1624].

2-[3,4-Bis(*tert*-butyldimethylsilanyloxy)phenyl]ethanol, (21): IR (neat) 3348, 3033, 2957, 2883, 2854, 2710, 1605, 1576, 1515 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 6.76 (d, *J* = 6.5 Hz, 1H), 6.70 (d, *J* = 2.1 Hz, 1H), 6.66 (dd, *J* = 2.1, 8.0 Hz, 1H), 3.79 (t, *J* = 6.5 Hz, 2H), 2.75 (t, *J* = 6.5 Hz, 2H), 0.98 (s, 18H), 0.19 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 147.1, 145.6, 131.5, 130.0, 122.1, 121.3, 64.0, 38.7, 26.1, 25.9, 18.6, −2.7, −3.8; HRMS (ES+) *m*/*z* 383.2434 [(M + H)$^+$; calcd for $C_{20}H_{39}O_3Si_2$ 383.2437].

2-[3-(*tert*-Butyldimethylsilanyloxy)phenyl]ethanol, (25): IR (neat) 3348, 2929, 2884, 2858, 1609, 1510, 1257 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.16 (dd, *J* = 7.6, 8.8 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.71 (m, 2H), 3.84 (t, *J* = 6.4 Hz, 2H), 2.82 (t, *J* = 6.5 Hz, 2H), 0.99 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 154.1, 131.3, 129.3, 127.8, 121.4, 118.8, 63.0, 34.4, 26.0, 18.4, −3.9; HRMS (ES+) *m*/*z* 253.1611 [(M + H)$^+$; calcd for $C_{14}H_{25}O_2Si$ 253.1624].

2-[2-(*tert*-Butyldimethylsilanyloxy)phenyl]ethanol, (26): IR (neat) 3332, 2931, 2858, 1609, 1510, 1259 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.17 (dd, *J* = 1.7, 7.5 Hz, 1H), 7.11 (td, *J* = 1.8, 7.8 Hz, 1H), 6.90 (td, *J* = 1.1, 7.4 Hz, 1H), 6.81 (d, *J* = 7.1 Hz, 1H), 3.84 (q, *J* = 6.4 Hz, 2 H), 2.88 (t, *J* = 6.6 Hz, 2H), 1.02 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 154.1, 131.2, 129.3, 127.8, 121.4, 118.8, 63.0, 34.4, 26.0, 18.4, −3.9; HRMS (ES+) *m*/*z* 253.1612 [(M + H)$^+$; calcd for $C_{14}H_{25}O_2Si$ 253.1624].

3-[4-(*tert*-Butyldimethylsilanyloxy)phenyl]propan-1-ol, (27): IR (neat) 3342, 2929, 2884, 2858, 1609, 1510, 1258 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.04 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 7.9 Hz, 2H), 1.85 (m, 2H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 153.9, 134.6, 129.4, 120.1, 62.4, 34.6, 31.4, 25.9, 18.4, −4.2; HRMS (ES+) *m*/*z* 267.1772 [(M + H)$^+$; calcd for $C_{15}H_{27}O_2Si$ 267.1780].

[4-(*tert*-Butyldimethylsilanyloxy)phenyl]methanol, (28): IR (neat) 3325, 3059, 3031, 2929, 2857, 1609, 1510, 1471, 1256 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.23 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.61 (d, *J* = 5.8 Hz, 2H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 155.5, 133.9, 128.7, 120.3, 65.3, 25.9, 18.4, −4.2; HRMS (CI+) *m*/*z* 238.1391 [(M)$^+$; calcd for $C_{13}H_{22}O_2Si$ 238.1389].

(3a*S*,4*E*,5*S*,6a*R*)-(4-Ethylidene-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl)acetic acid 2-[4-(*tert*-butyldimethylsilanyloxy)phenyl]ethyl ester, (−)-15. To a solution of alcohol **19** (1.0 equiv, 2.15 mmol, 547 mg) and acid (−)-**10** (1.0 equiv, 2.15 mmol, 490 mg) in 5 mL of CH_2Cl_2 at 0 °C was added a solution of DCC (1.2 equiv, 2.62 mmol, 543 mg) and DMAP (0.1 equiv, 0.215 mmol, 30 mg) in 3 mL of CH_2Cl_2. The reaction was allowed to warm to room temperature over 30 min and stirred at this temperature overnight. The crude reaction mixture was placed directly onto a silica gel column and eluted with 15% ethyl acetate in hexanes to provide 860 mg (87%) of the desired ester as a colorless oil: $[\alpha]^{20}_D$ −94.0 (*c* = 0.1, $CHCl_3$); IR (neat) 3030, 2932, 2858, 1735, 1610, 1510, 1468 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.05 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 5.71 (q, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 5.6 Hz, 1H), 4.60 (dt, *J* = 3.8, 5.7 Hz, 1H), 4.24 (t, *J* = 7.1 Hz, 2H), 3.31 (br s, 1H), 2.86 (t, *J* = 7.1 Hz, 2H), 2.57 (dd, *J* = 4.6, 15.3 Hz, 1H), 2.26 (dd, *J* = 9.7, 15.3 Hz, 1H), 2.07 (ddd, *J* = 3.6, 8.3, 14.1 Hz, 1H), 1.75 (dt, *J* = 5.9, 14.1 Hz, 1H), 1.69 (d, *J* = 7.1 Hz, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.0, 143.4, 130.2, 129.7, 123.3, 120.0, 119.9, 111.1, 82.8, 79.2, 65.1, 39.0, 36.6, 36.0, 34.2, 27.7, 25.6, 25.5, 18.1, 14.2, −4.5; HRMS (ES+) *m*/*z* 483.2532 [(M + Na)$^+$; calcd for $C_{26}H_{40}O_5SiNa$ 483.2543].

(3a*S*,4*E*,5*S*,6a*R*)-(4-Ethylidene-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl)acetic acid 2-[3,4-bis(*tert*-butyldimethylsilanyloxy)phenyl]ethyl ester, (−)-14. Isolated as a colorless oil: $[\alpha]^{20}_D$ −71.1 (*c* = 0.09, CH_2Cl_2); IR (neat) 3034, 2930, 2858, 1738, 1605, 1577, 1512, 1472, 1298 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 6.74 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.63 (dd, *J* = 2.0, 8.2 Hz, 1H), 5.70 (q, *J* = 7.2 Hz, 1H), 4.77 (d, *J* = 5.3 Hz, 1H), 4.59−4.61 (m, 1H), 4.22 (t, *J* = 7.1 Hz, 2H), 3.32 (br s, 1H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.57 (dd, *J* = 9.7, 15.3 Hz, 1H), 2.09 (ddd, *J* = 3.7, 8.2, 11.8 Hz, 1H), 1.78 (dt, *J* = 5.8, 14.1 Hz, 1H), 1.68 (d, *J* = 7.2 Hz, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 0.98 (s, 9H), 0.97 (s, 9H), 0.18 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.3, 146.9, 145.8, 143.7, 130.9, 123.6, 122.0, 121.9,

121.2, 111.4, 83.1, 79.5, 65.4, 39.3, 36.9, 36.3, 34.6, 27.9, 26.2, 25.9, 18.7, 14.5, −3.9; HRMS (ES+) *m/z* 613.3351 [(M + Na)$^+$; calcd for $C_{32}H_{54}O_6Si_2Na$ 613.3357].

(3a*S*,4*E*,5*S*,6a*R*)-(4-Ethylidene-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl)acetic acid phenethyl ester, (−)-30. Isolated as a colorless oil: $[\alpha]^{20}_D$ −118.9 (*c* = 0.1, $CHCl_3$); IR (neat) 3086, 3063, 3028, 2982, 2933, 1732, 1454, 1378 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.20−7.34 (m, 5H), 5.70 (q, *J* = 7.0 Hz, 1H), 4.75 (d, *J* = 5.7 Hz, 1H), 4.57−4.60 (m, 1H), 4.30 (t, *J* = 7.0 Hz, 2H), 3.31 (br s, 1H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.57 (dd, *J* = 4.6, 15.4 Hz, 1H), 2.26 (dd, *J* = 15.3, 9.7 Hz, 1H), 2.05 (ddd, *J* = 3.5, 8.3, 14.0 Hz, 1H), 1.74 (dt, *J* = 5.9, 14.1 Hz, 1H), 1.68 (d, *J* = 7.1 Hz, 3H), 1.44 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 171.9, 143.4, 137.6, 128.9, 128.8, 128.4, 128.3, 126.5, 123.4, 111.1, 82.8, 79.1, 64.8, 39.0, 36.6, 36.0, 35.0, 27.6, 25.6, 14.2; HRMS (ES+) *m/z* 353.1715 [(M + Na)$^+$; calcd for $C_{20}H_{26}O_4Na$ 353.1729].

(3a*S*,4*E*,5*S*,6a*R*)-(4-Ethylidene-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl)acetic acid 2-(4-fluorophenyl)ethyl ester, (−)-31. Isolated as a colorless oil: $[\alpha]^{20}_D$ −84.5 (*c* = 0.1, $CHCl_3$); IR (neat) 3041, 2982, 2934, 1731, 1603, 1510, 1372, 1154 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.15 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 5.69 (q, *J* = 6.9 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 1H), 4.58 (dt, *J* = 3.9, 5.9 Hz, 1H), 4.26 (t, *J* = 7.1 Hz, 2H), 3.29 (br s, 1H), 2.90 (t, *J* = 7.1 Hz, 2H), 2.56 (dd, *J* = 4.7, 15.7 Hz, 1H), 2.25 (dd, *J* = 9.7, 15.5 Hz, 1H), 2.04 (ddd, *J* = 3.6, 8.3, 14.1 Hz, 1H), 1.74 (dt, *J* = 5.9, 14.1 Hz, 1H), 1.66 (d, *J* = 7.1 Hz, 3H), 1.44 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 171.9, 143.3, 130.2, 130.1, 123.4, 115.3, 115.2, 111.1, 82.8, 79.1, 64.7, 38.9, 36.6, 35.9, 34.2, 27.6, 25.5, 14.2; HRMS (ES+) *m/z* 329.1178 [(M + Na)$^+$; calcd for $C_{17}H_{19}O_4FNa$ 329.1165].

(3a*S*,4*E*,5*S*,6a*R*)-(4-Ethylidene-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl)acetic acid 2-[3-(*tert*-butyldimethylsilanyloxy)phenyl]ethyl ester, (−)-32. Isolated as a colorless oil: $[\alpha]^{20}_D$ −100.3 (*c* = 0.1, $CHCl_3$); IR (neat) 2931, 2858, 1735, 1603, 1585, 1486 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.15 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.69−6.71 (m, 2H), 5.70 (q, *J* = 7.1 Hz, 1H), 4.76 (d, *J* = 5.3 Hz, 1H), 4.60 (dd, *J* = 2.2, 3.6 Hz, 1H), 4.27 (t, *J* = 7.1 Hz, 2H), 3.31 (br s, 1H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.57 (dd, *J* = 4.5, 15.4 Hz, 1H), 2.27 (dd, *J* = 9.7, 15.4 Hz, 1H), 2.07 (ddd, *J* = 3.6, 8.3, 11.8 Hz, 1H), 1.75 (dt, *J* = 5.8, 14.1 Hz, 1H), 1.68 (d, *J* = 7.1 Hz, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 0.98 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.0, 155.7, 143.4, 139.1, 129.3, 123.3, 121.8, 120.6, 118.1, 111.1, 82.8, 79.2, 64.8, 38.9, 36.6, 36.0, 34.9, 27.6, 25.6, 25.5, 18.1, 14.2, −4.5; HRMS (ES+) *m/z* 483.2531 [(M + Na)$^+$; calcd for $C_{26}H_{40}O_5SiNa$ 483.2543].

(3a*S*,4*E*,5*S*,6a*R*)-(4-Ethylidene-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl)acetic acid 2-[2-(*tert*-butyldimethylsilanyloxy)phenyl]ethyl ester, (−)-33. Isolated as a colorless oil: $[\alpha]^{20}_D$ −102.0 (*c* = 0.1, $CHCl_3$); IR (neat) 2930, 2858, 1737, 1604, 1585, 1456 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.14 (d, *J* = 1.4, 7.4 Hz, 1H), 6.90 (t, *J* = 7.1 Hz, 1H), 6.87 (td, *J* = 0.9, 7.4 Hz, 1H), 5.70 (q, *J* = 7.0 Hz, 1H), 4.76 (d, *J* = 5.7 Hz, 1H), 4.57−4.61 (m, 1H), 4.26 (t, *J* = 7.1 Hz, 2H), 3.32 (s, 1H), 2.93 (t, *J* = 7.1 Hz, 2H), 2.55 (dd, *J* = 4.5, 15.3 Hz, 1H), 2.26 (dd, *J* = 9.7, 15.3 Hz, 1H), 2.06 (ddd, *J* = 3.7, 8.3, 14.1 Hz, 1H), 1.76 (dt, *J* = 5.8, 14.1 Hz, 1H), 1.68 (d, *J* = 6.0 Hz, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.01 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 171.9, 153.8, 143.4, 130.8, 128.0, 127.6, 127.5, 123.3, 120.9, 118.3, 111.1, 82.8, 79.2, 63.8, 39.0, 36.6, 36.0, 30.0, 27.6, 25.7, 25.6, 18.2, 14.2, −4.2; HRMS (ES+) *m/z* 483.2542 [(M + Na)$^+$; calcd for $C_{26}H_{40}O_5SiNa$ 483.2543].

(3a*S*,4*E*,5*S*,6a*R*)-(4-Ethylidene-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl)acetic acid 3-[4-(*tert*-butyldimethylsilanyloxy)phenyl]propyl ester, (−)-34. Isolated as a colorless oil: $[\alpha]^{20}_D$ −79.1 (*c* = 0.1, $CHCl_3$); IR (neat) 2930, 2858, 1737, 1604, 1585, 1488 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.02 (d, *J* = 8.1 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.71 (q, *J* = 6.8 Hz, 1H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.62 (dd, *J* = 2.2, 3.6 Hz, 1H), 4.07 (t, *J* = 7.1 Hz, 2H), 3.34 (br s, 1H), 2.56−2.62 (m, 3H), 2.28 (dd, *J* = 9.7, 15.3 Hz, 1H), 2.10 (ddd, *J* = 3.7, 8.2, 11.8 Hz, 1H), 1.88−1.92 (m, 2H), 1.80 (dt, *J* = 5.7, 14.0 Hz, 1H), 1.72 (d, *J* = 7.0 Hz, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.1, 153.8, 143.4, 133.6, 129.1, 123.3, 119.9, 111.1, 82.8, 79.1, 63.8, 39.0, 36.7, 36.0, 31.3, 30.3, 27.6, 25.6, 25.5, 18.1, 14.2, −4.5; HRMS (ES+) *m/z* 497.2698 [(M + Na)$^+$; calcd for $C_{27}H_{42}O_5SiNa$ 497.2699].

(3a*S*,4*E*,5*S*,6a*R*)-(4-Ethylidene-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl)acetic acid 4-(*tert*-butyldimethylsilanyloxy)benzyl ester, (−)-35. Isolated as a colorless oil: $[\alpha]^{20}_D$ −84.4 (*c* = 0.1, $CHCl_3$); IR (neat) 2931, 2858, 1737, 1610, 1509, 1377 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.20 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.70 (q, *J* = 7.2 Hz, 1H), 5.03 (s, 2H), 4.75 (d, *J* = 5.6 Hz, 1H), 4.56−4.60 (m, 1H), 3.36 (br s, 1H), 2.61(dd, *J* = 4.5, 15.4 Hz, 1H), 2.32 (dd, *J* = 9.7, 15.3 Hz, 1H), 2.09 (ddd, *J* = 3.7, 8.2, 11.8 Hz, 1H), 1.79 (dt, *J* = 5.7, 14.0 Hz, 1H), 1.68 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 3H), 1.31 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*171.9, 143.3, 129.9, 128.5, 123.4, 120.0, 82.8, 79.1, 66.1, 39.0, 36.6, 36.0, 27.6, 25.6, 14.2, −4.5; HRMS (ES+) *m/z* 469.2386 [(M + Na)$^+$; calcd for $C_{25}H_{38}O_5SiNa$ 469.2386].

(3a*S*,4*E*,5*S*,6a*R*)-(4-Ethylidene-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-5-yl)acetic acid pentyl ester, (−)-36. Isolated as a colorless oil: $[\alpha]^{20}_D$ −221.7 (*c* = 0.05, $CHCl_3$); IR (neat) 2958, 2933, 2861, 1735, 1456, 1379 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 5.71 (q, *J* = 7.1 Hz, 1H), 4.77 (dd, *J* = 1.0, 5.6 Hz, 1H), 4.61 (dt, *J* = 3.6, 8.1 Hz, 1H), 4.06 (t, *J* = 6.7 Hz, 2H), 3.34 (br s, 1H), 2.58 (dd, *J* = 4.6, 15.2 Hz, 1H), 2.27 (dd, *J* = 3.0, 15.3 Hz, 1H), 2.09 (ddd, *J* = 3.5, 8.2, 14.0 Hz, 1H), 1.79 (dt, *J* = 5.8, 14.2 Hz, 1H), 1.70 (dt, *J* = 1.2, 7.2 Hz, 3H), 1.61 (t, *J* = 7.1 Hz, 2H), 1.43 (s, 3H), 1.30−1.34 (m, 7H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.2, 143.4, 123.3, 111.1, 82.8, 79.2, 64.6, 39.0, 36.6, 36.0, 35.9, 28.2, 28.0, 27.6, 25.6, 22.2, 14.2, 13.8; HRMS (ES+) *m/z* 297.2079 [(M + H)$^+$; calcd for $C_{17}H_{29}O_4$ 297.2066].

(3*S*,4*E*)-4-Formyl-3-(2-oxoethyl)-4-hexenoic acid 2-(4-hydroxyphenyl)ethyl ester, (−)-Oleocanthal, (−)-1. To a solution of silylated phenol (−)-**15** (1 equiv, 0.273 mmol, 126 mg) in 2 mL of THF at 0 °C was added 0.55 mL of an HF buffered solution of TBAF (made by the addition of a 40% HF solution to a 1 M solution of TBAF in THF until the pH of the solution reached ∼6.5−7.0). The reaction was monitored by TLC until complete. Typical reaction times were 1−1.5 h. The reaction was quenched with water (5 mL) and extracted three times with diethyl ether (15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to provide a colorless oil. The phenol was taken forward with the benefit of further purification.

To a solution of phenol (0.273 mmol) in 2 mL of CH_3CN was added 1 mL of a 1 N HCl solution. The reaction was stirred for 45 min at room temperature. Water (1 mL) was added and the aqueous layer extracted three times with ethyl acetate. The combined organic extracts were combined and washed with brine, dried over $MgSO_4$, and concentrated to provide a viscous colorless oil. The diol was taken on without further purification.

To a solution of diol (0.273 mmol) in 2 mL of THF at 0 °C was added a solution of $NaIO_4$ (1.4 equiv, 0.382 mmol, 82 mg) in 1.5 mL of water at 0 °C. The reaction was stirred at this temperature for 15 min and at room temperature for 30 min. Water (1 mL) was added and the aqueous layer extracted three times with ethyl acetate. The combined organics were washed with a saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. Purification on silica gel with 30% ethyl acetate in hexanes provided (−)-oleocanthal as a colorless oil (66 mg, 80% three steps): R_f = 0.52 (60% ethyl acetate/hexanes); $[\alpha]^{20}_D$ −0.78 (*c* = 0.90, $CHCl_3$); ^{1}H 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, 2924, 1723, 1675, 1516, 1226 cm^{-1}; HRMS (ES+) m/z 327.1217 [(M + Na)$^+$; calcd for $C_{17}H_{20}O_5Na$ 327.1208]. For unnatural (+)-**1**: $[\alpha]^{20}_D$ +0.73 (c = 0.55, $CHCl_3$); all other data were the same.

(3*S*,4*E*)-4-Formyl-3-(2-oxoethyl)hex-4-enoic acid phenethyl ester, (−)-37. Isolated as a colorless oil: $[\alpha]^{20}_D$ −0.84 (c = 0.9, $CHCl_3$); IR (neat) 3058, 3029, 2945, 2722, 1733, 1681, 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 9.23 (d, J = 1.9 Hz, 1H), 7.19−7.31 (m, 5H), 6.62 (q, J = 7.1 Hz, 1H), 4.23−4.29 (m, 2H), 3.60−3.62 (m, 1H), 2.98 (dd, J = 8.6, 18.3 Hz, 1H), 2.91 (t, J = 7.0 Hz, 2H), 2.74 (dd, J = 5.5, 18.3 Hz, 1H), 2.61−2.69 (m, 2H), 2.07 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 195.0, 171.8, 154.1, 143.2, 137.6, 128.8, 128.4, 126.5, 64.9, 46.1, 36.8, 35.0, 27.2, 15.2; HRMS (ES+) m/z 311.1257 [(M + Na)$^+$; calcd for $C_{17}H_{20}O_4Na$ 311.1259].

(3*S*,4*E*)-4-Formyl-3-(2-oxoethyl)hex-4-enoic acid 2-(4-fluorophenyl)ethyl ester, (−)-38. Isolated as a colorless oil: $[\alpha]^{20}_D$ −6.5 (c = 0.23, CH_2Cl_2); IR (neat) 2957, 2832, 2723, 1729, 1679, 1602, 1511 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 9.24 (d, J = 1.9 Hz, 1H), 7.13−7.15 (m, 2H), 6.96−7.00 (m, 2H), 6.62 (q, J = 6.1 Hz, 1H), 4.17−4.25 (m, 2H), 3.59−3.62 (m, 1H), 2.93 (dd, J = 0.9, 8.5 Hz, 1H), 2.87 (t, J = 6.9 Hz, 2H), 2.72 (dd, J = 5.7, 18.3 Hz, 1H), 2.68 (dd, J = 8.6, 16.0 Hz, 1H), 2.61 (dd, J = 6.4, 16.1 Hz, 1H), 2.07 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 195.0, 171.8, 154.1, 130.3, 130.2, 115.3, 115.1, 64.7, 46.2, 36.7, 34.2, 27.1, 15.1; HRMS (ES+) m/z 329.1178 [(M + Na)$^+$; calcd for $C_{17}H_{19}FO_4Na$ 329.1165].

(3*S*,4*E*)-4-Formyl-3-(2-oxoethyl)hex-4-enoic acid 2-(3-hydroxyphenyl)ethyl ester, (−)-39. Isolated as a colorless oil: $[\alpha]^{20}_D$ −0.77 (c = 1.0, $CHCl_3$); IR (neat) 3443, 2957, 2727, 1731, 1681, 1453 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 9.22 (d, J = 1.9 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.68−6.72 (m, 3H), 6.63 (q, J = 7.1 Hz, 1H), 5.63 (s, 1H), 4.19−4.28 (m, 2H), 3.60−3.63 (m, 1H), 2.93 (dd, J = 0.9, 8.1 Hz, 1H), 2.84 (t, J = 7.0, 2H), 2.80 (dd, J = 5.7, 18.2 Hz, 1H), 2.61 (dd, J = 6.5, 15.8 Hz, 1H), 2.05 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 195.4, 171.8, 155.8, 154.7, 143.2, 139.6, 129.7, 121.0, 116.0, 113.6, 64.8, 46.2, 36.9, 34.7, 27.1, 15.2; HRMS (ES+) m/z 327.1217 [(M + Na)$^+$; calcd for $C_{17}H_{20}O_5Na$ 327.1208].

(3*S*,4*E*)-4-Formyl-3-(2-oxoethyl)hex-4-enoic acid 2-(2-hydroxyphenyl)ethyl ester, (−)-40. Isolated as a colorless oil: $[\alpha]^{20}_D$ −0.72 (c = 0.90, $CHCl_3$); IR (neat) 3443, 2957, 2727, 1731, 1681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 9.25 (d, J = 2.0 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.86 (t, J = 6.4 Hz, 1H), 6.80 (t, J = 7.9 Hz, 1H), 6.64 (q, J = 7.1 Hz, 1H), 5.73 (s, 1H), 4.21−4.27 (m, 2H), 3.62−3.64 (m, 1H), 2.95 (dd, J = 0.7, 8.2 Hz, 1H), 2.92 (t, J = 6.9 Hz, 2H), 2.79 (dd, J = 5.6, 18.2 Hz, 1H), 2.62−2.74 (m, 2H), 2.07 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 195.1, 172.3, 154.3, 143.2, 130.8, 128.2, 123.6, 120.7, 115.8, 64.4, 46.2, 36.8, 29.9, 27.1, 15.2; HRMS (ES+) m/z 327.1196 [(M + Na)$^+$; calcd for $C_{17}H_{20}O_5Na$ 327.1208].

(3*S*,4*E*)-4-Formyl-3-(2-oxoethyl)hex-4-enoic acid 3-(4-hydroxyphenyl)propyl ester, (−)-41. Isolated as a colorless oil: $[\alpha]^{20}_D$ −0.79 (c = 1.0, $CHCl_3$); IR (neat) 3353, 2954, 2359, 2341, 1682, 1637, 1518 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 9.29 (d, J = 2.0 Hz, 1H), 7.02 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 6.69 (q, J = 7.0 Hz, 1H), 4.90 (s, 1H), 4.03 (t, J = 6.6 Hz, 2H), 3.65 (m, 1H), 2.98 (dd, J = 1.1, 8.6 Hz, 1H), 2.79 (dd, J = 1.1, 5.6 Hz, 1H), 2.60−2.74 (m, 2H), 2.58 (t, J = 7.8 Hz, 2H), 2.12 (d, J = 7.0 Hz, 3H), 1.85−1.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 195.1, 172.0, 154.3, 143.3, 133.1, 129.3, 115.2, 63.8, 46.2, 36.7, 31.2, 30.2, 27.2, 15.3; HRMS (ES+) m/z 341.1380 [(M + Na)$^+$; calcd for $C_{18}H_{22}O_5Na$ 341.1365].

(3*S*,4*E*)-4-Formyl-3-(2-oxoethyl)hex-4-enoic acid 4-hydroxybenzyl ester, (−)-42. Isolated as a colorless oil: $[\alpha]^{20}_D$ −12.5 (c = 0.15, CH_2Cl_2); IR (neat) 3353, 2921, 1721, 1676, 1516, 1226 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 9.24 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 6.61 (q, J = 7.1 Hz, 1H), 5.04 (br s, 1H), 4.97 (s, 2H), 3.63−3.66 (m, 1H), 3.00 (ddd, J = 1.3, 8.6, 18.4 Hz, 1H), 2.72−2.80 (m, 2H), 2.65 (dd, J = 6.4, 15.9 Hz, 1H), 2.01 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 195.0, 171.8, 155.7, 154.4, 143.0, 130.3, 127.9, 115.4, 115.3, 66.0, 46.2, 36.8, 27.3, 15.2; HRMS (ES+) m/z 313.1057 [(M + Na)$^+$; calcd for $C_{16}H_{18}O_5Na$ 313.1052].

(3*S*,4*E*)-4-Formyl-3-(2-oxoethyl)hex-4-enoic acid pentyl ester, (−)-43. Isolated as a colorless oil: $[\alpha]^{20}_D$ −16.0 (c = 0.05, CH_2Cl_2); IR (neat) 2956, 2836, 2724, 1731, 1681, 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1H), 9.27 (d, J = 1.9 Hz, 1H), 6.68 (q, J = 7.1 Hz, 1H), 4.00 (t, J = 6.8 Hz, 2H), 3.63−3.66 (m, 1H), 2.98 (ddd, J = 1.1, 8.7, 18.3 Hz, 1H), 2.80 (dd, J = 5.7, 18.3 Hz, 1H), 2.71 (dd, J = 8.6, 16.0 Hz, 1H), 2.62 (dd, J = 6.4, 16.1 Hz, 1H), 2.11 (d, J = 7.1 Hz, 3H), 1.57 (pentet, J = 7.2 Hz, 2H), 1.24−1.33 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 195.5, 172.0, 154.1, 143.4, 64.6, 46.2, 36.8, 28.2, 28.0, 27.2, 22.2, 15.2, 13.8; HRMS (ES+) m/z 277.1402 [(M + Na)$^+$; calcd for $C_{14}H_{22}O_4Na$ 277.1416].

(3*S*,4*E*)-4-Formyl-3-(2-oxoethyl)hex-4-enoic acid methyl ester, (−)-44. Isolated as a colorless oil: $[\alpha]^{20}_D$ −50.0 (c = 0.05, CH_2Cl_2); IR (neat) 2954, 2836, 2723, 1730, 1681, 1639, 1437 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 9.28 (d, J = 2.0 Hz, 1H), 6.69 (q, J = 7.1 Hz, 1H), 3.62−2.66 (m, 1H), 6.61 (s, 3H), 2.98 (ddd, J = 1.1, 8.4, 18.3 Hz, 1H), 2.80 (dd, J = 5.7, 18.3 Hz, 1H), 2.71 (dd, J = 8.6, 16.0 Hz, 1H), 2.62 (dd, J = 6.4, 16.1 Hz, 1H), 2.11 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 195.0, 172.3, 154.2, 143.3, 51.5, 46.2, 36.6, 27.2, 15.2; HRMS (ES+) m/z 221.0791 [(M + Na)$^+$; calcd for $C_{10}H_{14}O_4Na$ 221.0790].

(−)-Deacetoxy-Oleuropein Aglycone, (−)-8. Isolated as a colorless oil: $[\alpha]^{20}_D$ −70.0 (c = 0.05, $CHCl_3$); IR (neat) 3355, 2920, 1723, 1677, 1516, 1226 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 9.21 (d, J = 2.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 1.9 Hz, 1H), 6.65 (q, J = 7.1 Hz, 1H), 6.61 (dd, J = 2.0, 8.1 Hz, 1H), 4.14−4.24 (m, 2H), 3.61−3.66 (m, 1H), 2.93 (dd, J = 1.0, 8.5 Hz, 1H), 2.79−2.81 (m, 3H), 2.77 (dd, J = 6.4, 16.1 Hz, 1H), 2.70 (dd, J = 6.6, 16.8 Hz, 1H), 1.25 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 195.6, 171.7, 155.0, 143.2, 143.1, 142.6, 130.6, 121.3, 116.2, 115.2, 65.1, 46.2, 36.9, 34.1, 27.1, 15.2; HRMS (ES+) m/z 343.1162 [(M + Na)$^+$; calcd for $C_{17}H_{20}O_6Na$ 343.1158].

(3*S*,4*E*)-3-(2-Hydroxyethyl)-4-hydroxymethylhex-4-enoic acid 2-(4-hydroxyphenyl)ethyl ester, (−)-45. A solution of (−)-oleocanthal (**1**) (45 mg, 0.148 mmol) in 1.0 mL of MeOH was cooled to 0 °C, and $NaBH_4$ (5.6 mg, 0.148 mmol) was added in one portion. The reaction was stirred at 0 °C for 30 min. The solution was reduced to half the original volume and placed directly onto a silica gel column. Elution with 4:1 ethyl acetate/hexanes provided 44 mg (97%) as a colorless oil: $[\alpha]^{20}_D$ −10.9 (c = 0.055, CH_2Cl_2); IR (neat) 3386, 2865, 2359, 2340, 1713, 1614, 1596 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, J = 8.3 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 6.28 (br s, 1H), 5.62 (q, J = 7.1 Hz, 1H), 4.19−4.29 (m, 2H), 3.99 (s, 2H), 3.58 (t, J = 7.2 Hz, 2H), 3.13−3.30 (m, 1H), 2.78 (t, J = 7.0 Hz, 2H), 2.48−2.69 (m, 3H), 1.71−1.85 (m, 3H), 1.68 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 154.7, 139.2, 129.9, 129.4, 126.3, 115.4, 65.8, 65.1, 60.8, 39.2, 35.9, 34.1, 32.7, 13.3; HRMS (ES+) m/z 331.1534 [(M + Na)$^+$; calcd for $C_{17}H_{24}O_5Na$ 331.1521].

(3*S*,4*E*)-4-Formyl-3-(2-hydroxyethyl)hex-4-enoic acid 2-(4-hydroxyphenyl)ethyl ester, (−)-46. To a solution of diol (−)-**45** (41 mg, 0.13 mmol, 1.0 equiv) in 1.0 mL of THF was added MnO_2 (70 mg, 0.80 mmol, 6 equiv) at 23 °C. The reaction was stirred for 48 h and filtered through a plug of Celite and purified by flash column chromatography with 2:1 hexanes/ethyl acetate to provide (−)-**46** (21 mg, 52%, 88% BORSM) as a colorless oil: $[\alpha]^{20}_D$ −12.0 (c = 0.075, CH_2Cl_2); IR (neat) 3353, 2954, 2359, 2342, 1698, 1518

cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (d, J = 1.8 Hz, 1H), 7.04 (d, J = 11.2 Hz, 2H), 6.75 (d, J = 11.4 Hz, 2H), 6.62 (q, J = 7.1 Hz, 1H), 5.04 (br s, 1H), 4.20 (t, J = 6.9 Hz, 2H), 3.53−3.58 (m, 1H), 3.39−3.43 (m, 1H), 3.29−3.32 (m, 1H), 2.82 (t, J = 7.0 Hz, 2H), 2.72 (dd, J = 8.6, 16.0 Hz, 1H), 2.65 (dd, J = 6.4, 16.1 Hz, 1H), 2.01 (d, J = 7.1 Hz, 3H), 1.89−1.94 (m, 1H), 1.74−1.80 (m, 1H), 1.53 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 172.1 153.4, 144.1, 130.0, 129.4, 115.3, 65.0, 60.5, 37.3, 35.1, 34.1, 29.6, 15.0; HRMS (ES+) m/z 329.1359 [(M + Na)$^+$; calcd for $C_{17}H_{22}O_5Na$ 329.1365].

(3*S*,4*R*)-4-Formyl-3-(2-oxoethyl)hexanoic acid 2-(4-hydroxyphenyl)ethyl ester, (+)-47. A solution of diol (−)-**20** (20 mg, 0.065 mmol, 1.0 equiv) in 10 mL of CH_2Cl_2 was placed into a Parr bomb. Crabtree's catalyst (11 mg, 0.02 equiv) was added, and the bomb was charged to 250 psi with H_2. After 3 h, the reaction was filtered through a silica gel plug and concentrated. Chromatography with 3:1 ethyl acetate/hexanes provided the desired compound as a colorless oil. The diol was then taken up in 0.5 mL of THF and cooled to 0 °C. A solution of $NaIO_4$ in 0.5 mL of H_2O was added dropwise, and the reaction stirred for 30 min at this temperature. After 1 h at room temperature, the reaction was extracted with two 5 mL portions of ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, and concentrated. The crude dialdehyde was chromatographed with 40% ethyl acetate/hexanes to yield (+)-**47** (13 mg, 64%) as a colorless oil: $[\alpha]^{20}_D$ +22.0 (c = 0.05, $CHCl_3$); IR (neat) 3353, 2920, 1733, 1720, 1516, 1226 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1H), 9.60 (s, 1H), 7.04 (d, J = 8.3 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 4.19 (m, 2H), 2.78 (m, 1H), 2.65 (t, J = 7.0 Hz, 2H), 2.08 (d, J = 7.1 Hz, 3H), 1.89−1.93 (m, 3H), 1.72−1.79 (m, 1H), 0.79 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 200.4, 171.8, 154.3, 129.5, 115.3, 94.5, 65.2, 55.4, 45.3, 35.9, 34.1, 28.8, 19.0, 12.0; HRMS (ES+) m/z 329.1365 [(M + Na)$^+$; calcd for $C_{17}H_{22}O_5Na$ 329.1365].

Acknowledgment. Financial support was provided by the National Institutes of Health through Grant No. GM-29028, the University of Pennsylvania and the Monell Chemical Senses Center. We also thank our collaborators Drs. Gary Beauchamp and Paul Breslin (Monell Chemical Senses Center) and Drs. Jianming Lin and Jana Pika (Firmenich, Inc.) for an authentic sample of natural (−)-oleocanthal (**1**), and Dr. Catherine Peyrot des Gachons (Monell Chemical Senses Center) for an authentic sample of (−)-deacetoxy-oleuropein aglycone (**8**). Finally, we thank Dr. G. Furst and Dr. R. K. Kohli for assistance in obtaining NMR spectra and high-resolution mass spectra, respectively.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO071146K