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Synthesis and Assignment of Absolute Configuration of (−)-Oleocanthal: A Potent, Naturally Occurring Non-steroidal Anti-inflammatory and Anti-oxidant Agent Derived from Extra Virgin Olive Oils

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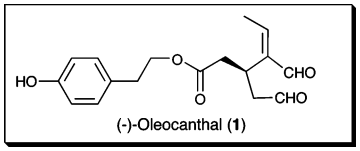
ABSTRACT



Effective total syntheses and the assignment of absolute configurations of both the (+)- and (−)-enantiomers of oleocanthal 1 (a.k.a. deacetoxy ligstroside aglycon), the latter derived from extra virgin olive oils and known to be responsible for the back of the throat irritant properties of olive oils, have been achieved. The absolute and relative stereochemistry of the naturally occurring enantiomer (−)-1 proved to be 3*S*,4*E*. Both syntheses begin with D-(−)-ribose, proceed in 12 steps, and are achieved with an overall yield of 7%. Both enantiomers proved to be non-steroidal anti-inflammatory and anti-oxidant agents.

Non-steroidal anti-inflammatory drugs (NSAIDs), currently widely prescribed as beneficial analgesics, possessing either nonselective or selective COX-1 and COX-2 enzyme inhibitory activities, are currently undergoing extensive review for clinical safety, both in the pharmaceutical industry and at the US Food and Drug Administration.[1] Naturally occurring non-steroidal anti-inflammatory agents found in human food stocks such as various fruits, vegetables, and/or vegetable oils may, however, play a significant role in the potential benefits of such diets rich in these eatables.[2] In this regard, we in collaboration with colleagues at the Monell Chemical Senses Center recently disclosed that (−)-oleocanthal (**1**, Figure 1), a naturally occurring irritant isolated from extra virgin olive oil, is both a potent non-steroidal anti-inflammatory agent, similar to that of ibuprofen,[3] and a powerful anti-oxidant similar to α-tocopherol.[4]

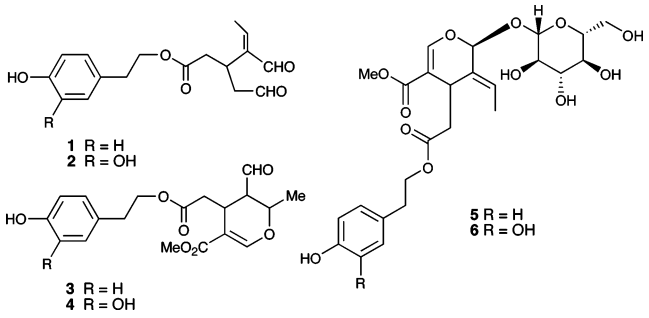


Figure 1. Oleocanthal (**1**) and related olive oil components.

Herein, we report the first total syntheses of both the (+)- and (−)-enantiomers of oleocanthal **1**, which not only

(1) FitzGerald, G. *N. Engl. J. Med.* **2004**, *351*, 1709−1711.
(2) (a) Hu, F. *N. Engl. J. Med.* **2003**, *348*, 2595−2596. (b) Trichopoulou, A.; Costacou, T.; Bamia, C.; Trichopoulos, D. *N. Engl. J. Med.* **2003**, *348*, 2599−2608. (c) Trichopoulou, A.; Katsouyanni, K.; Stuver, S.; Tzala, L.; Gnardellis, C.; Rimm, E.; Trichopoulos, D. *J. National Cancer Institute* **1995**, *87*, 110−116. (d) Owen, R. W.; Haubner, R.; Wurtele, G.; Hull, E.; Spiegelhalder, B.; Bartsch, H. *Eur. J. Cancer Prevention* **2004**, *13*, 319−326.

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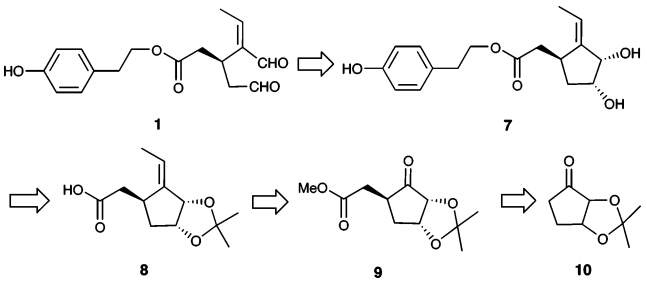
confirms the proposed structure of the olive oil irritant but also permits assignment of the absolute stereochemistry. Importantly, the syntheses provided ready access to an ample supply of totally synthetic material for further biological/sensory evaluation. The latter studies, reported elsewhere, demonstrate that the enantiomers of oleocanthal are both potent non-steroidal anti-inflammatory agents and strong antioxidants and that the levorotary enantiomer of **1** is the agent responsible for the back of the throat irritant properties often experienced upon ingestion of extra virgin olive oils (vide infra).[3]

In 1993, Montedoro and co-workers reported[5] the isolation of a new class of phenolic compounds (**1**−**4**), including the aglycons of ligstroside (**5**) and oleuropein (**6**) from virgin olive oils (Figure 1).[6] These phenolic compounds comprise important minor constituents that have been implicated in the organoleptic characteristics of olive oils, including bitterness, pungency, and astringency.[7] In addition, these agents have been suggested to contribute to the oxidative stability of virgin olive oils, and as such are often associated with the health benefits of olive oils, particularly their antioxidant/anti-cancer activities[8] and more recently their possible role in preventing cognitive decline due to neurodegenerative disorders such as Alzheimer's disease.[9]

Oleocanthal (**1**), the principle contributor to the potent back of the throat irritant (burning) sensation often associated with the consumption of high quality extra virgin olive oils, was subsequently identified by Busch and co-workers at Unilever Research and Development, Vlaardingen (The Netherlands).[7] Concurrent collaborative studies at the Monell Chemical Senses Center and at Firmenich, Inc., had reached the same conclusion.[3] The structure of **1** was assigned by both groups, employing a series of 1D and 2D NMR experiments,[3,7] in conjunction with comparison to literature data.[5] The absolute configuration of **1**, however, remained unknown. That **1** was responsible for the strong irritant (burning) sensation was based on extensive HPLC fraction analysis, omission analysis/correlation, and hydrolysis studies, in conjunction with human sensory studies. Busch and co-workers, however, acknowledged that "a co-elution compound causing the burning sensation could not be eliminated without completing a synthesis of **1**", which they stated to be "extremely challenging".

We envisioned both enantiomers of **1** to derive from the enantiomeric forms of cyclopentanediols **7** via oxidative cleavage of the diol moiety (Scheme 1). The requisite

Scheme 1



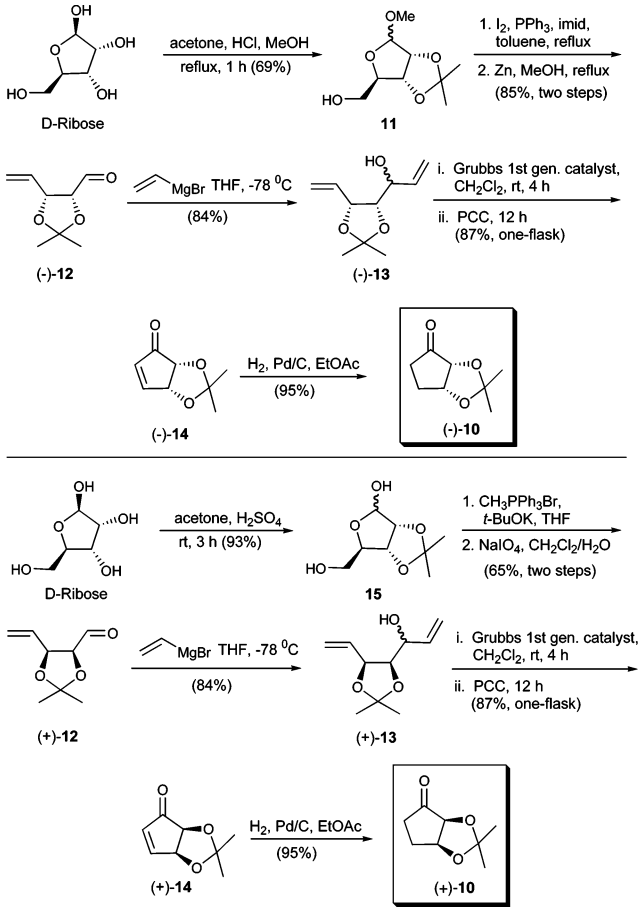
cyclopentanediols (**7**) in turn would be prepared from cyclopentanones (+)- and (−)-**10** via alkylation to introduce stereoselectively the side chain from the convex face, followed by stereoselective Wittig ethylenation, esterification, and removal of the acetonide moiety.

Toward this end, we initially prepared (+)- and (−)-cyclopentanones **10** either via the sulfoximine and/or via enzymatic protocols, the former introduced and developed by Johnson.[10] Although effective on modest scale (10−100 mg), the requirement for gram quantities of the oleocanthals demanded that we secure more scalable routes to the enantiomers of **10**. We therefore optimized a hybrid of known synthetic sequences[11] as outlined in Scheme 2. Importantly, both enantiomers of **10** could be prepared in multigram quantities in six steps, with an overall efficiency of 40% from inexpensive D-(−)-ribose. Key elements of both sequences entailed vinyl Grignard addition to the enantiomers of aldehyde **12**, followed in turn by ring closing metathesis (RCM), PCC oxidation, and hydrogenation (Scheme 2).

Alkylation of (+)- and (−)-cyclopentanone **10** with methyl bromoacetate was then anticipated to proceed from the less hindered convex face of the bicyclic skeleton to install the side chain in a stereoselective fashion. Initial attempts to alkylate (−)-**10** with methyl bromoacetate, employing LDA in the presence of HMPA, however, furnished only a

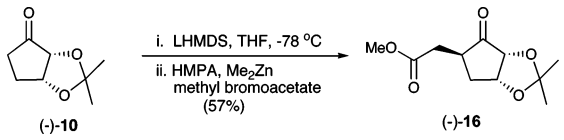
(3) Beauchamp, G.; Keast, R.; Morel, D.; Liu, J.; Pika, J.; Han, Q.; Lee, C.; Smith, A. B., III; Breslin, P. *Nature* **2005**, *437*, 45−46.
(4) Unpublished results.
(5) Montedoro, G.; Servili, M.; Baldioli, M.; Selvaggini, R.; Miniati, E.; Macchioni, A. *J. Agric. Food Chem.* **1993**, *41*, 2228−2234.
(6) Similar structural features have also been reported in the constituents of the *Jasminum*[6a,b] and related plant species.[6c] (a) Somanadhan, B.; Smitt, U.; George, V.; Pushpandadan, P.; Rajasekharan, S.; Duus, J.; Nyman, U.; Olsen, C.; Jaroszewski, J. *Planta Med.* **1998**, *64*, 246−50 and references therein. (b) Takenaka, Y.; Tanahashi, T.; Taguchi, H.; Nagakura, N.; Nishi, T. *Chem. Pharm. Bull.* **2002**, *50*, 384−389 and references therein. (c) Takenaka, Y.; Okazaki, N.; Tanahashi, T.; Nagakura, N.; Nishi, T. *Phytochemistry* **2002**, *59*, 779−787 and references therein.
(7) Andrewes, P.; Busch, J.; de Joode, T.; Groenewegen, A.; Alexandre, H. *J. Agric. Food Chem.* **2003**, *51*, 1415−1420 and references therein.
(8) (a) Owen, R. W.; Mier, W.; Giacosa, A.; Hull, W. E.; Spiegelhalder, B.; Bartsch, H. *Food Chem. Toxicol.* **2000**, *38*, 647−659. (b) Owen, R. W.; Giacosa, A.; Hull, W. E.; Haubner, R.; Spiegelhalder, B.; Bartsch, H. *Eur. J. Cancer* **2000**, *36*, 1235−1247. (c) Baldioli, M.; Servili, M.; Perretti, G.; Montedoro, G. F. *J. Am. Oil Chem. Soc.* **1996**, *73*, 1589−1593. (d) 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.
(9) (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. (c) Pasinetti, G. *J. Alzheimers Dis.* **2002**, *4*, 435−445. (d) Solfrizzi, V.; Panza, F.; Torres, F.; Masroianni, F.; Del Parigi, A.; Venezia, A.; Capurso, A. *Neurology* **1999**, *52*, 1563−1569. (e) Solfrizzi, V.; Panza, F.; Capurso, A. *J. Neural Trans.* **2003**, *110*, 95−110.
(10) (a) Johnson, C. R.; Penning, T. *J. Am. Chem. Soc.* **1988**, *110*, 4726−4735. (b) Johnson, C. R. *Acc. Chem. Res.*, **1998**, *31*, 333−341.
(11) (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.

Scheme 2



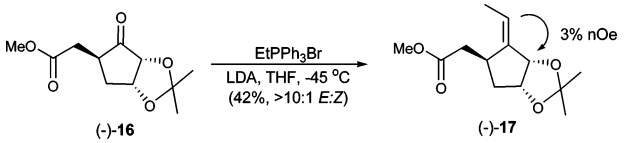
complex mixture containing trace amounts of (−)-**16**. Neither addition of Cu(I),[10a] reported to suppress side reactions, nor the use of the corresponding tin enolate [generated by treatment of (−)-**10** in THF with LDA, followed by HMPA and tributyltin chloride[12]] improved the situation. However, alkylation of the zinc enolate of (−)-**10** [generated by treatment of (−)-**10** in THF with 1.1 equiv of LHMDS, followed in turn by HMPA (3.0 equiv) and dimethylzinc[13] (1.0 equiv)] with methyl bromoacetate consistently furnished (−)-**16** in 55−60% yield as a single diastereomer (Scheme 3).[14]

Scheme 3



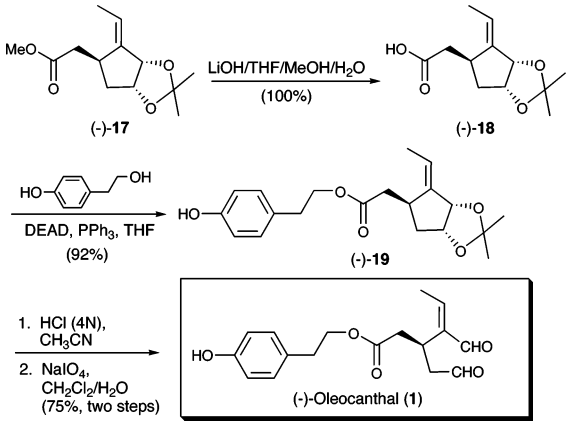
Wittig ethylenation of (−)-**16** was next achieved with ethyltriphenylphosphonium bromide. Best results were obtained employing lithium diisopropylamine (LDA) as base at −45 °C; although excellent stereoselectivity favoring the *E*-isomer (−)-**17** was achieved (ca. 10:1 *E*/*Z*), the yield was only modest (42%), the latter presumably due to the ease of enolization of (−)-**16**.[15] Interestingly, the stereoselectivity varied dramatically with reaction temperature. For example, at 0 °C, the *E*/*Z* selectivity was 3.3:1, while at room temperature the selectivity was 1.6:1. Assignment of the *E* geometry of the olefin was based on NMR NOE analysis (Scheme 4).

Scheme 4



Hydrolysis of ester (−)-**17** (LiOH/THF/MeOH/H_2O) next afforded acid (−)-**18** (Scheme 5), which was subjected to

Scheme 5



Mitsunobu esterification[16] with 4-hydroxyphenethyl alcohol to furnish phenol (−)-**19** in 92% yield. As expected, the Mitsunobu reaction proceeded with complete chemoselectivity at the primary hydroxyl.[17] Completion of the synthesis of (−)-oleocanthal (**1**) was then achieved via liberation of the vicinal diol moiety (4 N HCl/acetonitrile), followed by oxidative cleavage ($NaIO_4$); (−)-oleocanthal (**1**) was identical in all respects (e.g., ^1H and ^{13}C NMR, IR, and HRMS) with

(12) (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348−3349. (b) Nishiyama, H.; Sakuta, K.; Itoh, K. *Tetrahedron Lett.* **1984**, *25*, 223−226.

(13) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1787−1788.

(14) This reaction was fairly clean except some baseline materials. Using *t*-butyl bromoacetate instead of methyl bromoacetate did not improve the yield.

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

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

(17) Appendino, G.; Minassi, A.; Daddario, N.; Bianchi, F.; Tron, G. *Org. Lett.* **2002**, *4*, 3839−3841.

an authentic sample isolated from virgin olive oil, the latter possessing spectral data identical to that reported in the literature.[5] The structural assignment of **1** was also confirmed by COSY NMR analysis. Synthetic (−)-**1** displayed a small negative optical rotation ($[\alpha]^{25}_D$ −0.78, $c = 0.9$, $CHCl_3$) identical to that obtained from an authentic sample, isolated from extra virgin olive oil ($[\alpha]^{25}_D$ −0.90, $c = 2.0$, $CHCl_3$). Thus, the stereochemistry of (−)-oleocanthal (**1**) is 3*S*,4*E*. The enantiomer of the natural product (+)-**1** was prepared via a similar reaction sequence beginning with (+)-**10** to furnish (+)-**1** ($[\alpha]^{25}_D$ +0.73, $c = 0.55$, $CHCl_3$). See the Supporting Information for details.

In summary, effective, scalable syntheses of both enantiomers of oleocanthal **1** have been achieved, each in 12 steps (7% overall yield) from inexpensive D-(−)-ribose, requiring only six chromatographic purifications. The ready access to totally synthetic (−)-oleocanthal (**1**) subsequently permitted establishment of (−)-**1** as both a potent naturally occurring non-steroidal anti-inflammatory agent similar to ibuprofen and a powerful anti-oxidant responsible for the back of the throat irritant properties of extra virgin olive oil.[3] Importantly, the structural similarity of (−)-oleocanthal (**1**) to a number of related natural products constitutes a point of departure for the development of a new class of possible non-steroidal anti-inflammatory drugs (NSAIDs). Studies toward this end are ongoing in our laboratories.

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Supporting Information Available: Representative procedures, spectral data, and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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