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Total synthesis of (±)-heliannuol D, an allelochemical from *Helianthus annuus*

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Abstract

The total synthesis of (±)-heliannuol D and its epimer has been completed in 9 steps and 12% overall yield from 2-methylanisole. The benzoxepane moiety of the title compound, a common structural feature in the heliannuol family of natural products, is prepared by a biomimetic opening of an epoxide by a phenol. © 2000 Elsevier Science Ltd. All rights reserved.

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Maximizing the world's agricultural efficiency depends on controlling unwanted pests, especially weeds. A wide variety of synthetic herbicides have met the weed control needs of industrialized nations for over 50 years. Mounting ecological and human health concerns, however, are continuing to shift attention to alternative weed control technology based on cues from nature.[1,2] Allelopathy, the chemical interaction between plants and/or microorganisms, has been known for thousands of years.[3] Allelochemicals that suppress or eliminate competing plant species near the source plant have received special attention due to the potential of these compounds to serve as natural herbicides.[4] Indeed, this agricultural potential and the synthetic challenges to be found in the skeletons of allelopathic natural products are now beginning to attract the attention of organic chemists.[5]

The cultivated sunflower *Helianthus annuus* is allelopathic and shows activity against such troublesome weeds as morning glory, velvetleaf, pigweed, jimson weed, wild mustard, and others.[6] The heliannuols (**1**–**5**, Fig. 1) are a promising group of phenolic allelochemicals isolated from *H. annuus* that exhibit activity against dicotyledon plant species.[7] In addition to their value as natural herbicide models, the unusual structures of the heliannuols, comprised of previously unknown benzo-fused 6-, 7- and 8-membered cyclic ether skeletons, make them challenging synthetic targets.[8] Herein we report the total synthesis of (±)-heliannuol D (**4**) and its epimer **14**.[9]

We chose 2-methylanisole (**6**) as our starting material for the preparation of the differentially protected methylhydroquinone core (cf. **9**) that is common to all of the heliannuols (Scheme 1). Bromination of

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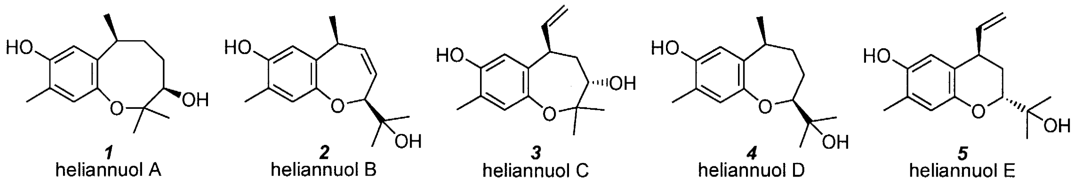
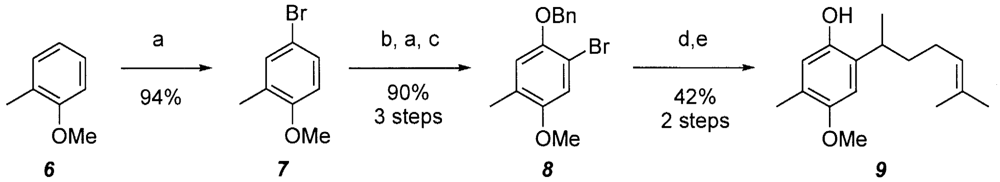


Fig. 1. Structures of the heliannuols

6 provided 4-bromo-2-methylanisole (**7**)[10] in excellent yield. The aryl lithium species prepared from **7** was reacted with triisopropylborate followed by oxidation of the resultant aryl borate ester with *tert*-butylhydroperoxide (TBHP) to provide 4-methoxy-3-methylphenol[11] in essentially quantitative yield. We have found the use of TBHP as the oxidant under very weakly acidic aqueous conditions (satd NH_4Cl solution) to be superior to H_2O_2 and dilute acetic or hydrochloric acids as previously described.[12] In the present case, for example, use of H_2O_2 and dilute HCl provided the phenol in only ~50% yield.

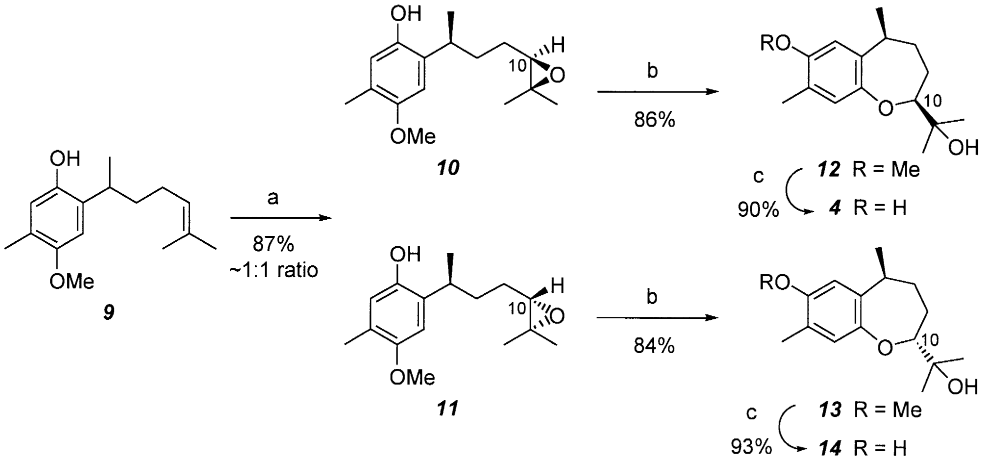


Scheme 1. Reagents and conditions: (a) Br_2, $CHCl_3$, 0°C. (b) (i) Li metal, Et_2O, reflux; (ii) $B(O^iPr)_3$, −78°C to rt; (iii) TBHP, aq. NH_4Cl. (c) (i) NaH, THF, 0°C; (ii) BnBr, DMF. (d) (i) *tert*-BuLi (2.2 equiv.), −78°C; (ii) $ZnCl_2$, THF; (iii) $CH_2{=}C(OTf)CH_2CH_2CH{=}C(CH_3)_2$, $Pd(PPh_3)_4$ (5 mol%), THF, reflux. (e) Li (6 equiv.), liquid NH_3

The crude 4-methoxy-3-methylphenol was immediately brominated at the less hindered *ortho* position followed by protection of the phenol as its benzyl ether to yield **8**. This sequence provided the aryl halide needed for attachment of the side chain in 4 steps and 85% yield from 2-methylanisole (**6**). Bromide **8** was subjected to metal–halogen exchange with *tert*-butyllithium and transmetallation with zinc chloride to provide the aryl zinc species, which was coupled to the enol triflate derived from 6-methyl-5-hepten-2-one[13] under palladium catalysis. The crude reaction mixture from the coupling was directly treated with excess lithium in liquid ammonia to reduce simultaneously the conjugated alkene and the benzyl ether group to provide aromatic bisabolane derivative **9**[14] in 42% yield for the 2 steps. This coupling–reduction strategy is a highly efficient method for the preparation of aromatic bisabolane skeletons, but apparently is sensitive to the triflate:aryl zinc stoichiometry or the quality of the Pd^0 catalyst. These issues will be examined further as we continue our studies in this area.[15]

Our strategy for the construction of the benzoxepane moiety of heliannuol D (**4**) mirrors the proposed biosynthesis of the compound, which involves a phenol-epoxide cyclization.[7b] The cyclization substrate was prepared by oxidation of **9** with *m*-CPBA to furnish a ~1:1 ratio of diastereomeric epoxides **10** and **11** that were easily separable using flash chromatography (Scheme 2). The relative stereochemistry of these epoxides and their cyclization products can be reliably assigned based on the magnitude of the coupling constants of the C-10 methine hydrogen resonance in the ^1H NMR spectrum.[16] Treatment of **10** with powdered KOH in warm DMSO resulted in an excellent yield of benzoxepane **12** via regiospecific attack of the phenoxide at the less hindered proximal position of the epoxide.[17] Epoxide **11** also underwent regiospecific cyclization to provide a good yield of cyclic ether **13** under similar conditions, but required longer reaction times or higher temperatures to achieve complete conversion of the starting epoxide.

The only remaining step in the synthesis was deprotection of the methyl ether in **11**. Reaction of **11** with excess sodium ethanethiolate in refluxing DMF[18] provided (±)-heliannuol D (**4**) in 90% yield after purification by flash chromatography. The IR, ^1H and ^{13}C NMR, and mass spectra of synthetic **4**



Scheme 2. Reagents and conditions: (a) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0°C. (b) powdered KOH, DMSO, 70−100°C. (c) NaSEt (15 equiv.), DMF, reflux

match the tabulated data reported for natural heliannuol D.[7b,19] Overall, the synthesis of heliannuol D (**4**) required 9 steps from 2-methylanisole (**6**) and proceeded in 12% yield. *epi*-Heliannuol D (**14**) was obtained in 93% yield (12% overall from **6**) after cleavage of the methyl ether in **13** under identical conditions employed for the preparation of **4**.

In summary, we have shown that the palladium-catalyzed coupling of the vinyl triflate derived from 6-methyl-5-hepten-2-one to the aryl zinc species prepared from **8** provides a streamlined approach to the aromatic bisabolane skeleton, a framework that is frequently encountered in natural products. Regiospecific cyclization of epoxides **10** and **11** under basic conditions gives high yields of the corresponding benzoxepanes **12** and **13**. We are currently pursuing syntheses of the other heliannuols based on the strategy developed above.

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16. For **10**: δH_{10}=2.79, app t, *J*=6.2 Hz; for **11**: δH_{10}=2.83, dd, *J*=9 and 3 Hz; The stereochemical assignment was confirmed by X-ray diffraction of a model 2-(5-methyl-2H,3H,4H,5H-benzo[*f*]oxepan-2-yl)propan-2-ol. Details of the stereochemical correlation will be reported in the full article describing this work.
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19. The melting point of our synthetic **4** is 162–163°C, 100 degrees higher than was reported for the natural material in the original work (Ref 7b). Professor Macías confirmed via personal communication that an error exists in the original paper, and that the melting point of natural heliannuol D is 159–161°C.