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Formal syntheses of heliannuols A and D, allelochemicals from *Helianthus annus*

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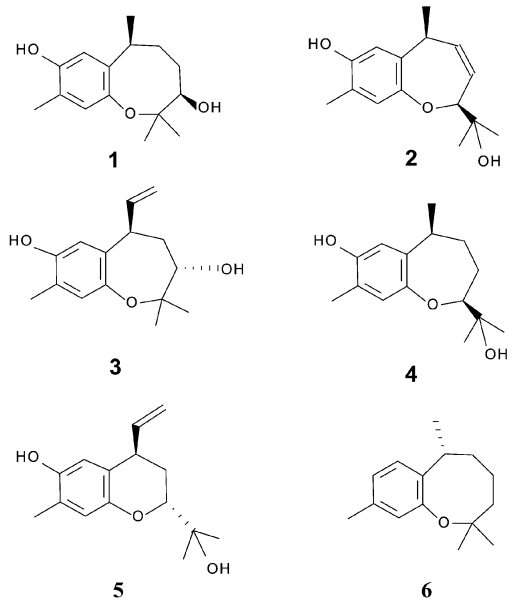
A synthesis of heliannuol A 1 is described involving hydrogenolysis of the cyclopropane fused benzoxepane compound 23 to generate the benzoxocane ring system of 1 and a fragmentation of methyl ether 25 furnished 4-methoxycurcuphenol 29, an advanced intermediate to heliannuol D 4.

Heliannuols A–E, **1**–**5**,[1] belong to a new group of phenolic sesquiterpenes isolated from the cultivated sunflowers *Helianthus annus* and are believed to be involved in the allelopathic activity displayed by these flowers. The significant bio-activity and the hitherto unknown benzo-fused 6-,7- and 8-membered cyclic ether skeleta enshrined in their structural network make them attractive synthetic targets. The corresponding hydrocarbon helianane **6**,[2] has been isolated from marine sponge.



Synthesis of **1**[3], **4**[4] and **6**[5] has been reported. We report here a facile synthesis of **1**, employing a ring expansion stratagem through cleavage of the central bond in a cyclopropane fused seven-membered ring to reveal the benzoxocane ring system of **1**. A fragmentation of the eight-membered ring to a previously reported intermediate to **4** completed a formal synthesis of **4**.

Initially, experiments were directed towards the simpler 4-deoxyheliannuol **15**, with a view to applying the developed methodology to an appropriate substrate containing the additional phenolic functionality at C-4 for transformation to **1**. Furthermore, it was envisaged that removal of the secondary hydroxy group in **15**, would lead to a synthesis of helianane **6**.

Reaction of the styrenol **8**,[6] obtained from decarboxylative alkaline hydrolysis of 4,7-dimethylcoumarin **7**, with chloroform in the presence of sodium hydroxide in refluxing acetone[7] furnished the *gem*-dimethyl incorporated carboxylic acid **9** in 70% yield as a semisolid and was characterised as the methyl ester **10**. This ester was reduced with lithium aluminium hydride to produce the alcohol **11** in 80% yield. When this alcohol was subjected to oxidation with PCC to obtain the corresponding aldehyde, the only product isolated in 60% yield after chromatography, was the benzoxepinenone **12**, resulting from the initially formed aldehyde undergoing an intramolecular carbonyl ene cyclisation and re-oxidation. PCC induced carbonyl ene cyclisation to lead to common rings is precedented,[8] however, the present case may perhaps be the first instance of such cyclisation to form a seven-membered ring. The crucial ring expansion of **12** to the required eight membered ring was carried out in the following way. Treatment of the benzoxepinenone **12** with diazomethane in the presence of palladium acetate afforded the cyclopropyl ketone **13** in 90% yield. When **13** was subjected to catalytic hydrogenation, it resulted in the facile cleavage of the more labile internal bond to reveal the eight membered ketone **14** exclusively in excellent yield (95%). Reduction of **14** with sodium borohydride afforded the 4-deoxyheliannuol **15** in 80% yield in a stereocontrolled manner (Scheme 1). The stereochemical assignment to this alcohol was based on a similar assignment in a previous synthesis of heliannuol A **1**[3] and additionally confirmed from NOE experiments between the C-7 and C-10 hydrogens.

Encouraged by the successful development of the above procedure for a synthesis of deoxyheliannuol, efforts were then trained to apply the sequence of transformations to an appropriately C-4 substituted derivative of **8**. Alkaline decarboxylative hydrolysis of 4,7-dimethyl-6-methoxycoumarin **16** furnished the required methoxy substituted styrenol **17** in 50% yield. Reaction of this styrenol **17** with chloroform in the presence of sodium hydroxide and acetone as for **8**, yielded the *gem*-dimethyl substituted carboxylic acid **18** in 85% yield, which was reduced with lithium aluminium hydride to the alcohol **19** (80%) (Scheme 1). Surprisingly, oxidation of this alcohol with PCC gave a complex mixture of products and no benzoxepinenone derivative. Hence, effecting a modification, **19** was oxidised first under Swern[9] conditions and afforded the aldehyde **20** in 80% yield. When this aldehyde **20** was treated with PCC, it underwent the expected cyclisation and reoxidation to furnish the benzoxepinenone, in a moderate yield (40%), as a mixture of exo and endocyclic isomers **21**. Brief treatment of this isomeric mixture in THF with a few drops of dilute sulfuric acid resulted in isomerisation to the desired endocyclic isomer **22**[10] (Scheme 2).Cyclopropanation of **22** to **23**[10] (72%) followed by catalytic hydrogenation (90%) delivered the eight membered ketone **24**[10] which was reduced with sodium borohydride to furnish the 4-methoxyheliannuol **25** in 90% yield (Scheme 1). The spectral data of **25**[10] matched the values recorded previously.[11] Since demethylation of **25** to heliannuol A **1** has previously been reported,[3] the present efforts concluded a synthesis of **1**.

Efforts at deoxygenation of **15** to obtain helianane **6** have not been successful. Attempted deoxygenation of the corresponding thionocarbonate **26** under radical conditions[12] resulted in a fragmentation and furnished curcuphenol **27**[13] in an overall yield of 50% (Scheme 3). A similar reaction sequence on **25** afforded 4-methoxycurcuphenol **29**[14] (55% overall) (Scheme 3), whose spectral data were fully consistent with those

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reported.[14] This phenol had previously served as an advanced intermediate in a synthesis of heliannuol D **4**,[4b] and hence the present work also constitutes a formal synthesis of **4**.

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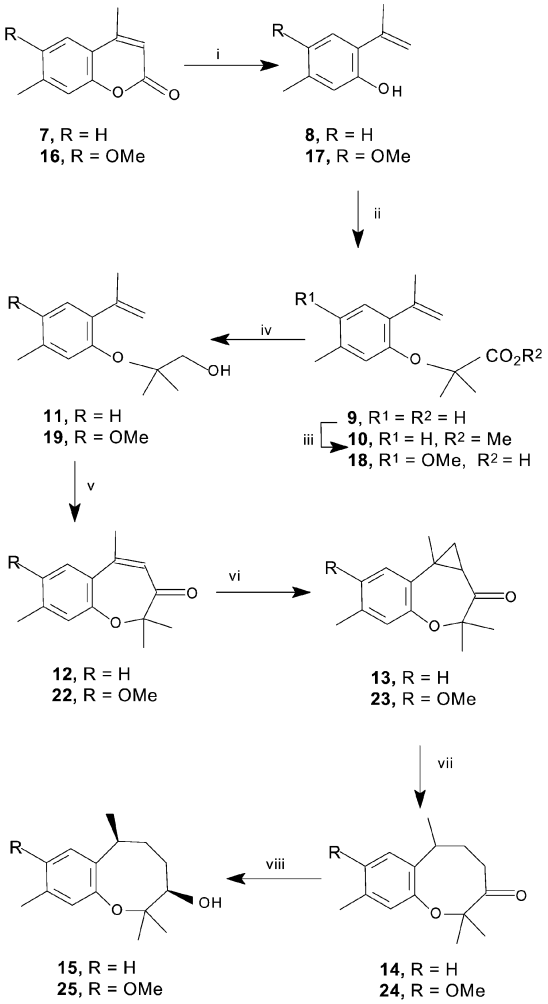
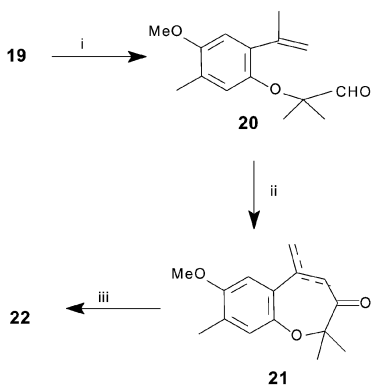
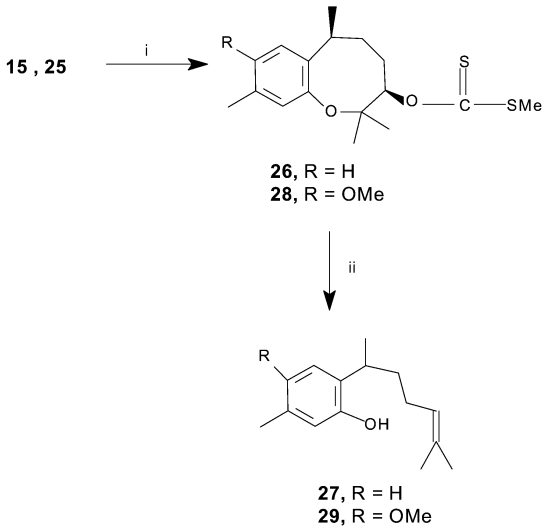


Scheme 1 *Reagents and conditions*: (i) KOH, ethylene glycol, 2 h reflux, 50% (R = OMe). (ii) $CHCl_3$, NaOH, acetone, 5 h reflux, 70% (R = H), 85% (R = OMe). (iii) CH_2N_2, ether. (iv) $LiAlH_4$, ether; 4 h reflux, 80% (R = H, OMe). (v) PCC, CH_2Cl_2, 24 h, 60% (R = H). (vi) CH_2N_2, ether; $Pd(OAc)_2$ (cat); 4 h, 0 °C, 90% (R = H), 72% (R = OMe). (vii) H_2/Pd-C, 95% (R = H), 90% (R = OMe). (viii) $NaBH_4$, MeOH; 4 h, rt, 80% (R = H), 90% (R = OMe).



Scheme 2 *Reagents and conditions*: (i) oxalyl chloride, DMSO, CH_2Cl_2, NEt_3; −68 °C, 45 min, 80%. (ii) PCC, CH_2Cl_2; 24 h, 40% (iii) H_2SO_4 (cat.), THF, 24 h, 90%.



Scheme 3 *Reagents and conditions*: (i) NaH, dry THF; CS_2, MeI; NH_4Cl, 20 h. (ii) Tributyltin hydride, AIBN; dry toluene; 4 h reflux, 50% for 2 steps (R = H), 55% (R = OMe).

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10 All new compounds reported here gave analytical and spectral data consistent with assigned structures. *Selected spectral data*: for **22**: IR 1647cm^{-1}; ^{1}H NMR (300 MHz) δ 1.32 (s, 6H), 2.23 (s, 3H), 2.33 (s, 3H), 3.84 (s, 3H), 6.28 (s, 1H), 6.80 (s, 1H), 6.90 (s, 1H); ^{13}C NMR (75 MHz) δ 16.16, 24.17, 25.20, 55.76, 86.99, 108.69, 125.98, 128.56, 130.48, 146.48, 147.40, 154.21, 203.46. For **23**: IR 1678 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.22 (m, 1H), 1.26 (s, 3H), 1.48 (s, 3H), 1.53 (s, 3H), 2.10 (m, 1H), 2.13 (s, 3H), 2.93 (t, *J* 5.1 Hz, 1H), 3.80 (s, 3H), 6.68 (s, 1H), 6.79 (s, 1H); ^{13}C NMR (75 MHz) δ 15.61, 21.10, 23.17, 25.84, 26.77, 27.12, 38.09, 55.69, 87.75, 110.26, 125.21, 126.74, 133.04, 145.85, 154.62, 210.71. For **24**: IR 1712 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.35 (d, *J* 5.1Hz, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 2.14 (s, 3H), 3.12 (m, 1H), 3.77 (s, 3H), 6.57 (s, 1H), 6.73 (s, 1H); ^{13}C NMR (75 MHz) δ 15.74, 20.39, 23.42, 24.32, 34.42, 35.99, 55.42, 85.88, 108.70, 124.34, 127.42, 136.88, 145.93, 154.83, 212.95. For **25**: IR 3446 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.19 (d, *J* 7 Hz, 3H), 1.28 (s, 3H), 1.34 (s, 3H), 2.07 (s, 3H), 3.11 (m, 1H), 3.31 (d, *J* 8.9 Hz, 1H), 3.72 (s, 3H), 6.53 (s, 1H), 6.66 (s, 1H); ^{13}C NMR δ 16.27, 21.39, 23.46, 26.07, 32.34, 33.23, 36.39, 55.98, 76.03, 83.06, 107.86, 124.17, 127.29, 138.96, 146.03, 154.85.
11 Personal correspondence from Dr E. L. Grimm (Ref. 3). It has been noted that in the synthetic **25**, the secondary methyl group was undefined in the ^{1}H NMR spectrum due to the presence of conformational isomers. However, in our case we have found a clear doublet signal for the secondary methyl group. The conversion of **25** to 4-methoxycurcuphenol **29**, further attested to the structure of our **25**.
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