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Synthesis of heliannuol D, an allelochemical from *Helianthus annus*

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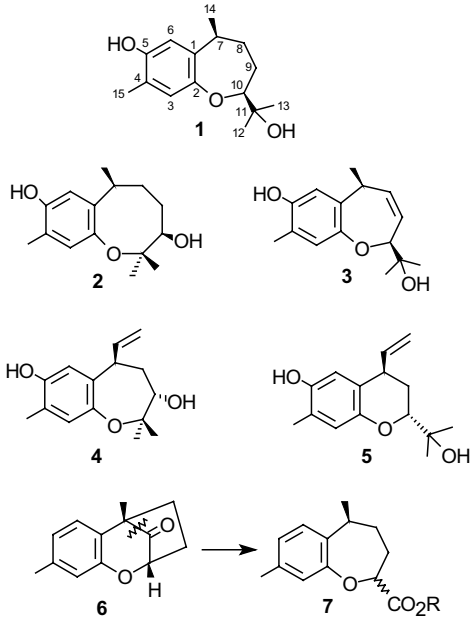
Abstract—A synthesis of heliannuol D **1** is described involving regioselective oxidation of the benzoxabicyclo[3.2.1]octanone **20** followed by hydrogenolysis to generate the benzoxepane ring system of **1**.

Heliannuol D **1**, along with its siblings heliannuols A–C and E, **2**–**5**, comprise a new group of phenolic sesquiterpenes isolated from the cultivated sun flowers *Helianthus annus*.[1] These compounds are believed to be involved in the allelopathic activity displayed by these flowers. Allelopathy, which is concerned with biochemical plant–plant and plant–microorganism interactions, including positive and negative effects, has been proposed[2] as a possible alternative weed management policy. Due to the increasing concern in recent years regarding the natural ecological balance and to reduce further the risk posed by the use of synthetic pesticides, allelochemicals and their analogues are being looked upon as useful pest control agents without hazardous side effects. In this context heliannuols, in view of their significant bio-activity as natural herbicide models and the hitherto unknown benzo-fused six-, seven- and eight-membered cyclic ether skeleta enshrined in them, have attracted the attention of synthetic chemists from many laboratories.[3] We recently reported[4] a synthesis of heliannuol A. A fragmentation sequence encountered in the course of this synthesis had resulted in an advanced intermediate, which had been utilised by others[3b] for the synthesis of **1**, thus also concluding a formal synthesis of **1**. Herein we disclose an alternative synthesis of **1** employing a regioselective oxidation of a benzoxabicyclo[3.2.1]octanone to generate the required benzoxepane ring system present in **1**.

In connection with our synthesis of an A-ring aromatic trichothecene analogue, we have reported[5] a synthesis of the benzoxabicyclo[3.2.1]octanone **6**. We envisaged that if the bridge-locked ketone could be cleaved regioselectively at the site indicated, it would generate the basic benzoxepane ring system of **1** with the proper functionality for transformation to the isopropanol moiety present in **1** (Scheme 1). If this strategy were successful, it could then be applied to an appropriate substrate containing the additional phenolic functionality at C-5. A versatile procedure for cleavage of non-enolisable ketones is the Haller–Bauer reaction.[6] However, under various conditions employed for effecting this cleavage, the bridged ketone **6** remained obdurately unchanged or



Scheme 1.

Keywords: Allelochemical; Heliannuol D; Benzobicyclo[3.2.1]octanone oxidative cleavage; Benzoxepane ring system.

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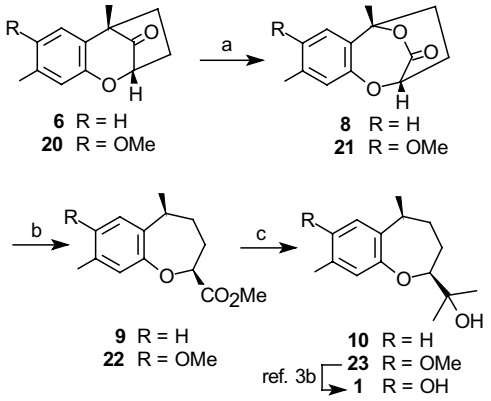
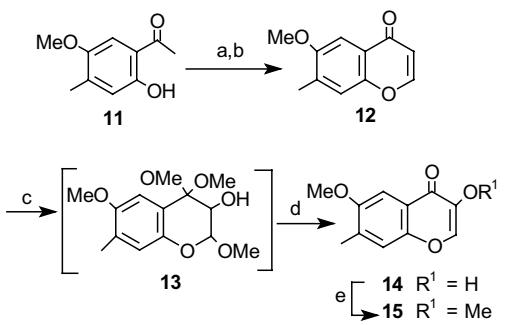
resulted in decomposition products. Success was finally achieved through peroxide induced oxidation under Baeyer–Villiger conditions. Thus, when the ketone **6** was subjected to oxidation with *meta*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane with added trifluoroacetic acid, it furnished the lactone[7] **8** in 68% yield through a regioselective migration of the more substituted bond. The structural assignment of lactone **8** was based on its ^{1}H NMR spectrum, which showed the lone bridge-head proton adjacent to the carbonyl group at δ 4.75 as it was expected that, in the case of the isomeric lactone, this proton, sandwiched between two oxygen atoms would have shifted further downfield. Additional support for the assigned structure came from further transformations. This lactone being benzylic in nature, was expected to undergo ready hydrogenolysis to reveal the benzoxepane ring system of **1**. In anticipation of this, when a methanolic solution of the lactone **8** containing perchloric acid was subjected to hydrogenation in presence of Pd–C, it afforded the bicyclic ester[7] **9** in 72% yield after chromatography, encouragingly as a single isomer. The ^{1}H NMR spectrum of **9** showed the expected doublet for the secondary methyl group at δ 1.23, corroborating the regioselectivity in the oxidation of the ketone **6**. The delivery of hydrogen from the side opposite to the carboxylic acid function during hydrogenation was expected to lead to the desired *cis* disposition of the two substituents in the bicyclic ester **9**. Reaction of the ester **9** with an excess of methyl magnesium iodide furnished 5-deoxyheliannuol D[7] **10** in 97% yield (Scheme 2). The stereochemical assignment of **10** was supported by its ^{1}H NMR spectrum where the C-10 proton appeared as a distinct doublet of doublets at δ 3.36 well separated from the C-7 proton, a multiplet at δ 3.0, similar to the analogous protons in the spectrum of 5-*O*-methylheliannuol D **23**, which was made available to us.[3b] Furthermore, the C-14 secondary methyl doublet at δ 1.26 merged with the singlet due to the C-12 and C-13 methyl groups, again in conformity with the same pattern in the spectrum of **23**. In the corresponding epimer of **23**, the C-10 proton does not show any clean splitting pattern and the multiplet at δ 3.25 appears closer to the C-7 proton multiplet at 3.0. The C-14 methyl doublet is well separated from the singlet due to the C-12 and C-13 methyl groups.

With the successful synthesis of 5-deoxyheliannuol D, we turned our attention to the application of the above procedure on an appropriately C-5 substituted derivative of **6** for a synthesis of heliannuol D **1**. Condensation of the acetophenone **11**[8] with ethyl formate in the presence of sodium hydride followed by dehydration of the resulting chromanol furnished the 6-methoxy-7-methyl chromone **12** in an overall yield of 85%. Reaction of this chromone with iodobenzene diacetate[9] and subsequent acid treatment of the intermediate trimethoxy chromanol **13** yielded the 3-hydroxychromone **14** in 70% yield, which was duly methylated to give the 3,6-dimethoxy-7-methyl chromone **15** (Scheme 3).

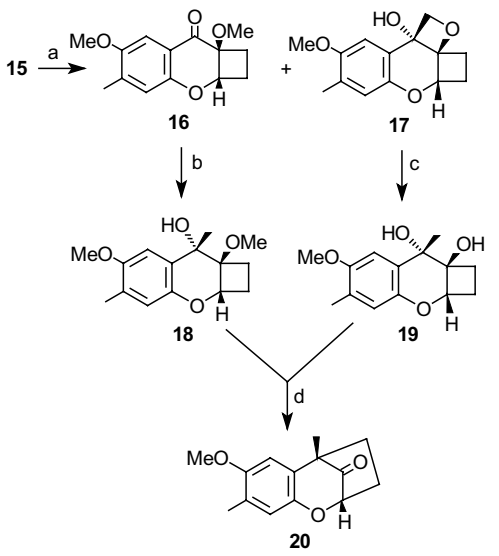
Irradiation of a benzene solution of **15**, which was subjected to a continuous flow of ethylene furnished a mixture of the adduct[7] **16** and the oxetanol[7] **17** in a 4.5:1 ratio in 62% total yield. These were easily separated by column chromatography. Reaction of the adduct **16** with methyl magnesium iodide afforded the alcohol[7] **18** in 87% yield. The assignment of stereochemistry to this alcohol was based on the easier attack from the *exo* face, as observed by us on a previous occasion.[10] Reduction of the oxetanol **17** with lithium aluminium hydride yielded the diol[7] **19** in excellent yield (90%). Treatment of a benzene solution of either the alcohol **18** or the diol **19** with a catalytic amount of boron trifluoride etherate resulted in the expected pinacol–pinacolone rearrangement affording the bridged ketone[7] **20** in very good yield (85%) (Scheme 4). The preparation of this appropriately substituted substrate set the stage for the next sequence of reactions. Oxidation of **20** with *m*-CPBA as for **6** furnished the crucial lactone[7] **21** regioselectively in 71% yield. Hydrogenolysis of a methanol solution of **21** proceeded as before and delivered the bicyclic ester[7] **22** in 74% yield (Scheme 2). In the present case, however, it appeared from ^{13}C NMR that this was contaminated with some of the *trans* isomer. Separation at this stage proved somewhat difficult and hence this mixture was treated with an excess of methyl magnesium iodide to furnish the tertiary alcohols in quantitative yield. GC analysis of the product showed the presence of two components in a 15.6:1 ratio with close retention times.



Scheme 2. Reagents and conditions: (a) *m*-CPBA, TFA, CH_2Cl_2, 6 h, 68% (for **8**), 71% (for **21**); (b) Pd–C (10%), H_2, CH_3OH, $HClO_4$, 8 h, 72% (for **9**), 74% (for **22**); (c) MeMgI, $(C_2H_5)_2O$, reflux, 5 h, 97% (for **10**), 89% (for **23**).



Scheme 3. Reagents and conditions: (a) HCO_2Et, NaH, THF, rt, 14 h; (b) PTS, PhH, reflux, 8 h, 85% (two steps); (c) Ph–I$(OAc)_2$, KOH, CH_3OH, 10 h; (d) concd HCl, 5 h, 70% (two steps); (e) MeI, K_2CO_3, acetone, reflux, 87%.



Scheme 4. Reagents and conditions: (a) *hv*, $CH_2{=}CH_2$, PhH, 6 h, 62%; (b) MeMgI, $(C_2H_5)_2O$, reflux, 5 h, 87%; (c) LAH, THF, reflux, 8 h, 90%; (d) $BF_3{\cdot}Et_2O$, PhH, rt, 2 h, 85%.

Careful preparative thin layer chromatography allowed separation of the less polar major component and furnished (±)-5-*O*-methylheliannuol D **23** in 89% yield (Scheme 2), whose spectral data (^{1}H NMR and ^{13}C NMR) fully matched the data recorded previously.[3b] Since this has been demethylated[3b] to (±)-heliannuol D **1**, the present efforts concluded a formal synthesis of racemic **1**.

In summary, we have developed an efficient synthesis of heliannuol D **1**, employing a regioselective oxidative cleavage of a benzoxabicyclo[3.2.1]octanone to generate the benzoxepane ring system present in **1**, affording the final compound in good overall yield.

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7. All new compounds reported here gave analytical and spectral data consistent with the assigned structures. *Selected spectral data:* For **8**: IR 1760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.82 (3H, s), 2.28 (3H, s), 4.75 (1H, dd, *J* 0.9, 6 Hz). For **9**: IR 1750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.23 (3H, d, *J* 7.1 Hz), 2.21 (3H, s), 2.99 (1H, m), 3.74 (3H, s), 4.12 (1H, dd, *J* 1.9, 11.3 Hz). For **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.27 (3H, s), 3.0 (1H, m), 3.36 (1H, dd, *J* 1.1, 11.0 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ_C 19.2, 21.1, 24.8, 25.8, 25.9, 32.2, 38.7, 72.9, 90.7, 122.4, 124.8, 129.8, 136.9, 137.7, 158.4. For **20**: IR 1765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.32 (3H, s), 2.06 (3H, s), 3.69 (3H, s), 4.09 (1H, d, *J* 5.7 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ_C 14.5, 16.2, 26.1, 37.9, 48.0, 56.4, 76.9, 106.6, 118.6, 128.0, 129.4, 145.3, 153.1, 214.2. For **21**: IR 1761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.83 (3H, s), 2.15 (3H, s), 3.77 (3H, s), 4.72 (1H, d, *J* 5.1 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ_C 16.9, 26.4, 27.8, 37.5, 57.3, 74.2, 84.0, 108.9, 122.5, 124.8, 131.0, 148.1, 153.2, 169.8. For **22**: IR 1749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.32 (3H, d, *J* 7.1 Hz), 2.13 (3H, s), 2.99 (1H, m), 3.79 (3H, s), 3.80 (3H, s), 4.11 (1H, d, *J* 10.1 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ_C 15.4, 18.5, 28.8, 31.3, 38.2, 52.1, 55.5, 81.1, 110.5, 124.3, 136.7, 150.0, 154.0, 171.8, 194.5. For **23**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.23 (3H, d, *J* 7.2 Hz,), 2.06 (3H, s), 2.88 (1H, m), 3.22 (1H, dd, *J* 1.2, 11.1 Hz), 3.71 (3H, s); ^{13}C ($CDCl_3$, 75 MHz) δ_C 15.5, 18.5, 24.4, 25.5, 26.0, 31.7, 39.0, 55.6, 72.4, 90.4, 111.2, 123.5, 125.0, 137.3, 151.3, 153.5.
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