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A short, rapid synthesis of heliannuol D, an allelochemical from *Helianthus annus* employing ring-closing metathesis

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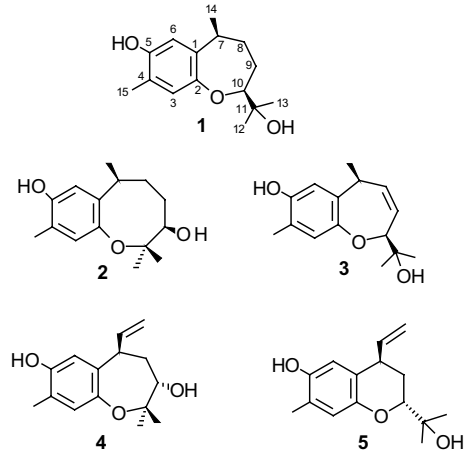
Abstract—A facile, very short synthesis of the allelochemical heliannuol D is described involving the application of ring-closing metathesis to generate the benzoxepane ring system of **1**.

Heliannuol D **1**, is a bicyclic sesquiterpene with a previously unknown carbon skeleton and along with the other members of this group, A–C and E, **2**–**5**, was isolated from the cultiver sun flowers *helianthus annus*.[1] These compounds have been implicated in the allelopathic activity displayed by these flowers. The characteristic phytotoxic activity and the unique structural features enshrined in these compounds have made them attractive targets for synthesis.[2] We have initiated a comprehensive programme towards the synthesis of these compounds and recently have reported a synthesis of heliannuols A[3] and D.[4] The synthesis of **1**[4] had relied on a regioselective oxidative ring opening of a benzobicyclo[3.2.1]octanone to develop the benzoxepane ring system. A base catalysed intramolecular cyclisation of a phenolic epoxide constituted the key step in the other two reported syntheses.[2b,c] We now disclose a short synthesis of **1** employing ring-closing metathesis to generate the benzoxepane core of **1.**



During the last decade, there has been an exponential growth in the application of olefin metathesis, particularly the intramolecular version for the construction of various carbocyclic ring systems.[5] The attractive features of this method relating to the catalytic nature of the reaction including its operational simplicity and remarkable tolerance of the catalyst to various functionalities, have made it a highly versatile procedure for the facile construction of carbocyclic systems. In our present efforts, application of this methodology has provided a ready access to the benzoxepane ring system of **1**.

Reaction of the styrenol **6**,[3] obtained from the decarboxylative hydrolysis of 4,7-dimethoxy-6-methyl coumarin, with ethyl bromoacetate in the presence of potassium carbonate in refluxing acetone furnished the O-alkylated product **7**[6] in 80% yield. Alkylation of the enolate from **7**, generated through interaction with LDA at −78 °C, with allyl bromide, afforded the diene **8**[6] in 78% yield, properly set up for the crucial ring-closing experiment. Initially, we tried the reaction employing the well-studied catalyst **A**, which is more selective, but cost effective. At room temperature, in methylene chloride, even after an extended reaction time (24 h) no change was observed. When the reaction was carried out at 50 °C (bath temperature) for 7 h, the cross metathesis

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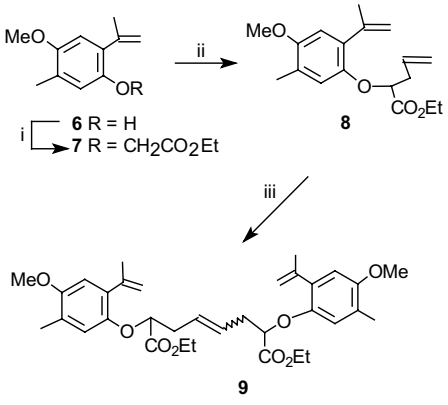
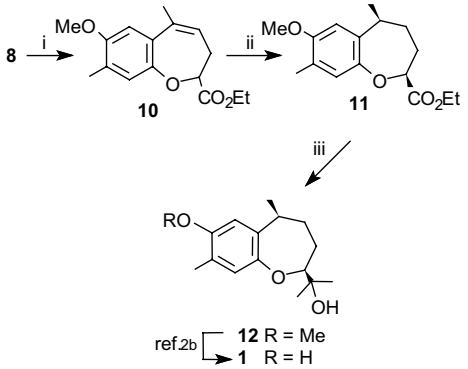
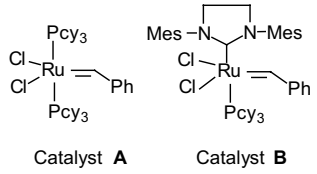
product **9**[6] was obtained in 55% yield (Scheme 1). The vinylic olefin protons were retained at δ 5.0 and the newly generated olefinic proton appeared at δ 5.56. The restricted utility of catalyst **A** when applied to sterically demanding olefin systems has been observed by others.[5] In view of this, we turned to the later version of the catalyst, catalyst **B**, which is reported to perform better in such cases.[5] Indeed, when the diene in dichloromethane (0.01 M) was stirred for 4.5 h using 5 mol % of the catalyst, it underwent a clean intramolecular cyclisation yielding the benzoxepine ester **10**,[6] in excellent yield (94%). The presence of a single olefinic proton at δ 5.94 attested to the formation of this product and was supported by subsequent experiments. This olefinic ester was subjected to quantitative catalytic hydrogenation furnishing selectively the saturated ester **11**,[6] together with traces of the *trans* isomer (ca. 5%). The desired major isomer could easily be separated by thin layer chromatography. This showed spectral features (^{1}H NMR and ^{13}C NMR) in excellent agreement with those of the analogous methyl ester, which we had synthesised earlier.[4] Additional confirmation was secured from interaction of **11** with excess methyl magnesium iodide to afford the tertiary alcohol **12**[6] (Scheme 2), identical in all respects with our previous sample,[4] which had been demethylated to heliannuol D.[2b]



Scheme 1. Reagents and conditions: (i) K_2CO_3, $BrCH_2CO_2Et$, acetone, reflux, 8 h, 80%; (ii) LDA, THF, −78 °C to rt, $CH_2{=}CHCH_2Br$, 10 h, 78%; (iii) Catalyst **A** (5 mol %) CH_2Cl_2, 50 °C, 7 h, 55%.



Scheme 2. Reagents and conditions: (i) Catalyst **B**, (5 mol %), CH_2Cl_2, rt, 5 h, 94%. (ii) Pd–C (10%), H_2, EtOH, 5 h, 90%; (iii) MeMgI, Et_2O, reflux, 3 h, 96%.



In summary, we describe a very short and facile synthesis of the allelochemical, heliannuol D, employing ring-closing metathesis to develop the benzoxepane ring system of **1**. The present synthesis furnishes **1** in 6 steps from the styrenol **6** in a very good overall yield.

Acknowledgements

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6. All new compounds reported here gave analytical and spectral data consistent with the assigned structures. *Selected spectral data*: For **10**: IR 1750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.30 (3H, t, *J* 7.2 Hz), 2.12 (3H, s), 2.19 (3H, s), 2.48 (2H, m), 3.80 (3H, s), 4.22 (2H, q, *J* 7.2 Hz), 4.88 (1H, dd, *J* 5.0, 9.7 Hz), 5.94 (1H, t, *J* 6.9 Hz), 6.69 (1H, s), 7.04 (1H, s); ^{13}C ($CDCl_3$, 75 MHz) δ_C 14.6, 16.3, 22.9, 31.3, 56.1, 61.4, 86.4, 108.9, 123.6, 125.6, 128.8, 131.6, 136.5, 148.5, 154.4, 171.8.