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Total synthesis of heliannuol B, an allelochemical from *Helianthus annuus*

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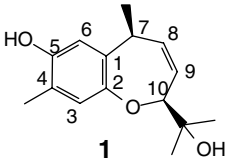
Abstract—A total synthesis of the allelochemical heliannuol B **1** is described employing ring closing metathesis to generate the central benzoxepane ring system.

Heliannuol B **1**, consisting of a unique benzoxepane ring system belongs to a novel group of allelopathic sesquiterpenes isolated from the cultivar sunflowers *Helianthus annus*.[1] The other primary constituents are heliannuols A and C–E **2**–**5** and these have been implicated in the powerful allelopathic activity displayed by sunflowers.[2] Subsequently, other oxidized variants of some of these primary compounds have also been isolated from these flowers.[3] The structure of **1** was determined from extensive spectral studies and additionally confirmed from conversion to heliannuol D **4** by hydrogenation. Allelopathy, involving plant–plant and plant–microorganism interactions, has been proposed as an alternative weed management policy.[4] The growing concern on the natural ecological balance and the arguments against indiscriminate use of synthetic pesticides have provided an impetus for exploration of allelochemicals for effective weed control devoid of any hazardous side effects. In this context, the heliannuols, due to their novel structural features and associated bio-activity, have served as attractive targets for synthesis in many laboratories.[5] We have initiated a comprehensive programme for the synthesis of these sesquiterpenes and have reported the synthesis of heliannuols A **2**, C **3**, D **4** and an isomer of the methyl ether of **5**.[6] We report here our efforts directed towards the synthesis of heliannuol B **1** culminating in its total synthesis.



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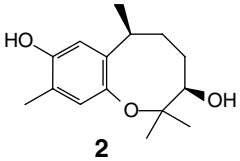

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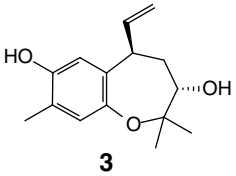

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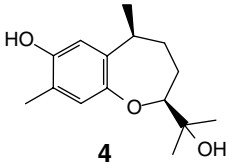

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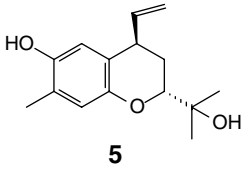

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As can be seen, heliannuols B **1**, C **3** and D **4** are based on a benzoxepane ring system. The presence of an endocyclic double bond in **1** distinguishes it from its dihydro analogue **4**. We have developed three distinct approaches, including ring closing metathesis, for the generation of the benzoxepane ring system *en route* to the synthesis of **3** and **4**.[6c–e] We envisaged that a ring closing metathesis of an appropriately patterned diene would serve the purpose of constructing the benzoxepane ring system of **1** with the double bond in the correct position. Herein, we describe the successful implementation of this strategy to realize the synthesis of **1**.

Keywords: Allelochemicals; Heliannuol B; Ring closing metathesis.
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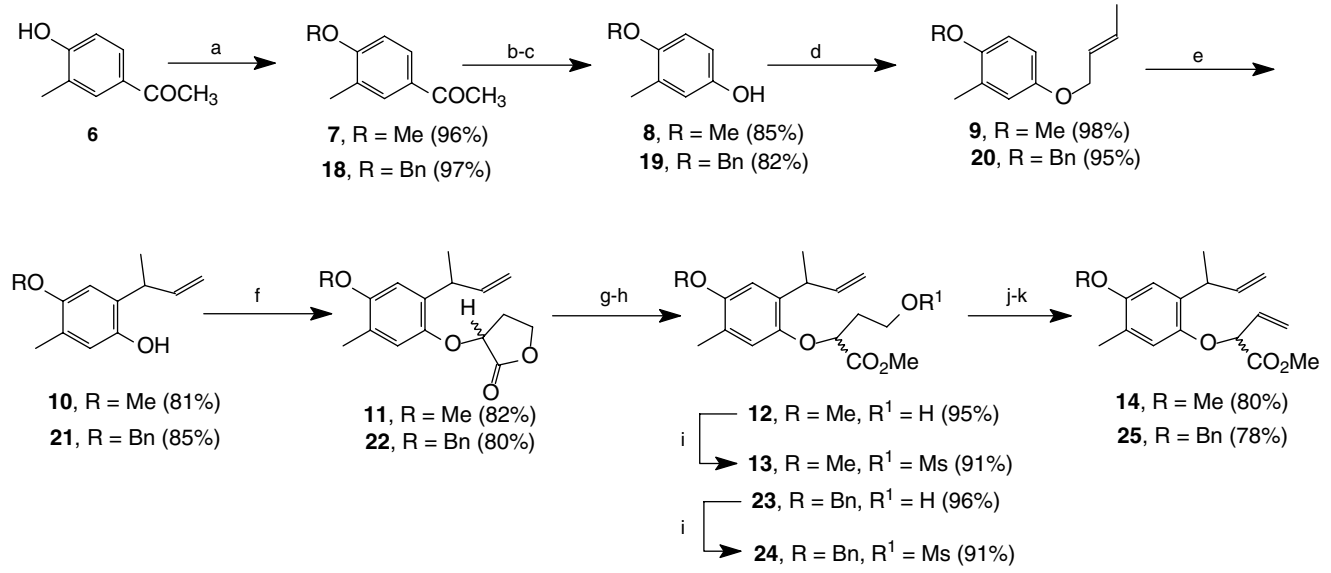
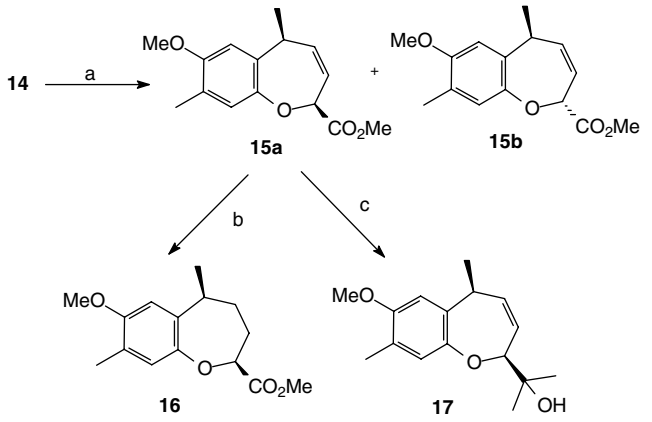
The synthesis began with 3-methyl-4-hydroxyacetophenone **6**, which was converted to methyl ether **7** in 96% yield through reaction with methyl iodide in the presence of potassium carbonate in refluxing acetone. Baeyer–Villiger oxidation of **7** followed by hydrolysis furnished methoxy protected phenol **8** in an 85% yield. This phenol was alkylated with crotyl bromide and the resultant ether **9** subjected to a thermal Claisen rearrangement to furnish styrenol **10**[7] in an overall yield of 79%. The presence of the aromatic protons as two singlets at δ 6.60 and 6.62 attested to the regioselectivity of the rearrangement. Transformation of this styrenol to a properly structured diene for ring closing metathesis required introduction of a moiety, which could be suitably elaborated to reveal an alkene component for the cyclization and another functionality convertible to the isopropanol group at C-10. To this end, styrenol **10** was subjected to an alkylation with 2-bromobutyrolactone in the presence of potassium carbonate in DMF, which afforded lactone ether(s) **11**[7] in very good yield (82%), as a 1:1 mixture of epimers as was evident from the ^{1}H NMR spectrum. Separation of the mixture was delayed until the cyclization step for ease of identification as will be evident later. Controlled alkaline hydrolysis of lactone(s) **11** followed by treatment of the resultant hydroxy ester with diazomethane furnished hydroxyester(s) **12**, which were converted to ester mesylate(s) **13** through reaction with methanesulfonyl chloride in the presence of pyridine. Displacement of the mesylate with *o*-nitrophenyl selenocyanate followed by in situ oxidative elimination[8] delivered ester diene(s) **14**[7] in an overall yield of 69% from lactone ether(s) **11**, suitably functionalised for the crucial ring closing metathesis (Scheme 1).

In the event, treatment of this diene(s) **14** with Grubbs' 2nd generation catalyst in methylene chloride resulted in clean cyclization furnishing benzoxepane carboxylate(s) **15a** and **15b**[7] in 85% yield. The two isomers were present in a 1:1 ratio and were easily separated by column chromatography. The identity of the desired cis diastereoisomer **15a** was established after catalytic hydrogenation to furnish benzoxepane carboxylate **16**, which was spectroscopically identical with a sample previously prepared in this laboratory.[6c,d] Reaction of **15a** with excess methyllithium afforded *O*-methyl heliannuol B **17**[7] (Scheme 2). In the ^{1}H NMR spectrum of **17**, the position of the protons at C-7, C-8, C-9 and C-10 closely matched the values reported for heliannuol B. The final demethylation to complete the synthesis of **1** was, however, fraught with unanticipated problems and all efforts at this demethylation employing various reagents (BBr_3, TMSiI, EtSH and Na) were unsuccessful and gave only decomposed products.

The failure of the crucial and final demethylation step in the synthesis of **1** indicated the need to use a different protecting group amenable to cleavage. There was also the need for the proposed functionality to withstand the basic and acidic conditions employed in the synthetic process. Hence, we chose to use a benzyl protecting group and the successful completion of the synthesis of **1**, following the same reaction sequence is described. Alkylation of hydroxyacetophenone **6** with benzyl bromide in the presence of potassium carbonate in refluxing acetone furnished benzyl ether **18**, which was converted to phenol **19** through a Baeyer–Villiger oxidation as before. Alkylation with crotyl bromide followed by Claisen rearrangement delivered styrenol **21** in an overall yield of 81%. This styrenol was subjected to the same sequence of reactions as **10** involving alkylation with 2-bromobutyrolactone followed by ring opening and alkene formation to finally provide the diene carboxylate(s) **25** (Scheme 1). Ring closing metathesis of this



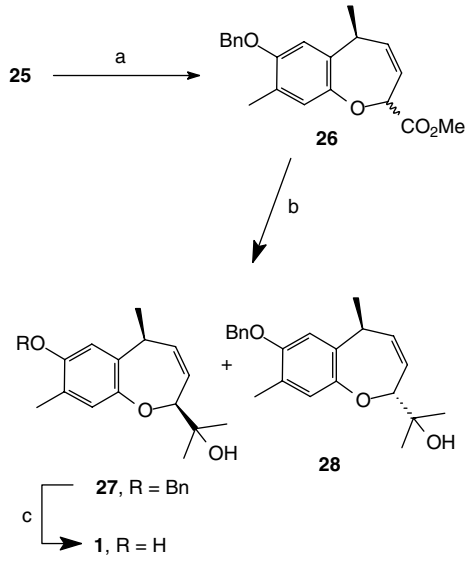
Scheme 1. Reagents and conditions: (a) K_2CO_3, acetone, MeI (for **7**)/BnBr (for **18**), reflux, 5 h; (b) *m*-CPBA, CH_2Cl_2, rt, 14 h; (c) NaOH, MeOH, rt, 5 h, H_3O^+; (d) K_2CO_3, acetone, $CH_3CH{=}CHCH_2Br$, reflux, 3 h; (e) $PhNEt_2$, 180 °C, 12 h; (f) K_2CO_3, 2-bromo-butyrolactone, DMF, 90 °C, 8 h; (g) NaOH, MeOH, rt, 4 h, H_3O^+; (h) CH_2N_2, Et_2O, 0 °C, 2 h; (i) MsCl, Py, CH_2Cl_2, rt, 14 h; (j) *o*-NO_2–PhSeCN, $NaBH_4$, DMF, rt, 8 h; (k) H_2O_2, THF, rt, 3 h.



Scheme 2. Reagents and conditions: (a) Grubbs' 2nd generation catalyst, rt, 8 h (85%), (b) Pd–C, H_2, rt, 8 h, (83%), (c) MeLi, Et_2O, 0–5 °C, 3 h (95%).

diene employing Grubbs' 2nd generation catalyst as before furnished benzoxepane carboxylate(s) **26**[7] in 87% yield as a 1:1 mixture. Attempted separation of the components at this stage was unrewarding and hence the mixture was subjected to reaction with excess methyllithium to afford *O*-benzyl heliannuol B **27**[7] and its epimer **28** in a combined yield of 92%. Separation of this mixture could be achieved by preparative thin layer chromatography. Finally, debenzylation of **27** employing sodium and *n*-butanol[9] furnished heliannuol B **1**, whose spectral data (^{1}H NMR and ^{13}C NMR) fully matched with those reported (Scheme 3).[1,10]

In summary we have described a total synthesis of the allelochemical heliannuol B, employing ring closing metathesis for generation of the central benzoxepane core of the natural product.



Scheme 3. Reagents and conditions: (a) Grubb's 2nd generation catalyst, rt, 8 h (87%), (b) MeLi, Et_2O, 0–5 °C, 3 h (92%) (c) Na, ^{n}BuOH, 80 °C, 3 h (84%).

Acknowledgement

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7. All new compounds reported here gave analytical and spectral data consistent with assigned structures. *Selected spectral data*: For **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, $J = 7.2$ Hz, 3H), 2.15 (s, 3H), 3.71 (m, 1H), 3.78 (s, 3H), 4.77 (br s, 1H), 5.13–5.20 (m, 2H), 6.01–6.13 (m, 1H), 6.60 (s, 1H), 6.62 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 18.8, 37.6, 56.1, 110.3, 114.1, 118.8, 125.8, 127.9, 142.4, 146.9, 152.0. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97;

H, 8.39%. Found: C, 74.93; H, 8.38%. For **11**: IR (neat) ν_{max} 1781 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30, 1.32 (2d, $J = 6.9$ Hz, 3H), 2.18 (s, 3H), 2.42–2.51 (m, 1H), 2.62–2.68 (m, 1H), 3.78 (s, 3H), 3.91 (m, 1H), 4.31 (dd, $J = 15.7$, 8.5 Hz, 1H), 4.46–4.53 (m, 1H), 4.79 (t, $J = 7.8$ Hz, 1H), 4.98–5.11 (m, 2H), 5.96–6.05 (m, 1H), 6.63, 6.64 (2s, 1H), 6.88, 6.89 (2s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.76 (19.81), 30.2, 35.72 (35.79), 55.92 (55.93), 65.33 (65.39), 74.43 (74.49), 109.8 (110.0), 113.1 (113.3), 118.1 (118.2), 125.32 (125.34), 133.2 (133.6), 142.6 (143.0), 148.3 (148.4), 153.37 (153.39), 174.1. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30%. Found: C, 69.56; H, 7.28%. For **14**: IR (neat) ν_{max} 1754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32, 1.35 (2d, $J = 7.2$ Hz, 3H), 2.15 (s, 3H), 3.77 (s, 6H), 4.01–405 (m, 1H), 5.02–5.13 (m, 3H), 5.38 (d, $J = 10.5$ Hz, 1H), 5.58 (d, $J = 17.4$ Hz, 1H), 6.01–6.11 (m, 2H), 6.59 (s, 1H), 6.64, 6.65 (2s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 19.92 (19.96), 35.90 (35.96), 52.9, 56.24 (56.25), 79.4 (79.6), 110.4 (110.5), 113.36 (113.39), 116.99 (117.16), 119.3 (119.4), 125.2, 132.7 (132.8), 133.5 (133.7), 143.1 (143.2), 148.49 (148.50), 153.2, 171.0. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64%. Found: C, 70.30; H, 7.65%. For **15a**: IR (neat) ν_{max} 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, $J = 7.2$ Hz, 3H), 2.15 (s, 3H), 3.35 (m, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 4.95 (br s, 1H), 5.63 (dd, $J = 11.6$, 0.9 Hz, 1H), 5.99–6.06 (m, 1H), 6.53 (s, 1H), 6.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 22.7, 39.4, 52.7, 55.8, 78.9, 109.8, 124.5, 124.7, 125.8, 135.2, 137.6, 149.0, 154.5, 170.2. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92%. Found: C, 68.70; H, 6.91%. For **15b**: IR (neat) ν_{max} 1748 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, $J = 7.5$ Hz, 3H), 2.17 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 4.05 (br s, 1H), 4.98–5.00 (m, 1H), 5.48–5.53 (m, 1H), 5.78–5.84 (m, 1H), 6.58 (s, 1H), 6.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 18.9, 32.9, 52.6, 55.8, 79.1, 107.2, 124.0, 124.4, 124.7, 136.5, 138.4, 148.5, 154.4, 169.9. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92%. Found: C, 68.67; H, 6.90%. For **17**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.32 (s, 3H), 1.45 (d, $J = 7.2$ Hz, 3H), 2.16 (s, 3H), 2.76 (br s, 1H), 3.18–3.23 (m, 1H), 3.79 (s, 1H), 4.06 (br s, 1H), 5.49 (d, $J = 12.0$ Hz,1H), 5.96–6.03 (m, 1H), 6.53 (s, 1H), 6.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 23.4, 24.8, 25.4, 40.3, 55.8, 72.5, 87.3, 106.3, 110.3, 123.4, 124.1, 125.81, 125.86, 134.0, 137.7. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%. Found: C, 73.24; H, 8.46%. For **26**: IR (neat) ν_{max} 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40, 1.48 (2d, $J = 7.4$ Hz, 3H), 2.23 (s, 3H), 3.35 (m, 1/2H), 3.82, 3.85 (2s, 3H), 4.06 (br, 1/2H), 4.98–5.05 (m, 3H), 5.50–5.54 (m, 1/2H), 5.64 (dd, $J = 11.8$, 1.2 Hz, 1/2H), 5.78–5.80 (m, 1/2H), 5.96–6.09 (m, 1/2H), 6.62, 6.66 (2s, 1H), 6.98, 7.0 (2s, 1H), 7.33–7.46 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.2 (22.9), 33.2 (39.5), 52.8 (52.9), 70.8 (70.9), 79.2 (79.4), 109.3, 111.7, 116.5 124.3 (124.6), 124.7 (125.1), 126.2 (126.7), 127.6 (127.6), 128.2 (128.9), 135.5, 136.8 (137.8), 137.9 (137.9), 138.7, 149.1(149.6), 153.9 (154.0), 170.2 (170.4); HRMS (ES+ve) calcd for $C_{21}H_{22}O_4Na$ $[M+Na]^+$ 361.1416, found 361.1414. For **27**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.33 (s, 3H), 1.45 (d, $J = 7.0$ Hz, 3H), 2.22 (s, 3H), 2.75 (br s, 1H), 3.19 (m, 1H), 4.08 (br s, 1H), 5.02 (s, 2H), 5.50 (d, $J = 11.7$ Hz, 1H), 5.96–6.03 (m, 1H), 6.62 (s, 1H), 6.87 (s, 1H), 7.32–7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 23.7, 25.1, 25.7, 40.5, 70.9, 72.8, 87.5, 112.3, 124.5, 126.0, 126.7, 127.6, 128.2, 128.9, 134.3, 137.9, 138.0, 150.6, 153.7; HRMS (ES+ve) calcd for $C_{22}H_{26}O_3Na$ $[M+Na]^+$ 361.1779, found 361.1784. For **1**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.32 (s, 3H), 1.43 (d, $J = 7.4$ Hz, 3H), 2.19 (s, 3H), 2.73 (br s, 1H), 3.15 (m, 1H), 4.06 (br s, 1H), 4.51 (s, 1H), 5.47–5.51 (m, 1H), 5.94–6.01 (m, 1H), 6.51 (s, 1H), 6.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 23.3, 24.8, 25.4,29.8, 39.8, 72.4, 87.4, 114.9, 122.7, 124.1, 125.7, 133.9, 138.3, 150.0; HRMS (ES+ve) calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1311, found 271.1317.

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