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Expeditious synthesis of helianane and C-10 halogenated heliananes employing ring-closing metathesis

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$A \hspace{0.1in} B \hspace{0.1in} S \hspace{0.1in} T \hspace{0.1in} R \hspace{0.1in} A \hspace{0.1in} C \hspace{0.1in} T$

An expeditious synthesis of the marine sesquiterpene helianane enclosing an unusual benzoxocane ring system is described employing ring-closing metathesis as the key step. Helianane has been further converted to the naturally occurring C-10 bromo and chloro derivatives.

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Helianane **1**, an atypical sesquiterpene enclosing a benzoxocane ring system was isolated from the marine sponge *Haliclona fascigera*.¹ This is the only aromatic bisabolene structural type to have been found in marine source. Its closest ally, the allelopathic sesquiterpene heliannuol A **2**, has its origin in the plant species *Helianthus annus*.² Recently **1**, along with two halogenated variants **3** and **4**, was isolated from another marine sponge *Spirastrella hartmani*.³ Although **1** itself is devoid of any biological profile, the chlorohelianane **4** has been reported to display in vitro activity against selected human tumour cell lines.

The uncommon structural motif present in **1** has been the subject of synthetic investigations. Snieckus et al. synthesised **1** by generating the eight-membered oxacyclic ring employing ring-closing metathesis.^{4a} Their method however, involved multistep sequences and difficult reaction conditions, not always accompanied by good yields. Our own various syntheses of **1** had featured, as the key steps, a FVP ring expansion, selective cleavage of a cyclopropyl carbinyl radical and application of the Bargellini condensation.^{4b-d} In view of the current interest in the structure of **1**, arising from the biological activity displayed by chlorohelianane **4**, we have devised an expeditious and high yield synthesis of **1**, **3** and **4** and present here the details of this investigation.

Alkylation of the styrenol $\mathbf{5}^5$ with ethyl α -bromopropionate in the presence of potassium carbonate in refluxing acetone furnished the phenoxy ester **6** in 90% yield. Further alkylation of this ester with 1-bromo-3-butene employing LDA as the base delivered the diene **7** in 80% yield, which was properly set up for ring-closing metathesis.

In the event, treatment of this diene with Grubbs 2nd generation catalyst 'A' resulted in the expected cyclisation to afford the benzoxocene ester **8**⁶ in moderate yield (50%), along with the crossmetathesis product **9** in varying yields. Varying the reaction conditions by further dilution did not improve the yield of **8**. Catalytic hydrogenation of **8** furnished the benzoxocane carboxylate **10**⁶ as a mixture of diastereomers in near quantitative yield. (Scheme 1).

In view of the poor yield in the crucial cyclisation step, an alternate scheme was fashioned which would lead to a less encumbered diene with the possibility of a better yield during the RCM protocol. This started with the *m*-cresyl crotyl ether which was subjected to a Claisen rearrangement employing stannic chloride as the catalyst following our previously reported conditions⁷ to furnish the rearranged styrenol 12 in 80% yield. This was alkylated with ethyl α -bromopropionate and the resultant phenoxy ester 13 was subjected to a further alkylation with allyl bromide in the presence of LDA to furnish the diene 14 in 80% yield. Ring-closing metathesis of this diene employing catalyst 'A' afforded the benzoxocene carboxylate 15⁶ as a mixture of diastereomers in 90% yield, which was separable by chromatography. However, further transformations were carried out with the mixture since separation was irrelevant in the subsequent reactions. Catalytic hydrogenation of 15 yielded the same benzoxocane carboxylate 10 in almost quantitative yield (Scheme 2).

No attempt was made to effect the separation of the diastereomers in **10** since the next step required the conversion of the ester functionality to a methyl group to complete the synthesis. This was carried out as reported in our earlier synthesis of **1**.^{4b} Thus, lithium aluminium hydride reduction of **10** proceeded to afford the alcohol **16** (88%) which was converted to the tosylate **17** (91%) by interaction with toluene-*p*-sulfonyl chloride. Finally, reduction of **17** with





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Scheme 1. Reagents and conditions: (a) K_2CO_3 , ethyl α -bromopropionate, acetone, reflux, 7 h, 90%; (b) LDA, 1-bromo-3-butene, HMPA, THF, -78 °C to rt, 7 h, 80%; (c) Grubbs 2nd generation cat. (15 mmol %), dichloro methane, 9 h, 50%; (d) H_2 /Pd-C (10%), ethanol, 4 h, 98%.



Scheme 2. Reagents and conditions: (a) SnCl₄, dichloro methane, 0 °C to rt, 80%; (b) K₂CO₃, ethyl α -bromopropionate, acetone, reflux, 6 h, 81%; (c) LDA, allyl bromide, HMPA, THF, -78 °C to rt, 8 h, 80%; (d) Grubbs 2nd generation cat. (1.5 mmol %), dichloro methane, 24 h, 90%; (e) H₂/Pd-C (10%), ethanol, 3 h, 98%;



Scheme 3. Reagents and conditions: (a) LiAlH₄, THF, reflux, 5 h, 88%; (b) *p*-TsCl, Py, DMAP, 22 h, 91%; (c) NaBH₃CN, HMPA, 130 °C, 20 h, 65%; (d) NBS, acetonitrile, rt, overnight, 98%; (e) NCS, acetonitrile, rt, overnight, 80%.

sodium cyanoborohydride in HMPA furnished helianane **1** in 65% yield, which was spectroscopically identical with a previous sample.^{4b} Overnight treatment of helianane with *N*-bromosuccinimide effected quantitative conversion to bromohelianane **3**, whose spectral data were comparable with those reported (Scheme 3).^{3,8} Similarly, overnight treatment of **1** with *N*-chlorosuccinimide furnished chlorohelianane **4** in 80% yield whose spectral data also were comparable with the reported values.^{3,8}

In summary, we have described an expeditious synthesis of helianane and the C-10 halogenated heliananes employing simple reagents and readily accessible reaction conditions to furnish the target molecules in good overall yield.

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- All new compounds reported here gave spectral data consistent with the assigned 6 structures. Selected spectral data: For 8: IR 1749 cm⁻¹: ¹H NMR (300 MHz, CDCl₃) δ 1.23 (t, *J* = 7.1, 3H), 1.52 (s, 3H), 2.02 (s, 3H), 2.14 (dd, *J* = 7.3, 14.4 Hz, 2H), 2.25 (s, 3H), 2.35 (dd, *J* = 6.5, 14.2 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 5.83 (t, *J* = 6.5 Hz, 2H), 5.83 (t, J = 6.5 Hz (a) 517, 2.55 (dt, J = 0.5, 14.2 112, 211, 4.15 (dt, J = 7.1 16, 211, 5.05 (t, J = 0.5 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.96 (s, 1H), 7.07 (d, J = 7.8 Hz, 1H); ¹³C (75 MHz, CDCl₃) δ 14.5, 21.3, 21.9, 24.4, 30.0 35.1, 61.4, 94.5, 122.2, 124.9, 125.0, 127.1, 132.2, 137.9, 138.4, 154.3, 174.1. For **10**: IR 1751 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.30 (m, 3H) 1.47 (c, 2H) 1.57 (m, 2H) 2H) CDCl₃) δ 1.30 (m, 3H), 1.47 (s, 3H), 1.55, 1.60 (2s, 3H) 1.72–1.82 (m, 2H), 1.84– 2.07 (m, 4H), 2.29 (s, 3H), 3.10–3.19 (m, 1H), 4.21 (m, 2H), 1.62 (s, 5H) (m, 2H), 1.62 (s, 2H), 6.88 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 4.21 (m, 2H), 6.83, 6.93 (2s, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H). ¹³C (75 MHz, CDCl₃) δ 14.5, 19.6, 19.7, 21.1, 22.8, 25.7, 28.8, 30.0, 33.1, 34.7, 40.8, 61.4, 81.2, 81.6, 124.4, 125.2, 126.2, 126.3, 135.3, 135.5, 136.9, 137.0, 153.3, 153.8, 173.8, 174.4. For **15** (one diastereomer): IR 1752 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.24 (m, 6H), 1.31 (m, 3H), 2.19 (s, 3H), 2.23 (m, 1H), 2.69 (m, 1H), 3.75-3.76 (m, 1H), 4.20-4.26 (q, J = 7.2 H2, 2H), 5.35 (m, H), 5.59 (dd, J = 6.3, 10.8 Hz, H), 6.74 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H); ¹³C (75 MHz, CDCl₃) δ 14.3, 19.8, 20.9, 22.3, 33.1, 36.1, 61.3, 82.8, 120.7, 120.8, 125.2, 125.7, 126.8, 136.9, 140.3, 153.0, 173.8. For **3**: ¹H NMR (300 MHz, CDCl₃) δ 1.23 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 3H), 1. 40 (m, 1H), 1.41 (s, 3H), 1.55 (m, 4H), 1.75 (m, 1H), 2.31 (s, 3H), 3.15 (m, 1H), 6.77 (s, 1H), 7.31 (s, 1H); ^{13}C (75 MHz, CDCl₃) 21.0, δ 21.7, 22.5, 26.5, 29.1, 29.7, 38.0, 39.4, 81.4, 119.7, 127.3, 129.9, 134.9, 141.6, 152.3. For 4: ¹H NMR (300 MHz, CDCl₃) δ 1.23 (s, 3H), 1.26 (d, J = 6.9, 3H), 1.39 (m, 1H), 1.41 (s, 3H), 1.58 (m, 4H), 1.72 (m, 1H), 2.29 (s, 3H), 3.16 (m, 1H), 6.76 (s, 1H), 7.13 (s, 1H); ^{13}C (75 MHz, CDCl₃) δ 19.8, 21.2, 21.9, 26.6, 29.2, 29.8, 37.6, 39.5, 81.5, 116.2, 126.8, 127.4, 133.1, 141.3, 151.7.
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- 8. We attribute the minor deviations in the spectral values to a change of solvent in our case (CDCl₃) and possibility of conformational isomers (see Ref. 2).