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

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ABSTRACT

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.

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 multi-step 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 **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 cross-metathesis 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 conditions[7] 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 **15**[6] 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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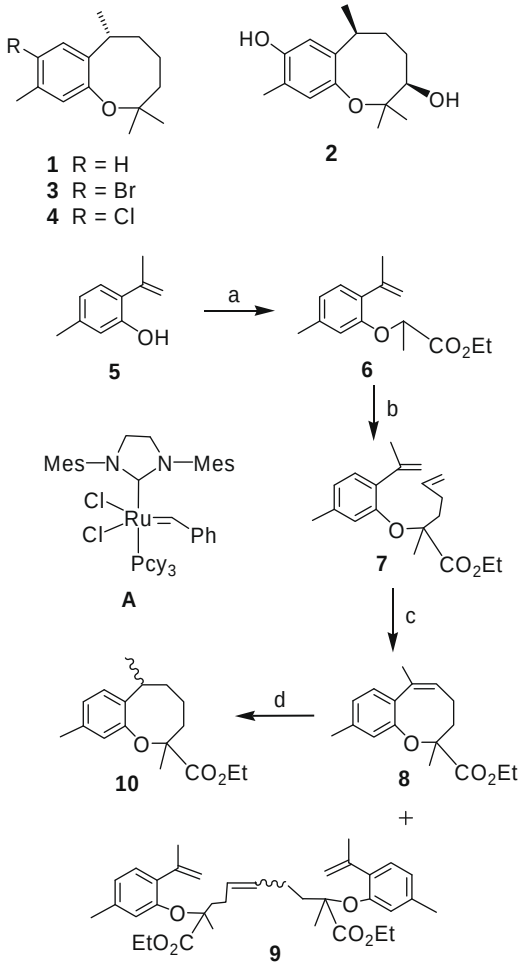
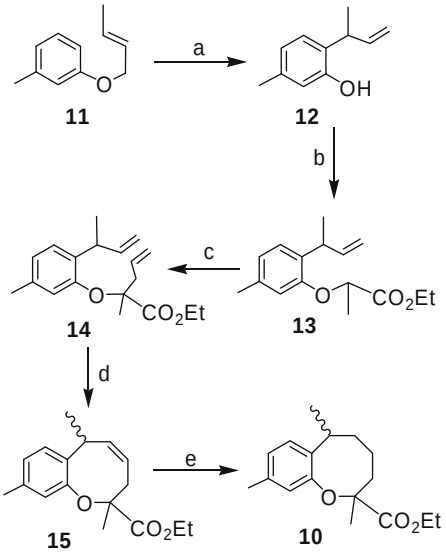
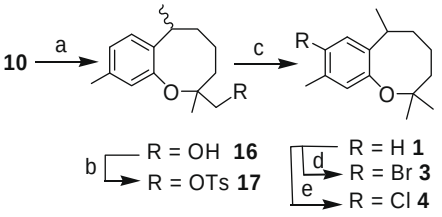


Scheme 1. Reagents and conditions: (a) K_2CO_3, ethyl α-bromopropionate, acetone, reflux, 7 h, 90%; (b) LDA, 1-bromo-3-butene, HMPA, THF, −78 °C to rt, 7 h, 80%; (c) Grubbs 2nd generation cat. (15 mmol %), dichloro methane, 9 h, 50%; (d) H_2/Pd-C (10%), ethanol, 4 h, 98%.



Scheme 2. Reagents and conditions: (a) $SnCl_4$, dichloro methane, 0 °C to rt, 80%; (b) K_2CO_3, 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) H_2/Pd-C (10%), ethanol, 3 h, 98%;



Scheme 3. Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 5 h, 88%; (b) *p*-TsCl, Py, DMAP, 22 h, 91%; (c) $NaBH_3CN$, 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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6. *All new compounds reported here gave spectral data consistent with the assigned structures. Selected spectral data*: For **8**: IR 1749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.96 (s, 1H), 7.07 (d, *J* = 7.8 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) 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, $CDCl_3$) 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), 6.83, 6.93 (2s, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H). ^{13}C (75 MHz, $CDCl_3$) 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, $CDCl_3$) 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 Hz, 2H), 5.35 (m, 1H), 5.59 (dd, *J* = 6.3, 10.8 Hz, 1H), 6.74 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) 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, $CDCl_3$) 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, $CDCl_3$) 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, $CDCl_3$) 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, $CDCl_3$) 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 ($CDCl_3$) and possibility of conformational isomers (see Ref. 2).