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Synthesis of helianane, an unusual marine sesquiterpene employing ring-expansion by flash vacuum thermolysis

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This paper is respectfully dedicated to Professor G. Mehta for his varied and innovative contributions to organic synthesis

Abstract—A total synthesis of the marine sesquiterpene helianane **1** is described involving the thermal rearrangement of the benzoxabicyclo[4.2.0]octenone **4** to generate the dienone **5** incorporating the benzoxocane ring system of **1**. This dienone was converted to the key ketone **11**, which on interaction with methylmagnesium iodide followed by hydrogenation of the resulting alkene **18** furnished helianane **1**.

Helianane **1**, a novel heterocyclic sesquiterpene, was isolated from the marine sponge *Haliclona fascigera*.[1] It contains a benzoxocane ring system, hitherto unprecedented in marine natural products. Its closest ally, the sesquiterpene heliannuol A **2**, was isolated from the plant species *Helianthus annus* and possesses the same ring system with two additional hydroxy groups. Heliannuol A displays significant allelopathic activity.[2] Besides the difference in their source, **1** and **2** also differ in respect of the absolute stereochemistry at the methyl bearing carbon atom, being *S* in **1** and *R* in **2**.

A synthesis of **1**, employing ring-closing metathesis to generate the oxacyclic eight-membered ring, has been reported.[3] We disclose here a synthesis of **1**, wherein the oxocane ring has been developed through a thermal rearrangement of an oxabicyclo[4.2.0] octene system. In connection with our previous efforts towards the synthesis of heliannuol A,[4] the benzoxocane ring was generated through ring expansion involving cleavage of the central bond in a cyclopropane fused seven-membered ring. We had also synthesised 4-deoxyheliannuol A by this method,[4] hoping to convert this to helianane through deoxygenation. In the event that transformation could not be achieved. Herein we report an alternative synthesis of this unusual sesquiterpene.

Central to the synthetic design was the thermal rearrangement of a benzoxabicylo[4.2.0]octenone **4** to generate the oxacyclic system. Tricyclic ketone **4** was expected to give the benzoxocene ring system **5**. Saturation of the olefinic bonds, conversion of the ester functionality to a *gem*-dimethyl group and transformation of the carbonyl function to a methyl group was expected to lead to helianane **1**. The realisation of the above strategy is presented here.

Photolytic addition of acetylene to 2-ethoxycarbonyl-7-methyl chromone **3**[5] furnished the required tricyclic keto-ester **4** in 80% yield. Ring expansion of this keto-ester was achieved by flash vacuum thermolysis (FVT) at 520 °C at 0.01 mmHg and afforded the expected di-enone **5** in an excellent yield (95%) (Scheme 1).[6]

Exhaustive hydrogenation of **5** resulted in saturation of the double bonds and reduction of the ketone to furnish benzoxocane ester **6** in 94% yield. Reaction of this ester with methyl iodide in the presence of LDA afforded the *gem*-methyl carboxylate **7**[6] in excellent yield (90%). Next the ester function in **7** was reduced with lithium aluminium hydride in refluxing THF to alcohol **8** in 88%. Conversion to tosylate **9** and hydride displacement with sodium cyanoborohydride in HMPA led to the formation of the benzoxocane **10**[6] in an overall yield of 67% from the alcohol **8**. Benzylic oxidation to benzoxocanone

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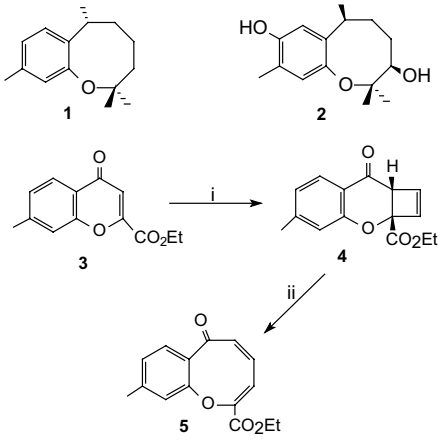
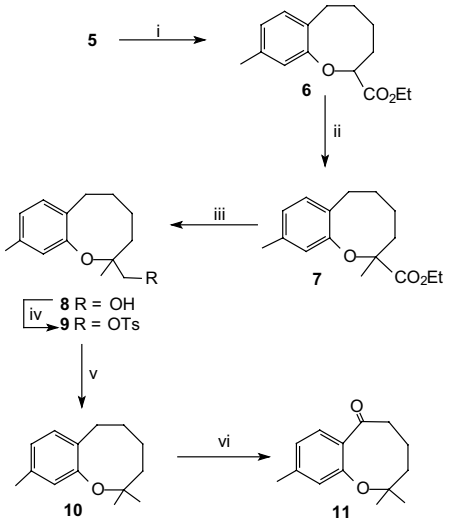


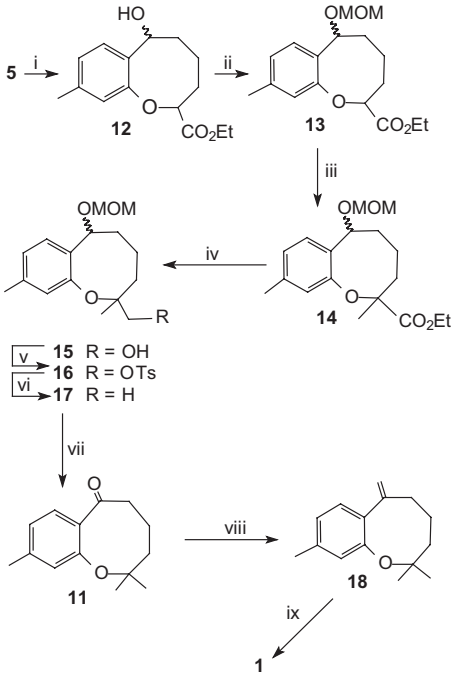
Scheme 1. Reagents and conditions: (i) hν, acetylene, acetone, 10 h, 80%; (ii) 520 °C, 0.01 mmHg pressure, 95%.

11,[6] proceeded sluggishly in a low yield of 18% (Scheme 2).

An alternative higher yielding method for the synthesis of **11** involved controlled hydrogenation of **5**, which resulted in saturation of the double bonds and reduction of the ketone giving hydroxy-ester **12** as a mixture of isomers in 87% yield. Protection of the hydroxy function as the MOM ether **13** was readily achieved in excellent yield (95%) through condensation with chloromethyl methyl ether. Alkylation with methyl iodide in the presence of LDA furnished the methylated carboxylate **14** (87%), which was reduced to the alcohol **15** (85%) with lithium aluminium hydride. Conversion to the corresponding tosylate **16** (95%) and displacement with sodium cyanoborohydride afforded **17**[6] in 68% yield. Finally, cleavage of the MOM protecting group with dimethyl sulfide and $BF_3{\cdot}Et_2O$, followed by Jones' oxidation of the resultant alcohol, delivered the benzoxocanone **11** in a yield of 60% from **17** (Scheme 3).



Scheme 2. Reagents and conditions: (i) H_2, Pd–C (10%), ethanol, 6 h, 94%; (ii) LDA, THF, −78 °C to rt, HMPA, CH_3I, 5 h, 90%; (iii) $LiAlH_4$, THF, reflux, 88%; (iv) *p*-TsCl, Py, DMAP, 24 h, 96%; (v) $NaBH_3CN$, HMPA, 130 °C, 24 h, 70%; (vi) CrO_3, glacial CH_3COOH, H_2O, 5 h, 18%.



Scheme 3. Reagents and conditions: (i) H_2, Pd–C (10%), ethanol, 3 h, 87%; (ii) MOMCl, *i*-Pr_2NH, DCM, 14 h, 95%; (iii) LDA, THF, −78 °C to rt, HMPA, CH_3I, 6 h, 87%; (iv) $LiAlH_4$, THF, 5 h, 85%; (v) *p*-TsCl, Py, DMAP, 26 h, 95%; (vi) $NaBH_3CN$, HMPA, 130 °C, 26 h, 68%; (vii) $(CH_3)_2S$, $BF_3{\cdot}Et_2O$, −10 °C, 2 h; Jones' oxidation, 60% (two steps); (viii) CH_3MgI, ether, reflux, 3 h, 96%; (ix) H_2, Pd–C (10%), ethanol, 4 h, 95%.

With the key benzoxocanone in hand, it only remained to incorporate a methyl group on the carbonyl carbon to complete the synthesis of **1**. Treatment of ketone **11** with methylmagnesium iodide in refluxing ether produced the *exo*-methylene derivative **18**[6] in 96% yield (Scheme 3). This olefin underwent facile hydrogenation in excellent yield to furnish helianane **1**, whose spectral features (^{1}H NMR) were consistent with those made available to us.

In summary we have described a synthesis of helianane, a sesquiterpene with an unusual bicyclic skeleton employing flash vacuum thermolysis to generate the eight-membered oxacyclic ring.

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6. Spectral, analytical data of **5**, **7**, **10**, **11**, **17**, **18**. For **5**: IR ($CHCl_3$) 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, *J* 7.2 Hz, 3H), 2.40 (s, 3H), 4.32 (q, *J* 7.2 Hz, 2H), 6.45 (m, 2H), 6.96 (d, *J* 5.4 Hz, 1H), 7.10 (d, *J* 7.8 Hz, 1H), 7.44 (s, 1H), 7.81 (d, *J* 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 21.8, 62.3, 124.4, 124.5, 127.5, 128.1, 129.1, 132.0, 134.9, 146.5, 149.1, 158.7, 162.6, 191.2; Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.42. Found: C, 69.73; H, 5.38. For **7**: IR ($CHCl_3$) 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, *J* 7.1 Hz, 3H), 1.40–1.49 (m, 2H), 1.55 (s, 3H), 1.69–1.93 (m, 4H), 2.27 (s, 3H), 2.53–2.60 (m, 1H), 2.74–2.82 (m, 1H), 4.29 (q, *J* 7.1 Hz, 2H), 6.77 (s, 1H), 6.85 (d, *J* 7.3 Hz, 1H), 6.99 (d, *J* 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 20.8, 24.4, 24.8, 30.8, 31.3, 33.6, 61.0, 85.3, 125.2, 125.5, 130.0,135.2, 136.1, 151.9, 173.6; Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.28; H, 8.39. Found: C, 72.95; H, 8.03. For **10**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 6H), 1.42–1.49 (m, 2H), 1.51–1.61 (m, 4H), 2.12 (s, 3H), 2.58–2.65 (m, 2H), 6.65 (s, 1H), 6.79 (m, 1H), 6.93 (d, *J* 3.0 Hz, 1H); ^{13}C NMR (75 MHz) δ 20.9, 23.4, 27.6, 27.7, 31.1, 31.2, 37.4, 80.9, 124.7, 125.9, 130.0, 135.7, 140.3, 152.9; Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.13; H, 9.51. For **11**: IR ($CHCl_3$) 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (br s, 6H), 1.41–1.57 (m, 4H), 1.88–1.94 (m, 2H), 2.36 (s, 3H), 6.82 (s, 1H), 7.01 (d, *J* 8.0 Hz, 1H), 7.95 (d, *J* 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 21.3, 26.8, 29.5, 32.7, 39.9, 80.5, 125.1, 127.8, 129.4, 131.1, 145.1, 155.2, 200.7; Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.06; H, 8.25. Found: C, 76.83; H, 7.92. For **17**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.35–1.55 (m, 3H), 1.44 (s, 3H), 1.59–1.75 (m, 2H), 2.13–2.19 (m, 1H), 2.31 (s, 3H), 3.38 (s, 3H), 4.55 (AB_q, *J* 6.5 Hz, 2H), 4.97 (dd, *J* 2.8, 10.4 Hz, 1H), 6.74 (s, 1H), 6.97 (d, *J* 7.7 Hz, 1H), 7.31 (d, *J* 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 21.4, 27.6, 28.8, 38.0, 38.7, 55.9, 73.9, 81.8, 94.9, 125.5 (2C), 126.0, 135.2, 137.2, 152.6; Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.72; H, 9.09. Found: C, 72.33; H,8.85. For **18**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 6H), 1.38–1.56 (m, 2H), 1.75–1.84 (m, 2H), 2.29 (s, 3H),2.81 (t, *J* 6.5 Hz, 2H), 4.92 (s, 1H), 5.42 (s, 1H), 6.72 (s, 1H), 6.88 (d, *J* 8.0 Hz, 1H), 7.48 (d, *J* 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 26.6, 27.7 (2C), 33.7, 34.1, 81.2, 113.0, 125.6, 127.4, 128.2, 129.9, 138.5, 147.4, 152.2; Anal. Calcd for $C_{15}H_{20}O$: C, 83.33; H, 9.25. Found: C, 83.03; H, 8.91.