COMMUNICATION

Synthesis of tricholomenyn A and epitricholomenyn A by a palladium-catalysed β-halo enone coupling route

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The synthesis of tricholomenyn A is described *via* a route employing two palladium-catalysed Sonogashira coupling reactions; an efficient, stereoselective route to epitricholomenyn A is also reported.

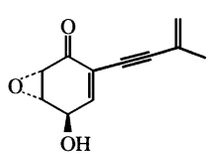
The discovery of the anti-mitotic natural products harveynone **1**[1] and tricholomenyn A **2**[2] introduced acetylenic variants to the epoxycyclohexenone family of bioactive natural products, which includes the complex manumycin antibiotics[3] and relatively simple examples such as bromoxone **3**[4] and LL-C10037α **4**.[5] Recently, more complex tricholomenyns, such as tricholomenyn C **5**, have also been isolated.[6] Given our interest in the synthesis of the halo-[7] and amino-substituted[8] epoxycyclohexenone antibiotics, we decided to look at synthetic approaches to these new analogues.

Initial studies[9] showed that harveynone could be prepared by two related routes involving palladium-catalysed acetylenic coupling[10,11] to β-iodo enone **6** or α-iodo enone **7** (Scheme 1). Here we describe the extension of these studies to the synthesis of tricholomenyn A **2** and its epimer.

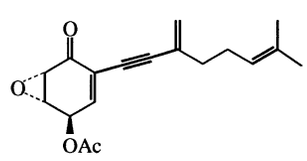
We first explored the α-iodo enone coupling route shown in Scheme 2.‡ The requisite silyl alkyne **10** was readily prepared from commercially available ketone **8** *via* Sonogashira coupling of trimethylsilylacetylene with enol trifluoromethanesulfonate **9** (a similar preparation of **10** has recently been published[12]). Stannyl alkyne **11** was then prepared directly from **10** using Buchwald's procedure, with bis(tributyltin) oxide and catalytic tetrabutylammonium fluoride (TBAF).[13] Stille coupling[10] of stannyl alkyne **11** with α-iodo enone **7** using a range of palladium catalysts and solvents, including the optimum conditions established during the harveynone synthesis,[9] produced at best a low yield (*ca.* 20%) of adduct **12** contaminated by tin by-products. It should be noted that the low reactivity of α-halo enones is well known:[12,14] Kamikubo and Ogasawara experienced similar problems in their tricholomenyn A synthesis and eventually succeeded by carrying out the coupling reaction of the alcohol **13**.[12]

We decided to develop a route which overcame the need for alcohol protection and reduction–reoxidation sequences. We therefore investigated the Sonogashira coupling[11] reactions of the readily available,[9] crystalline β-iodo enone **6** as shown in Scheme 3. We had already established that the palladium-catalysed coupling of **6** with trimethylsilylacetylene proceeded smoothly (68%)[9] and desilylation of this adduct gave alkyne **14**. A second Sonogashira coupling between **14** and enol trifluoromethanesulfonate **9** successfully completed the elaboration of the tricholomenyn side chain to form **15**, albeit in low yield. The introduction of the complete side chain in a single reaction was therefore investigated. The free alkyne **10** (R = H) proved rather volatile and so it was generated by treatment of silyl alkyne **10** (R = $SiMe_3$) with TBAF–SiO_2 and then coupled *in situ* to iodo enone **6**. Using this procedure, adduct **15** was obtained in 86% yield based on **6**. Reduction of **15** with superhydride (−78 °C, THF) proceeded with total stereoselectivity (by ^{1}H NMR spectroscopy) to give **16** with a *syn*-hydroxy epoxide arrangement. Acetylation of unpurified **16** gave **17** which was deprotected directly by treatment with Montmorillonite K10.[15] This three step sequence produced epitricholomenyn A **18** in 57% overall yield from **15**. A similar sequence, but employing DIBAL-H in the reduction step, gave a mixture of **18** and tricholomenyn A **2** itself (46% overall yield, *ca.* 1 : 1.8) which could be separated by column chromatography. The selectivity in favour of the *anti*-isomer of **16** using DIBAL-H was expected by analogy to earlier studies.[7,9] The ^{1}H and ^{13}C NMR data for tricholomenyn A **2** were entirely consistent with those published and were significantly different to those from the epimer **18**. The coupling constants of the vinyl methine [**2**: δ 6.77 (dd, *J* 5, 2.5 Hz); **18**: δ 6.57 (t, *J* 3 Hz)] and α-acetoxy methine [**2**: δ 5.84 (dt, *J* 5, 1 Hz); **18**: δ 5.85 (t, *J* 3 Hz)] were particularly diagnostic.

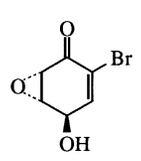
We are currently applying this methodology to the synthesis of other members of the tricholomenyn family and optimising an enantioselective variant of the synthetic route shown in Scheme 1.[16]



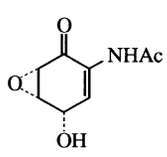
Harveynone **1**



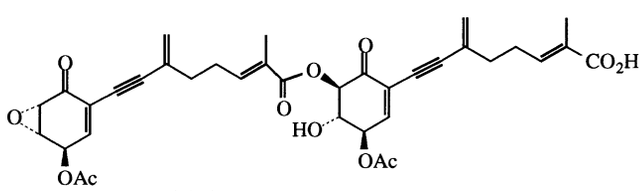
Tricholomenyn A **2**



Bromoxone **3**



LL-C10037α **4**



Tricholomenyn C **5**

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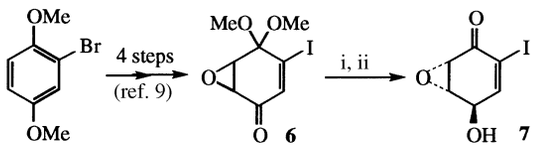
‡ All new compounds (except **11**) were fully characterised by high field ^{1}H and ^{13}C NMR spectroscopy and by elemental analysis or high resolution mass spectrometry.

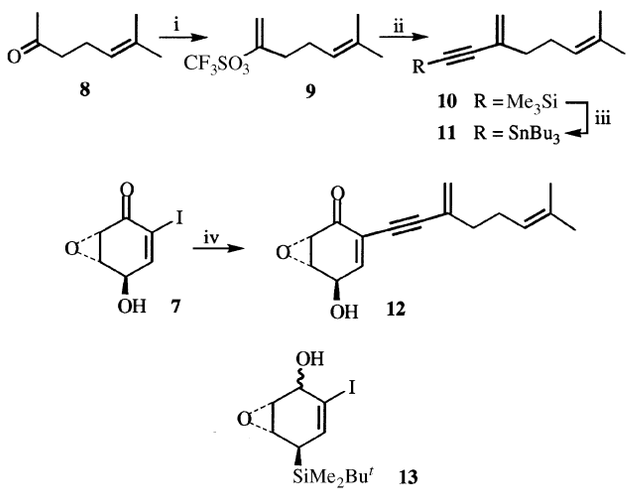
Experimental

Preparation of tricholomenyn A 2 and epitricholomenyn A 18 from β-iodo enone 6

Silyl acetylene **10** (200 mg, 0.97 mmol) was dissolved in THF (10 ml) and tetrabutylammonium fluoride on silica (1 mmol g^{-1}, 1 g, 1 mmol) was added and the reaction stirred for 10 min. Enone **6** (60 mg, 0.2 mmol), copper iodide (1.9 mg, 0.01 mmol, 5 mol%), palladium acetate (2.3 mg, 0.01 mmol, 5 mol%) and triethylamine (0.5 ml) were added and the reaction stirred at room temperature for 4 h. The solvent was then removed *in vacuo* to give a black oil which was purified by silica gel chromatography (light petroleum–ethyl acetate, 9:1) to give adduct **15** (52 mg, 86%) as a yellow oil {HRMS: found (CI): $[M + H]^+$, 303.1603. $C_{18}H_{23}O_4$ requires 303.1596 (2.4 ppm error)}, R_f 0.72 (light petroleum–ethyl acetate, 4:1), which was fully characterised by IR and NMR spectroscopy.



Scheme 1 *Reagents and conditions*: i, DIBAL-H, −78 °C; ii, Montmorillonite K10

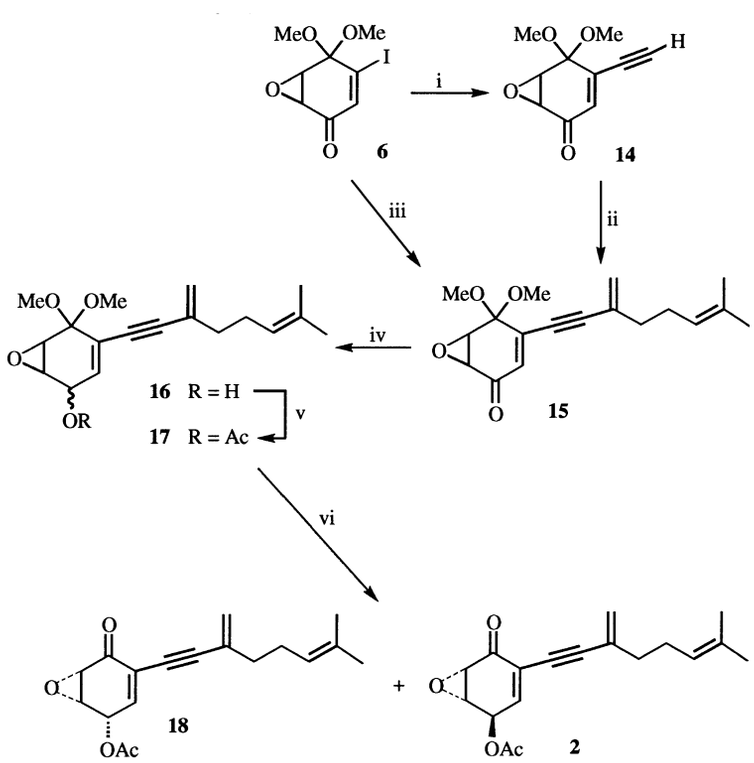


Scheme 2 *Reagents and conditions*: i, LDA, −78 °C, then $(CF_3SO_2)_2$-NPh, 89%; ii, $Me_3SiC{\equiv}CH$, cat. $(PPh_3)_2PdCl_2$–CuI, 99%; iii, $(Bu_3Sn)_2O$, cat. TBAF, 52%; iv, **11**, cat. $(PPh_3)_2PdCl_2$–CuI (see text)

Adduct **15** (100 mg, 0.33 mmol) was dissolved in THF (25 ml) under nitrogen and the solution cooled to −78 °C. To this was added DIBAL-H (1 M solution in THF, 0.4 ml, 0.4 mmol) dropwise over 5 min and the reaction maintained at −78 °C for 1 h, after which time no starting material was present by thin layer chromatography (TLC). The reaction was quenched at −78 °C with methanol (20 ml) and the solution allowed to warm to room temperature and stirred at this temperature for 1 h. The precipitated aluminium salts were removed by filtration through a Celite pad and the solvent removed under reduced pressure to give crude alcohol **16** (R_f 0.1, light petroleum–ethyl acetate, 9:1) which was used directly in the next step.

Unpurified alcohol **16** was dissolved in dry dichloromethane (25 ml) and acetic anhydride (0.1 ml, 1.05 mmol), pyridine (0.1 ml) and DMAP (10 mg) were added. The reaction was stirred at room temperature and monitored by TLC. After 1 h the reaction was complete and aqueous copper sulfate (5%, 20 ml) was added. Standard work up with dichloromethane (3 × 20 ml) followed by drying and removal of the solvent under reduced pressure gave the crude product as a yellow oil. This was flushed through a silica plug to remove the excess acetic anhydride and pyridine to yield the crude acetate **17** as a yellow oil (73 mg, R_f 0.22, light petroleum–diethyl ether, 1:1) which was used directly in the next step.

Acetate **17** (73 mg) was dissolved in dichloromethane (10 ml), Montmorillonite K10 (500 mg) was added and the reaction stirred at room temperature for 30 min. The K10 was removed by filtration through Celite and the Celite pad was washed with dichloromethane (3 × 10 ml). The solvent was removed and the crude product was purified by column chromatography (light



Scheme 3 *Reagents and conditions*: i, $Me_3SiC{\equiv}CH$, cat. $(PPh_3)_2PdCl_2$–CuI (ref. 9), then K_2CO_3, MeOH, 58%; ii, **9**, cat. $Pd(OAc)_2$–CuI, 41%; iii, **10**, TBAF–SiO_2, then cat. $Pd(OAc)_2$–CuI, 86%; iv, $LiBHEt_3$ or DIBAL-H (see text); v, Ac_2O, pyridine; vi, Montmorillonite K10

petroleum–diethyl ether, 4:1) to give tricholomenyn A **2** (24 mg, 24% from **15**) as a yellow oil {HRMS: found (CI): $[M + NH_4]^+$, 318.1702. $C_{18}H_{24}NO_4$ requires 318.1705 (0.8 ppm error)}, R_f 0.19 (diethyl ether–light petroleum, 1:1), which gave NMR data consistent with those published.[2] Further elution gave a mixed fraction of **2** and **18** (*ca.* 1:1, 8 mg, 8%) followed by *epitricholomenyn A* **18** (14 mg, 14% from **15**) as a yellow oil {HRMS: found (CI): $[M + NH_4]^+$, 318.1708. $C_{18}H_{24}NO_4$ requires 318.1705 (0.9 ppm error)}; R_f 0.12 (diethyl ether–light petroleum, 1:1); ν_{max}/cm^{-1} 2927, 1746, 1705, 1371, 1227, 1029 and 912; $\delta_H(CDCl_3$, 270 MHz) 1.62 (3 H, s), 1.68 (3 H, s), 2.18–2.20 (4 H, m), 2.21 (3 H, s), 3.56 (1 H, d, *J* 4§), 3.90 (1 H, m), 5.10 (1 H, m), 5.33 (1 H, d, *J* 1), 5.43 (1 H, d, *J* 2), 5.85 (1 H, t, *J* 3) and 6.57 (1 H, t, *J* 3); $\delta_C(CDCl_3$, 67.5 MHz) 17.7, 20.7, 25.7, 26.6, 37.0, 51.6, 52.5, 66.7, 81.6, 94.7, 122.5, 123.0, 123.3, 130.5, 132.4, 142.5, 170.1 and 189.3.

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§ *J* Values given in Hz.

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