Hypophosphite mediated carbon–carbon bond formation:[1] total synthesis of epialboatrin and structural revision of alboatrin

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1-Ethylpiperidine hypophosphite (1-EPHP) has been used in the key radical-cyclisation step in a 6-step synthesis of the phytotoxic metabolite alboatrin and its epimer from orcinol. The synthesis demonstrates that the stereochemistry of the structure initially proposed for alboatrin requires revision.

We recently reported the use of hypophosphorous acid and its *N*-ethylpiperidine salt[2] in carbon–carbon bond formation, building on the earlier defunctionalisation reactions[3] of Barton *et al.* and of Jang and suggesting that this reagent has excellent prospects in replacing tributyltin hydride in organic synthesis. Not only do hypophosphite salts avoid the problems of toxicity associated with Bu_3SnH, but the water-solubility of hypophosphite salt derived by-products allows swift and efficient purification of reaction products. In addition, hypophosphite salts provide a cost-effective alternative to silicon-based reagents such as tristrimethylsilylsilane (TTMSS).[4] The advantages of the reagent are rapidly being appreciated.[5–7] We now report the successful use of 1-ethylpiperidine hypophosphite (1-EPHP) in constructing the **B**,**C** ring system *en route* to the total synthesis of the proposed structure of alboatrin **1**.[8]

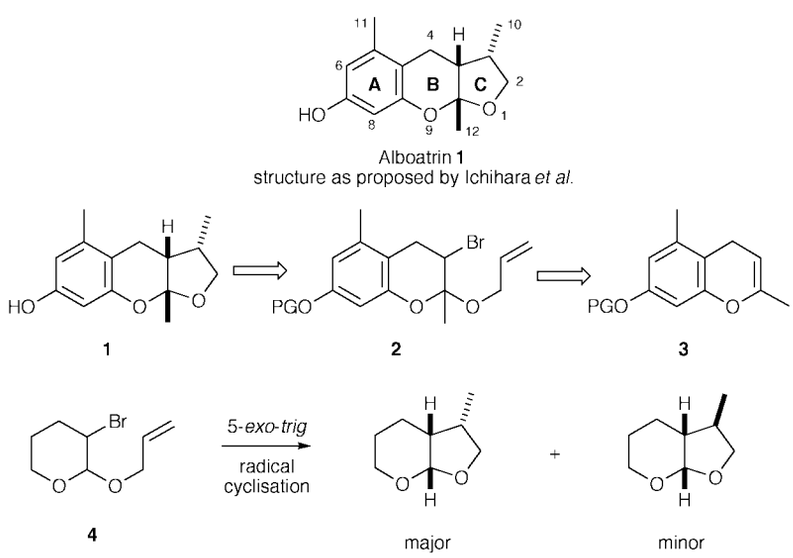
Alboatrin is a phytotoxic metabolite first isolated from the culture filtrate of *Verticillium alboatrum*. The structure of alboatrin had been determined by spectroscopic and degradative methods.[8,9] The stereochemistry at the three contiguous chiral centres is a key feature of the molecule, and the relative configurations have been determined by nuclear Overhauser experiments. Our plan was to use bromochroman **2**, in turn derived from chromene **3**, in a 1-EPHP mediated 5-*exo-trig* radical cyclisation to construct the [6.6.5] linearly fused heterocyclic framework present in alboatrin **1**.

The presence of the ketal moiety would provide an additional stringent test for 1-EPHP, due to its acidity. If the acid-sensitive ketal could withstand the reagent and undergo successful cyclisation, the status of the reagent would be enhanced even further. Alboatrin would be a very suitable target from a synthetic viewpoint, since Beckwith *et al.*[10] and Schäfer *et al.*[11] recently demonstrated the stereoselectivity of radical cyclisations of systems **4** similar to the desired **B**, **C** ring system. The predominant isomer is the desired *cis-anti* isomer (Scheme 1).

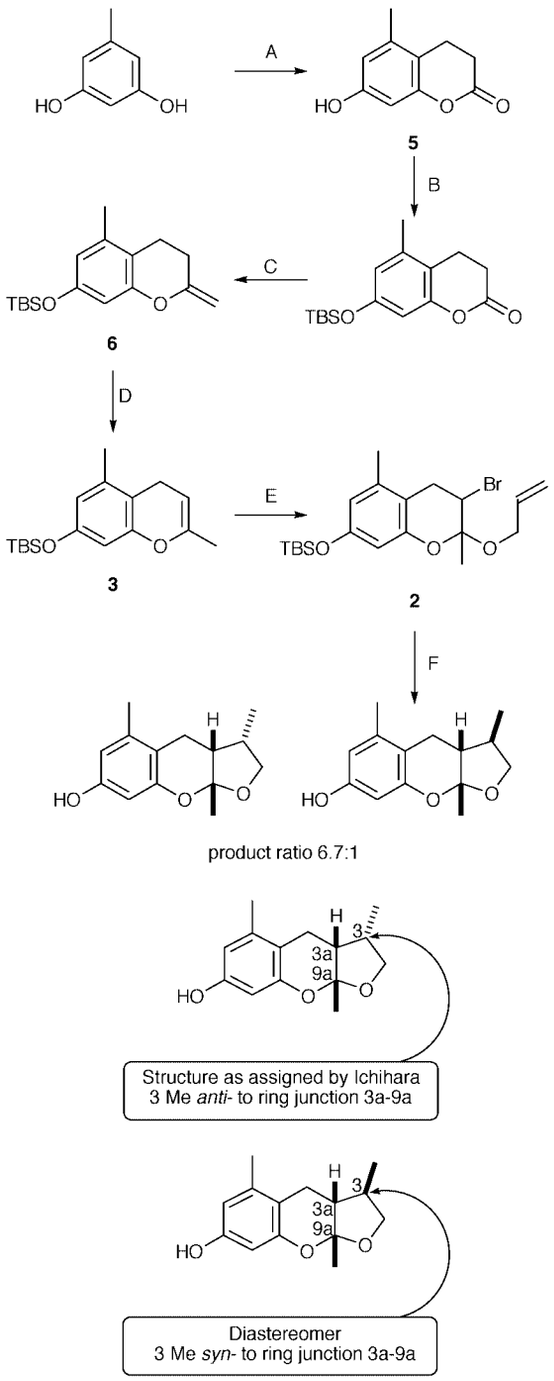
tert-Butyldimethylsilyl ether was chosen as the phenolic protecting group for both chromene **3** and bromochroman **2** intermediates. Deprotection of TBS-ethers has been found to occur in our laboratories when treated with 1-EPHP in refluxing benzene or toluene.[12] (No radical initiator was required to effect the transformation, with cleavage presumably due to the acidity of the solution.) Orcinol was chosen as the bulk starting material for the synthesis. Acid catalysed (Amberlyst 15®) reaction[13] with acrylic acid allowed formation of 5-methyl-7-hydroxy-3,4-dihydrocoumarin **5**. TBS-protection was subsequently achieved under standard conditions (Scheme 2).

5-Methyl-7-*O*-*tert*-butylsilyloxy-3,4-dihydrocoumarin provided an ideal substrate for Tebbe methodology using a literature procedure described by Grubbs.[14] The resulting exocyclic enol ether **6** was isomerised quantitatively using Amberlyst 15® resin to yield chromene **3**. Coupling of **3** with allyl alcohol and *N*-bromosuccinimide in a one-pot procedure afforded the desired bromochroman **2**. Treatment of **2** with 1-EPHP in refluxing benzene efficiently yielded the skeletal framework of alboatrin **1**.

Surprisingly, the major product formed in the reaction was found to be the diastereomer of the naturally occurring compound as reported by Ichihara.[8] NMR studies showed the presence of a mixture of two, distinct diastereomers (6.7 : 1 ratio). Data matching those of naturally occurring alboatrin were displayed by the minor isomer. Thus, it appeared that either Ichihara's assignment of the structure of naturally occurring



Scheme 1



Scheme 2 *Reagents and conditions*: A 87%, acrylic acid, Amberlyst 15® resin, PhMe, 4 h; B 97%, TBSCl, NEt_3, CH_2Cl_2, rt, 6 h; C 70%, Tebbe's reagent, PhMe, −40 °C–rt, 4 h; D 100%, Amberlyst 15® resin, $CHCl_3$, 60 °C, 12 h; E 72%, allyl alcohol, NBS, CH_2Cl_2, 0 °C–rt, 6 h; F 77%, 1-EPHP, AIBN, C_6H_6, 4 h. Overall yield, 6 steps, 33%.

alboatrin required revision, or the 1-EPHP mediated 5-*exo-trig* radical cyclisation proceeded contrary to the predictions of both Schäfer and Beckwith.

Crystal structure analysis[15] was used to determine the relative stereochemistry of the major product unambiguously as shown in Fig. 1.

In conclusion, 1-EPHP has been used for the first time in a synthesis of a natural product. The reactions proceed efficiently and afford the expected isomer. X-Ray single-crystal structure analysis confirms that the stereochemistry of the radical-cyclisation follows the predictions of Beckwith and Schäfer, and that the published structure of alboatrin is not correct.

Preparation of epialboatrin

A solution of 2-allyloxy-2,5-dimethyl-3-bromo-7-*tert*-butyl-dimethylsilyloxychroman (75 mg, 0.175 mmol) and 1-ethylpiperidine hypophosphite (313 mg, 1.75 mmol) in benzene (2 ml) was heated at reflux for 1 h. AIBN (3 mg) was added as radical initiator, a second portion of AIBN being added after a further 0.5 h. Reflux was maintained for 2 h after which time there was no observable starting material. On cooling, the reaction was concentrated *in vacuo* and diluted with ethyl acetate (5 ml), the organic solution was washed with hydrochloric acid (2 M, 2 × 5 ml) and brine (5 ml). The remaining organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Epialboatrin and alboatrin were obtained as a mixture of diastereoisomers (6.7:1) (32 mg, 77%). Isomers were separated by HPLC and recrystallisation from diethyl ether–petroleum ether (bp 40–60 °C) yielded crystals of epialboatrin. Mp 143–144 °C (lit. mp for naturally occurring isomer 146–148 °C) [Found: M^+ (EI) 234.1261, $C_{14}H_{18}O_3$ requires: *M* 234.1256]; ν_{max}(KBr)/cm^{-1} 3325, 1614, 1462, 1090, 834; δ_H (400 MHz, $CDCl_3$) 0.88–0.90 (3H, d, *J* 7, 10-CH_3), 1.56 (3H, s, 12-CH_3), 2.25 (3H, s, 11-CH_3), 2.43–2.69 (2H, m, 3a-H and 3-H), 2.72–2.74 (2H, m, ArCH_2), 3.50–3.61 (1H, dd, *J* 6.7, 8.5, 2-Ha), 4.12–4.18 (1H, dd, *J* 8.5, 8.5, 2-Hb), 6.31–6.33 (1H, d, *J* 2.4, ArH), 6.33–6.36 (1H, d, *J* 2.4, ArH).

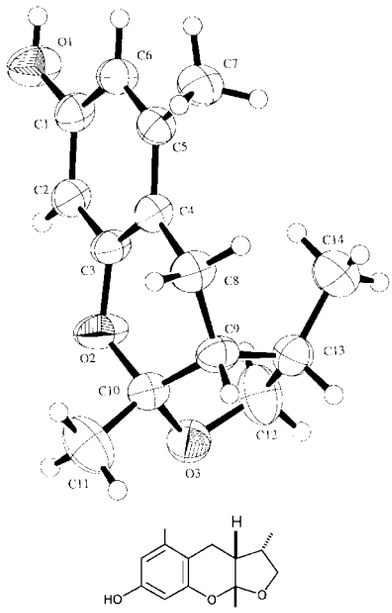


Fig. 1 Crystal structure for major product from radical cyclisation.

Acknowledgements

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15 Crystal data: $C_{14}H_{18}O_3$, $M = 234.28$, monoclinic, $P2_1/n$, $a = 8.886(4)$ Å, $b = 13.659(6)$ Å, $c = 10.369(6)$ Å, $V = 1246$ Å^3, $T = 295$ K, $Z = 4$, $\mu = 0.087$ mm^{-1}, final R indices ($I > 2\sigma(I)$) $R1 = 0.0529$, $wR2 = 0.1502$, 4049 measured reflections of which 1973 were independent, $R_{int} = 0.0692$. CCDC reference number 207/358. See http://www.rsc.org/suppdata/p1/1999/3071 for crystallographic files in .cif format.

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