Diastereoselective Total Syntheses of (±)-Triptoquinone B and C

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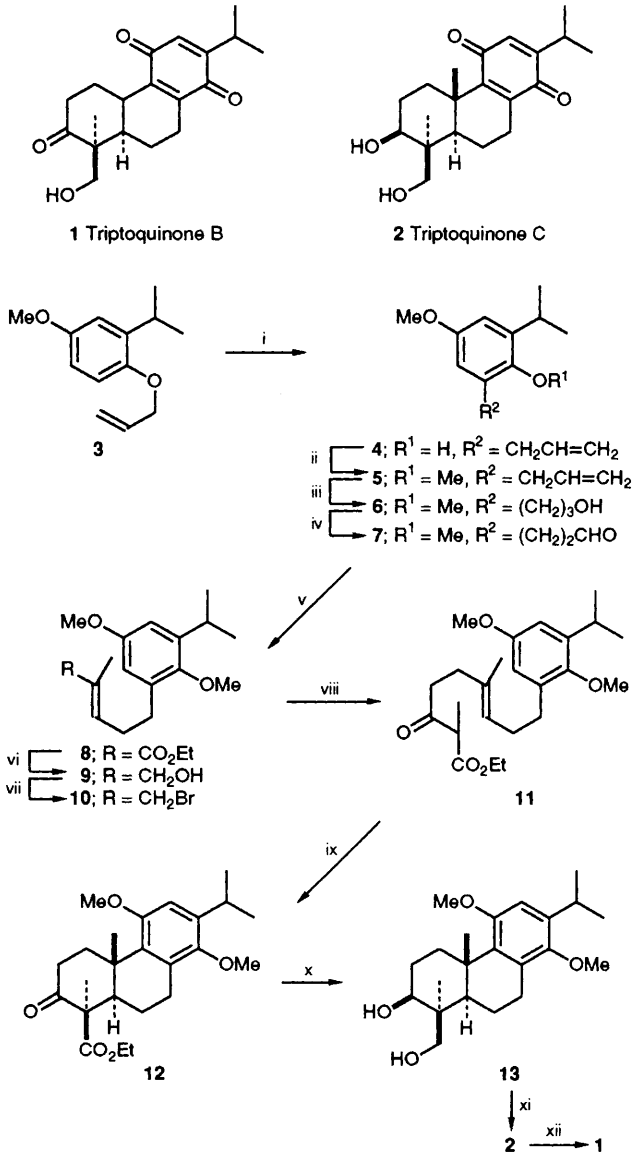
The first and efficient total syntheses of (±)-triptoquinone B **1** and C **2** have been achieved from the allyl ether **3**; the key steps are the construction of the four contiguous stereogenic centres present in **2** by the Mn^{III} mediated oxidative free radical cyclisation followed by metal hydride reduction.

Triptoquinone B **1**[1] and C **2**[2] are structurally novel diterpenoid quinones recently isolated from the extracts of the *Triptery-gium wilfordii* var. *regelii* by us and exhibit potent *in vitro* activity against interleukin-1α and -1β releases for human peripheral mononuclear cells. The structures of these compounds were elucidated mainly by NMR spectroscopic techniques. Herein we report the first diastereoselective total syntheses of (±)-triptoquinone B and C starting from the readily available allyl ether **3** without using any protection–deprotection steps.

As the initial synthetic target we chose **2**, which is converted into **1** by selective oxidation of the secondary alcohol moiety at C-3. The four contiguous stereogenic centres present in **2** are constructed by using a combination of a diastereoselective Mn^{III} mediated oxidative radical cyclization[3] of the olefinic keto ester **11** and lithium aluminium hydride (LAH) reduction leading to the key intermediate 1,3-diol **13**.

Claisen rearrangement of **3**,† derived from 4-bromo-2-isopropylphenol[4] by allylation followed by methoxylation with sodium methoxide in the presence of copper(II) iodide, provided the phenol **4**. On sequential methylation, hydroboration, and Swern oxidation, **4** was converted into the aldehyde **7** in 74% overall yield from **3**. Wittig olefination followed by reduction with diisobutylaluminium hydride of **7** led to the allyl alcohol **9** which was exposed to tetrabromomethane and triphenylphosphine to give the bromide **10** in 78% overall yield for the three steps. Treatment of the dianion, generated *in situ* from ethyl methylacetoacetate, with **10** in tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA) furnished the olefinic keto ester **11** in 68% yield. Subsequent exposure of **11** to 3 mol equiv. of manganese acetate in acetic acid at room temp. caused a clean cyclisation to provide a 70% yield of the tricyclic keto ester **12**‡ as the only isolated product. Although the exact stereochemistry of the only generated diastereoisomer could not be established at this point, proof of it was obtained at the next stage. Thus, reduction of **12** with LAH provided the single 1,3-diol **13**§ in 90% yield. The stereochemical assignment was based on the occurrence of nuclear Overhauser enhancements (NOE) of one of the methylene protons of the C-4 hydroxymethyl moiety and the C-3 axial proton (δ 3.51, dd, *J* 12.0 and 4.7 Hz) on irradiations of angular methyl protons and the C-5 methine proton, respectively. This assignment is consistent with the expected stereochemical course for the oxidative radical cyclization. Finally, oxidation of **13** with cerium ammonium nitrate in aqueous acetonitrile gave triptoquinone C, which was identical (400 MHz ^{1}H NMR, IR, MS, TLC) with an authentic sample of natural **2**, in 87% yield. Conversion of **2** to **1** was accomplished uneventfully by using a chemoselective oxidation procedure developed by Stevens.[5] Thus, treatment of **2**



Scheme 1 *Reagents and conditions*: i, 200 °C, 91%; ii, Me_2SO_4, K_2CO_3, acetone, 99%; iii, BH_3·SMe_2, THF then $^-$OOH, 91%; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 90%; v, $Ph_3P{=}C(Me)CO_2Et$, benzene, 96%; vi, Bu^i_2AlH, toluene, 99%; vii, Ph_3P, CBr_4, 82%; viii, ethyl methylacetoacetate, NaH, Bu^nLi, THF, HMPA, 68%; ix, $Mn(OAc)_3$, AcOH, 70%; x, $LiAlH_4$, THF, 90%; xi, $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O, 87%; xii, 7% aq. NaOCl, AcOH, 91%; DMSO = dimethyl sulfoxide

† All new compounds gave spectral data (IR, NMR and MS) in accord with the assigned structure and satisfactory combustion analysis or accurate mass measurement.

‡ All compounds reported in this paper are racemic. For convenience, only one enantiomer is shown.

§ *Spectral data* of **13**: Colourless prisms (from Et_2O), m.p. 177–178 °C; IR: ν_{max}/cm^{-1} ($CHCl_3$) 3381 (OH); NMR: δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8 Hz), 1.21 (3H, d, *J* 6.8 Hz), 1.23 (3H, s), 1.23–1.28 (1H, m), 1.32 (3H, s), 1.33 (1H, d, *J* 12.7 Hz), 1.38–1.51 (1H, m), 1.75–1.83 (1H, m), 1.88–2.01 (2H, m), 2.61 (1H, ddd, *J* 17.5, 12.3 and 6.3 Hz), 3.02 (1H, dd, *J* 17.5 and 4.2 Hz), 3.15 (1H, ddd, *J* 13.7, 3.7 and 3.7 Hz), 3.27 (1H, sept, *J* 6.8 Hz), 3.38 (1H, d, *J* 11.3 Hz), 3.51 (1H, dd, *J* 12.0 and 4.7 Hz), 3.67 (3H, s), 3.77 (3H, s), 4.32 (1H, d, *J* 11.3 Hz), and 6.57 (1H, s); MS: *m/z* 362 (M^+, 100%) and 219 (57%).

with 7% aqueous sodium hypochlorite in acetic acid produced a 91% yield of pure triptoquinone B, which was also indistinguishable both chromatographically and spectroscopically from natural **1**.

The highly diastereoselective total synthesis reported here is a practical method for the preparation of (±)-triptoquinone B and C since it requires 11 and 12 steps from the readily available **3** and proceeds in 21 and 20% overall yield, respectively.

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