

A Convergent Strategy Towards Taxol. A Facile Enantioselective Entry Into a Fully Functionalized Ring A System

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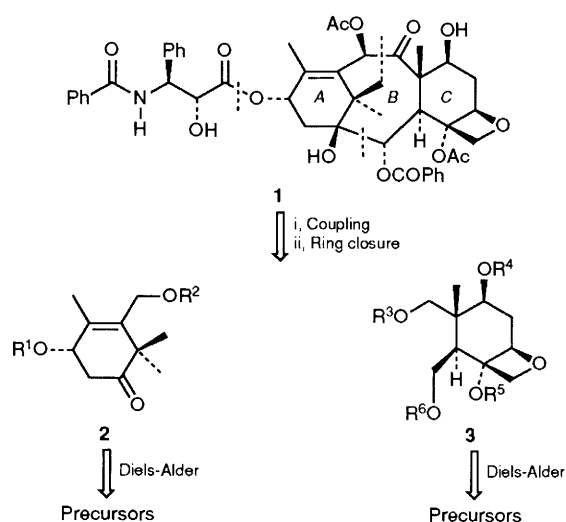
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Key intermediates **10–12** related to the taxol ring A system have been synthesized in enantiomerically pure form by a short and efficient route featuring a Diels–Alder reaction and a Corey oxazaborolidine reduction.

Taxol **1**, the novel polyoxygenated diterpenoid originally isolated from the western yew *Taxus brevifolia*,¹ has recently moved to centre stage as one of the most promising anticancer agents to emerge in recent times.² In this communication we disclose a convergent strategy³ towards this challenging molecule and a facile enantioselective entry into fully functionalized ring A systems.⁴

Scheme 1 outlines a highly convergent strategy for the total synthesis of taxol **1**. According to the plan, the 8-membered ring of taxol **1** is disassembled as indicated by the dotted lines unravelling key intermediates **2** and **3**. Each of these two intermediates could then be retrosynthetically traced to simple precursors *via* Diels–Alder reactions (Scheme 1). It is expected that rapid entries into key building blocks **2** and **3**,



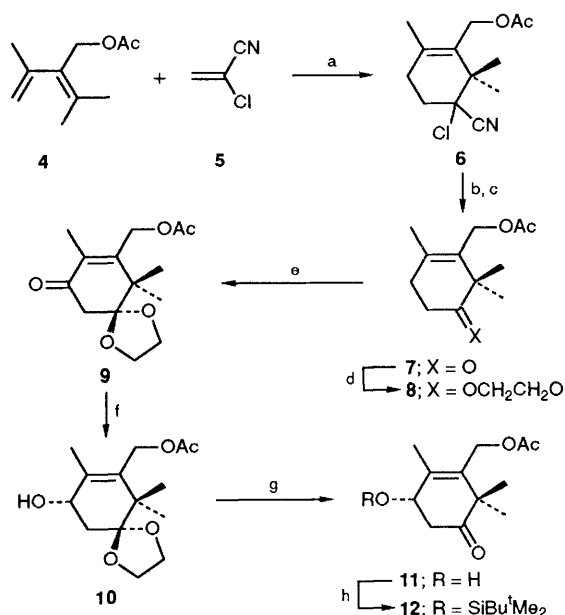
Scheme 1 Convergent strategy for the synthesis of taxol **1**

followed by coupling, ring closure and final elaboration would furnish taxol **1** by a relatively short and efficient route.

Scheme 2 presents a short and stereocontrolled construction[†] of key intermediates **10–12** related to general building block **2**. Thus heating of diene **4**⁵ with an excess of 2-chloroacrylonitrile **5** at 135 °C for 96 h in a sealed tube resulted in the formation of adduct **6**[‡] in 85% yield. Despite the high steric demands of this electronically favoured regiochemical pathway, compound **6** was the only observable product as proven by chromatographic, spectroscopic and X-ray crystallographic analysis.⁶ Generation of the carbonyl group from the chloronitrile **6** under basic conditions was accompanied by acetate hydrolysis to afford the correspond-

[†] All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

[‡] Selected physical properties of compounds. **6**: Colourless crystals, m.p. 86–88 °C (from diethyl ether); R_F 0.25 (silica, 10% diethyl ether in light petroleum); IR (neat): $\nu_{\max}/\text{cm}^{-1}$ 2979, 2205, 1730, 1436, 1371 and 1241 cm^{-1} ; ¹H NMR (500 MHz, CDCl_3): δ 4.62 (s, 2 H, CH_2OAc), 2.44–2.29 (m, 4 H, 2 x CH_2), 2.06 (s, 3 H, OAc), 1.72 (s, 3 H, allylic CH_3), 1.39 (s, 3 H, CH_3) and 1.25 (s, 3 H, CH_3); HRMS (FAB): Calc. for $\text{C}_{13}\text{H}_{18}\text{ClNO}_2$ ($\text{M}^+ + \text{Cs}^+$): 388.0080, found 388.0080. **9**: Colourless oil; R_F 0.5 (silica, 60% diethyl ether in light petroleum); IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 2978, 2884, 1737, 1672, 1652 and 1226; ¹H NMR (500 MHz, CDCl_3): δ 4.81 (s, 2 H, CH_2OAc), 3.95 (m, 4 H, OCH_2CH_2), 2.75 (s, 2 H, CH_2), 2.10 (s, 3 H, OAc), 1.84 (s, 3 H, allylic CH_3) and 1.20 (s, 6 H, 2 x CH_3); HRMS (FAB): Calc. for $\text{C}_{14}\text{H}_{20}\text{O}_5$ ($\text{M}^+ + \text{Cs}^+$): 401.0365, found 401.0353. **10**: Colourless oil; R_F 0.25 (silica, 60% diethyl ether in light petroleum); $[\alpha]_D^{20} -74.5$ (c 0.2 in CH_2Cl_2); IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3439, 2921, 1732 and 1223 cm^{-1} ; ¹H NMR (500 MHz, CDCl_3): δ 4.61, 4.58 (2 x d, J 12.8 Hz, 2 x 1 H, CH_2OAc), 4.10–3.82 (m, 4 H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.94 (brm 1 H, CHO), 3.12 (brd, J 11 Hz, 1 H, OH), 2.15 (dd, J 5.5 and 13.2 Hz, 1 H, CH_2), 2.05 (s, 3 H, OAc), 1.95 (dd, J 3.1 and 13.2 Hz, 1 H, CH_2), 1.82 (s, 3 H, allylic CH_3), 1.08 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3); HRMS (FAB): Calc. for $\text{C}_{14}\text{H}_{22}\text{O}_5$ ($\text{M} + \text{Na}^+$): 293.1365, found 293.1377.



Scheme 2 Synthesis of taxol ring A system **2**. *Reagents and conditions:* (a) **4** (1 equiv.), **5** (1.5 equiv.), 135 °C, 96 h, 85%; (b) KOH (5 equiv.) Bu^tOH, 70 °C, 4 h, 90% yield based on 70% conversion; (c) Ac₂O (1.3 equiv.), DMAP (1.3 equiv.), CH₂Cl₂, 25 °C, 1 h, 98%; (d) ethylene glycol (10 equiv.), CSA (0.2 equiv.), benzene, 70 °C, 1 h, 92%; (e) SeO₂ (1 equiv.), 1,4-dioxane, 100 °C, 2 h, then PCC (2 equiv.), 4Å molecular sieves, CH₂Cl₂, 25 °C, 75% overall yield; (f) Corey's (*R*)-oxazaborolidine⁸ (10 equiv.), catecholborane (2 equiv.), toluene, -78 to 0 °C, 3 h, 95% yield, ≥98% e.e.; (g) TsOH (0.3 equiv.), acetone-H₂O (10:1), 25 °C, 12 h, 65%; (h) Bu^tMe₂SiOTf (1.2 equiv.), 2,6-lutidine (1.5 equiv.), CH₂Cl₂, 0 °C, 15 min, 98% (DMAP = 4-dimethylaminopyridine; CSA = camphorsulfonic acid; PCC = pyridinium chlorochromate; Ts = *p*-MeC₆H₄SO₂; Tf = CF₃SO₂).

ing hydroxy ketone (90% yield based on 70% conversion) which was reacylated under standard conditions leading to ketoacetate **7** (98%). Ketalization of **7** with ethylene glycol furnished compound **8** in 92% yield. Allylic oxidation of **8** with SeO₂ followed by PCC oxidation proceeded regioselectively to afford enone **9** in 75% overall yield after chromatographic separation. Finally, asymmetric reduction of the prochiral enone **9** using Corey's oxazaborolidine procedure⁷ furnished, in 95% chemical yield, allylic alcohol **10**.[‡] Mosher ester⁸ NMR analysis indicated ≥98% enantiomeric excess (e.e.) for this intermediate (absolute configuration is assumed on the basis

of literature precedent).⁷ Further standard manipulations led to compounds **11** (65%) and **12** (98%) which may also serve as potential building blocks for taxol **1**.

The described chemistry paves the way for both a taxol total synthesis and the molecular design, chemical synthesis and biological evaluation of novel mimics of this natural product.

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