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

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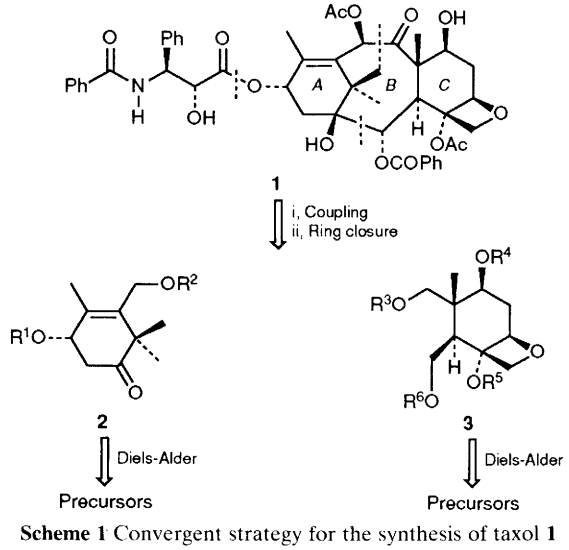
Key intermediates **10–12** related to the taxol ring *A* system have been synthesized in enantiomerically pure form by a short and efficient route featuring a Diels–Alder reaction and a Corey oxazaborolidine reduction.

Taxol **1**, the novel polyoxygenated diterpenoid originally isolated from the western yew *Taxus brevefolia*,[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 strategy[3] 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**, followed by coupling, ring closure and final elaboration would furnish taxol **1** by a relatively short and efficient route.

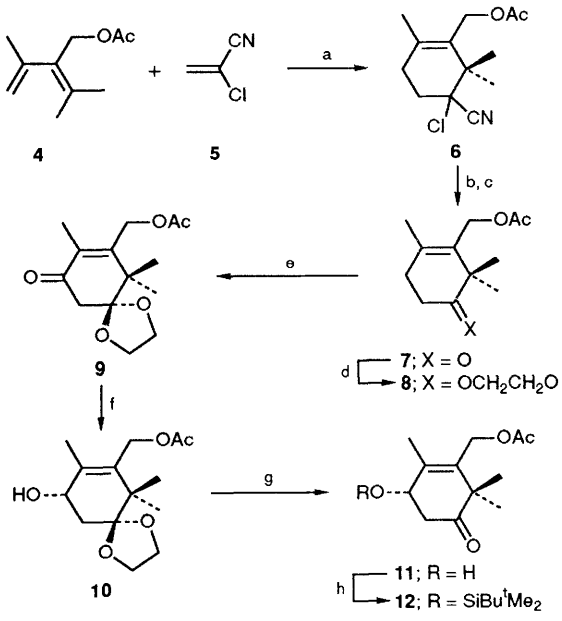


Scheme 1 Convergent strategy for the synthesis of taxol **1**

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): ν_{max}/cm^{-1} 2979, 2205, 1730, 1436, 1371 and 1241 cm^{-1}; ^{1}HNMR (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 $C_{13}H_{18}ClNO_2$ ($M^+ + Cs^+$): 388.0080, found 388.0080. **9**: Colourless oil; R_F 0.5 (silica, 60% diethyl ether in light petroleum); IR (neat) ν_{max}/cm^{-1} 2978, 2884, 1737, 1672, 1652 and 1226; ^{1}H 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 $C_{14}H_{20}O_5$ ($M^+ + Cs^+$): 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) ν_{max}/cm^{-1} 3439, 2921, 1732 and 1223 cm^{-1}; ^{1}H 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, OCH_2CH_2O), 3.94 (brm 1 H, *CH*O), 3.12 (brd, *J* 11 Hz, 1 H, O*H*), 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 $C_{14}H_{22}O_5$ (M + 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^{t}OH, 70 °C, 4 h, 90% yield based on 70% conversion; (c) Ac_2O (1.3 equiv.), DMAP (1.3 equiv.), CH_2Cl_2, 25 °C, 1 h, 98%; (d) ethylene glycol (10 equiv.), CSA (0.2 equiv.), benzene, 70 °C, 1 h, 92%; (e) SeO_2 (1 equiv.), 1,4-dioxane, 100 °C, 2 h, then PCC (2 equiv.), 4Å molecular sieves, CH_2Cl_2, 25 °C, 75% overall yield; (f) Corey's (*R*)-oxazaborolidine[8] (10 equiv.), catecholborane (2 equiv.), toluene, −78 to 0 °C, 3 h, 95% yield, ≥98% e.e.; (g) TsOH (0.3 equiv.), acetone–H_2O (10:1), 25 °C, 12 h, 65%; (h) Bu^{t}Me$_2$SiOTf (1.2 equiv.), 2,6-lutidine (1.5 equiv.), CH_2Cl_2, 0 °C, 15 min, 98% (DMAP = 4-dimethylaminopyridine; CSA = camphorsulfonic acid; PCC = pyridinium chlorochromate; Ts = *p*-Me$C_6H_4SO_2$; Tf = CF_3SO_2).

ing hydroxy ketone (90% yield based on 70% conversion) which was reacetylated 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 SeO_2 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 procedure[7] furnished, in 95% chemical yield, allylic alcohol **10**.‡ Mosher ester[8] 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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References

1 M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325.
2 For some recent articles see, W. P. McGuire, E. K. Rowinsky, B. B. Rosenshein, F. C. Grumbine, D. S. Ettinger, D. K. Armstrong and R. C. Donehower, *Ann. Internal Med.*, 1990, **111**, 273; E. K. Rowinsky, L. A. Casenaue, R. C. Dinehower, *J. National Cancer Inst.*, 1990, **82**, 1247; S. Borman, *Chem. Eng. News*, September 1991, **2**, 11; D. G. I. Kingston, G. Samaranayake and C. A. Ivey *J. Nat. Prod.*, 1990, **53**, 1.
3 For a review on synthetic approaches to taxol and related compounds, see: C. S. Swindel, *Org. Prep. Proc. Intl.*, 1991, **23**, 465.
4 For selected previous approaches to the ring *A* of taxol, see: L. Pettersson, T. Frejd and G. Magnusson, *Tetrahedron Lett.*, 1987, **28**, 2753; I. Kitagawa, H. Shibuya, H. Fujioka, A. Kajiwara, S. Tsujii, Y. Yamamoto and A. Tagaki, *Chem. Lett.*, 1980, 1001; A. S. Kende, S. Johnson, P. Sanfilippo, J. C. Hodges and L. N. Jungheim, *J. Am. Chem. Soc.*, 1986, **108**, 3513; R. A. Holton, R. R. Juo, H. B. Kim, A. D. Williams, S. Harusawa, R. E. Lowenthal and S. Yogai, *J. Am. Chem. Soc.*, 1988, **110**, 6558; C. S. Swindell and B. P. Patel, *J. Org. Chem.*, 1990, **55**, 3; Y. Ohtsuka and T. Oishi, *Chem. Pharm. Bull.*, 1988, **12**, 4711, 4722; S. Blechert and A. Kleine-Klausing, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 412; H. Neh, S. Blechert, W. Schnick and M. Jansen, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 905; K. J. Shea, J. W. Gilman, C. D. Haffner and T. K. Dougherty, *J. Am. Chem. Soc.*, 1986, **108**, 4953; R. V. Bonnert and P. R. Jenkins, *J. Chem. Soc., Perkin Trans. 1*, 1989, 413; *J. Chem. Soc., Chem. Commun.*, 1987, 1540.
5 This diene was obtained by reduction–acetylation of the corresponding ethyl ester: I. Alkonyi and D. Szabó, *Chem. Ber.*, 1967, **100**, 2773.
6 We thank Dr Raj Chadha of the Scripps Research Institute for this X-ray crystallographic analysis, full details of which will be published elsewhere.
7 E. J. Corey and R. K. Bakshi, *Tetrahedron Lett.*, 1990, **31**, 611; E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551.
8 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.