Synthesis of *ABC* Taxoid Ring Systems *via* a Convergent Strategy

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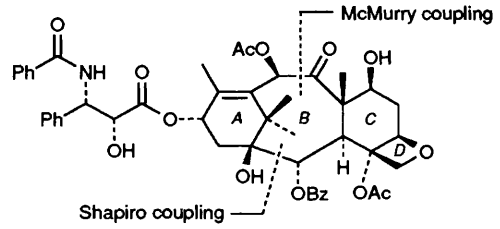
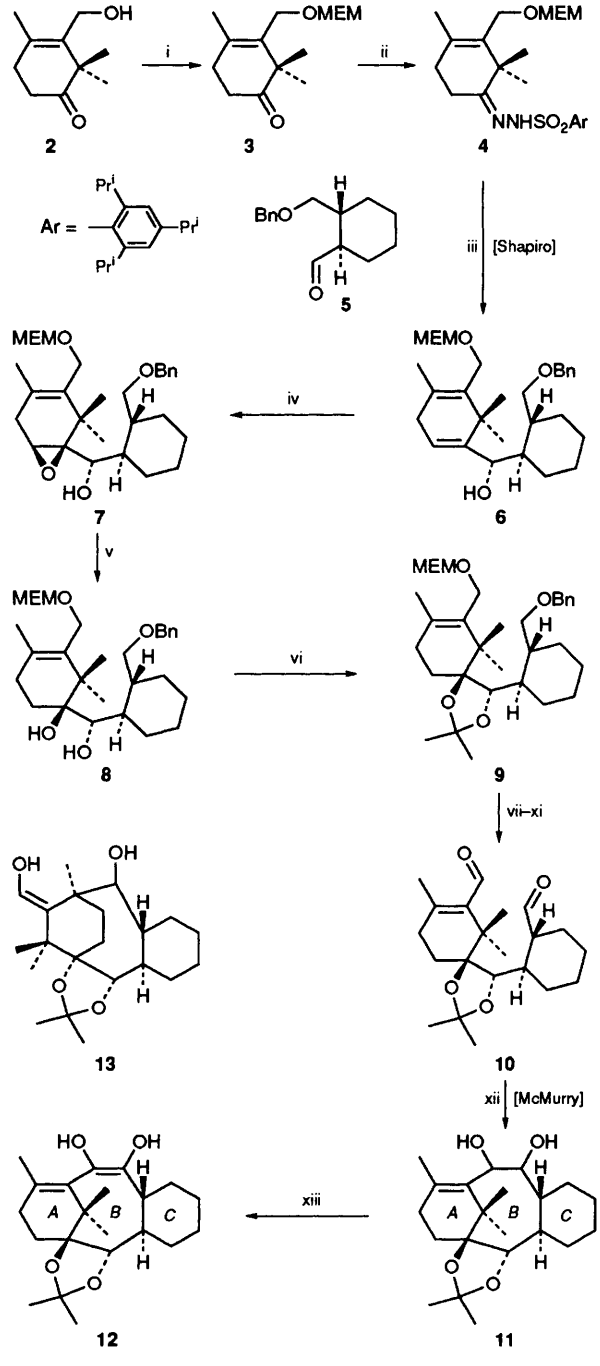
Intermediates **4** and **5** have been coupled *via* a Shapiro reaction to afford compound **6** which has been further elaborated to the *ABC* taxoid systems **11** and **12** *via* a McMurry pinacol cyclization to **11** followed by oxidation to **12**.

In previous communications[1,2] we reported a projected strategy for a convergent synthesis of taxol **1** and stereoselective constructions of the taxol *A*[1] and *C*[2] ring systems. We now disclose the realization of the coupling and ring closure steps of this strategy and the construction of an *ABC* taxoid skeleton. In the present model study, the Shapiro[3] reaction and the McMurry[4] titanium-mediated coupling reaction were utilized as the key operations to join and cyclize the two fragments, respectively, forming the requisite eight-membered ring of the taxoid skeleton. Even though the elegant



studies of Kende *et al.*[5] and Pattenden *et al.*[6] in this field were not so inviting due to the low yield of cyclization and the formation of an olefin rather than a pinacol in the McMurry step, we were prompted to reinvestigate this strategy by the recent McMurry disclosures[4] on modifications of the titanium-mediated coupling reaction to yield pinacol systems. Furthermore, we intended to facilitate ring closure *via* preorganization of the acyclic precursor using an acetonide ring.

Scheme 1 summarizes the construction of the *ABC* taxoid systems **11** and **12** illustrating the present strategy.† Thus, the hydroxy ketone **2**[1] was protected as its methoxyethoxy methyl (MEM) ether **3** (95%) and then converted to hydrazone **4** in 70% yield under standard conditions.[7] Reaction[3b] of **4** with n-butyllithium in tetrahydrofuran (THF) at −78–0 °C followed by addition of aldehyde **5**‡ furnished a mixture of diastereoisomeric alcohols in 83% total yield (*ca.* 2:1 ratio) from which the major isomer **6** was isolated by chromatography. The stereochemistry of **6** was proved by X-ray crystallographic analysis of a subsequent intermediate (*vide infra*). Vanadium-catalysed epoxidation of **6** by the method of Sharpless[8] led stereoselectively to epoxide **7** in 91% yield. Regioselective opening of the epoxide in **7** using $LiAlH_4$ resulted in the formation of **8** (96% yield) which was converted to its acetonide **9** in 77% yield. Sequential and selective protecting group manipulations followed by oxidation using $Pr^n_4NRuO_4$–NMO[9] furnished the dialdehyde **10** in 41% overall yield. Finally, intramolecular McMurry coupling reaction at 50 °C and under high dilution conditions gave the *ABC* ring system **11**§ (*ca.* 1:1 mixture of diastereoisomers,



Scheme 1 *Reagents and conditions*: i, 1.3 equiv. of Pr^i_2EtN, 1.2 equiv. of MEMCl, CH_2Cl_2, 25 °C, 3 h, 95% (ii), 1.0 equiv. of 2,4,6-triisopropylbenzenesulfonylhydrazide, MeOH, 25 °C, 4 h 70%; (iii), 1.2 equiv. of Bu^nLi, THF, −78 °C, 30 min then 0 °C; 1.2 equiv. of **5**, THF, 0 °C, 5 h, 83% (*ca.* 2:1 mixture); iv, 1.2 equiv. of Bu^tOOH, 0.014 equiv. of $VO(acac)_2$, PhH, 25 °C, 2 h, 91% v, 2.0 equiv. of $LiAlH_4$, diethyl ether, 0 °C, 20 min then 25 °C, 6 h, 96%; vi, 2.0 equiv. of 2,2-dimethoxypropane, 0.2 equiv. of CSA, CH_2Cl_2, 25 °C, 12 h, 77%; vii, H_2, 20% $Pd(OH)_2$ on C, EtOAc, 25 °C, 2 h; viii, 1.2 equiv. of $(Ac)_2O$, 1.3 equiv. of 4-DMAP, CH_2Cl_2, 25 °C; ix, 1.2 equiv. of $TiCl_4$, CH_2Cl_2, −78 °C, 30 min then −20 °C, 10 min; x, K_2CO_3, MeOH, 25 °C; xi, 5 mol% TPAP, 1.5 equiv. NMO, 4 A molecular sieves, CH_2Cl_2, 25 °C, 10 min (41% overall yield from vii); xii, 8.5 equiv. of $TiCl_3$–$(DME)_{1.5}$, 25 equiv. of Zn–Cu, DME, 50 °C, 5 h, 40% of **11**, 25% of **13**; xiii, excess of MnO_2, CH_2Cl_2, 25 °C, 20 min, 90%. Hacac = pentane-2,4-dione; CSA = camphorsulfonic acid; TPAP = tetrapropylammonium perruthenate; NMO = 4-methylmorpholine *N*-oxide; 4-DMAP=4-dimethylaminopyridine; DME = 1,2-dimethoxyethane.

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

‡ Aldehyde **5** was conveniently prepared from butadiene and diethylfumarate in 50% overall yield by the following sequence: (i) Diels–Alder reaction,[10] (ii) diisobutylaluminium hydride reduction, (iii) hydrogenation, (iv) monobenzylation and (v) pyridinium dichromate oxidation.

§ Selected physical properties of compounds. The following data was obtained from an inseparable mixture of stereoisomeric diols **11a** and **11b** (ratio *ca.* 1 1): **11**: R_f = 0.30 (silica, 50% diethyl ether in light petroleum); IR (neat): ν_{max}/cm^{-1} 3429, 2928, 2857, 1631, 1454, 1372, 1243, 1218, 1040; ^1H NMR selected peaks (500 MHz, $CDCl_3$); δ 5.00 (bd, *J* 6.0 Hz, 1 H, 10a-H), 4.67 (bs, 1 H, 10b-H), 4.52 (d, *J* 6.1 Hz, 1 H, 2-H), 4.32 (bd, *J* 4.1 Hz, 1 H, 9b-H), 3.95 (d, *J* 6.0 Hz, 1 H, 9a-H), 3.85 (d, *J* 7.2 Hz, 1 H, 2-H), 2.93 (bs, 1 H), 2.27 (bs, 1 H, 10a-H, OH), 2.02 (s, 2 H, CH_3), 1.80 (m, 1 H, 8a-H), 1.76 (s, 3 H, CH_3), 1.62 (m, 1 H, 3-H), 1.58 (s, 3 H, CH_3), 1.45 (m, 1 H, 3b-H), 1.36 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.32 (m, 1 H, 3a-H), 1.27 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3); HRMS (FAB): calc. for $C_{21}H_{34}O_4$ (M + Cs^+): 483.1511 found 483.1511.

For **12**: R_f = 0.48 (silica, 50% diethyl ether in light petroleum); IR (neat): ν_{max}/cm^{-1} 2980, 2856, 2708, 1722, 1671, 1615, 1455, 1373; ^1H NMR (500 MHz, C_6D_6); δ 10.05 (s, 1 H, OH), 9.35 (d, *J* 2.7 Hz, 1 H, OH), 4.16 (s, 1 H, OCH), 2.38–2.28 (m, 2 H, 2 × allylic CH), 2.09–2.05 (m, 1 H, allylic CH), 1.72–1.57 (m, 5 H), 1.63 (s, 3 H, allylic CH_3), 1.55 (s, 3 H, CH_3), 1.50–1.36 (m, 4 H), 1.42 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.10–0.97 (m, 3 H); HRMS (FAB): calc. for $C_{21}H_{32}O_4$ (M + Cs^+): 481.1355, found 481.1349.

unassigned stereochemistry at C-9 and C-10) in 40% yield, together with the isomeric by-product **13**[5] (25%). Oxidation of **11** with MnO_2 led to the enediol **12**§ in 90% yield. The indicated stereochemistry in all compounds (racemic) in Scheme 1 was confirmed by an X-ray crystallographic analysis¶ of compound **10**.

It is envisioned that compounds **11** and **12** could be converted to more advanced taxoids and that this strategy could be applied to the total synthesis of taxol **1** itself.

This work was financially supported by the National Institutes of Health, The Scripps Research Institute, and the University of California, San Diego. E. J. S. is the recipient of an ACS Organic Division Graduate Fellowship, 1992–1993.

Received, 29th March 1993; Com. 3/01798B

¶ We thank Dr Raj Chadha of The Scripps Research Institute for the crystallographic analysis.

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