Synthesis of a Fully Functionalized *CD* Ring System of Taxol

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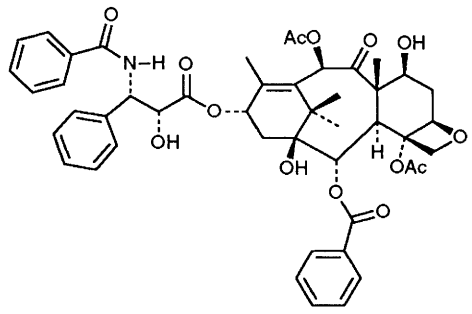
Key building blocks **16** and **17** related to taxol *CD* ring system have been synthesized in racemic form *via* a stereocontrolled and efficient sequence featuring a novel Diels–Alder reaction and oxetane formation.

In the preceding communication[1] we outlined a plausible convergent strategy for the total synthesis of taxol **1**[2] and a convenient synthesis of a suitable ring *A* equivalent, one of the two requisite fragments. In this communication we report a stereocontrolled and expedient entry into fully functionalized systems corresponding to the *CD* ring system which represents the other requisite segment for a projected taxol synthesis.

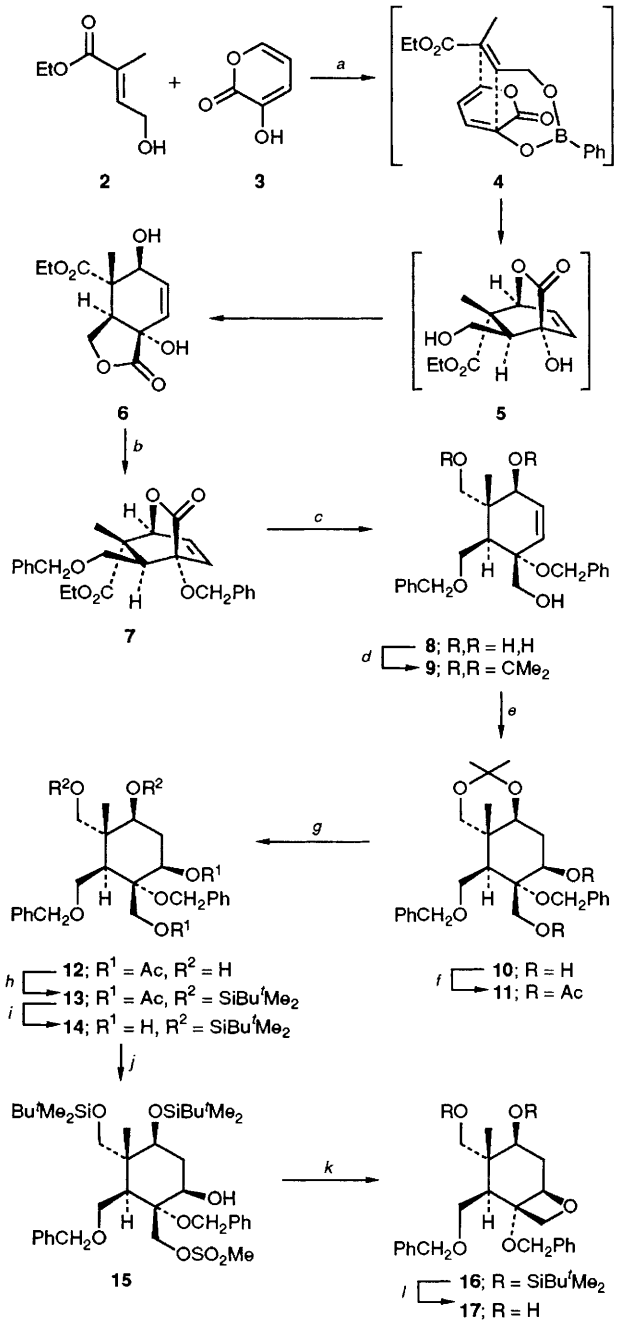
Scheme 1 summarizes the construction of the oxetane-containing fragments **16** and **17** in racemic forms. This approach is based on a Diels–Alder reaction of dienophile **2**†

† Dienophile **2** was prepared in *ca.* 70% overall yield from allyl alcohol by the following sequence: (*i*) silylation with Bu^tPh_2SiCl–imidazole; (*ii*) ozonolysis; (*iii*) condensation with $Ph_3P{=}CH(Me)$-CO_2Et; and (*iv*) desilylation using $Bu^n{}_4NF$.



Taxol: 1

and 3-hydroxy-2-pyrone **3**[3] and made intramolecular through the action of phenylboronic acid according to a procedure recently reported from the Narasaka group.[4] The presumed intermediacy of **4** ensures the desired regiochemical outcome of this cycloaddition reaction leading, initially, to product **5** which apparently rearranges under the reaction conditions to compound **6**‡§ (61% yield). The structure of **6** was supported by chemical and spectroscopic data (Scheme 2). Thus, acetylation of **6** (Scheme 2) gave a diacetate **18**, the ^{1}H NMR spectrum of which exhibited downfield shifts for protons H_a and H_b [300 MHz, $CDCl_3$, δ (**6**): H_a 4.59; H_b 3.10; (**18**): H_a 5.90; H_b = 3.95] as expected. Furthermore, oxidation of **6** led to enone **20** (Scheme 2), whereas persilylation afforded bis(silyl) ether **19** from which the crystalline diol **22** was prepared. An X-ray crystallographic analysis of **22** confirmed its structure and those of its precursors (assuming no skeletal changes under the conditions of the reactions shown in Scheme 2; exposure of **6** to DMAP or CSA in $CDCl_3$ resulted in no changes in its ^{1}H NMR spectrum). Dibenzylation of **6** (Scheme 2) under the influence of KH was accompanied by skeletal rearrangement back to a [2.2.2] bicyclic system, furnishing intermediate **7** (80%). The latter compound **7** was reduced with excess of Red-Al to the triol **8** (90%). Selective acetonide formation led to compound **9** in quantitative yield. Regio- and stereo-selective hydroboration of **9** was directed by the appropriately disposed hydroxymethyl group, leading to



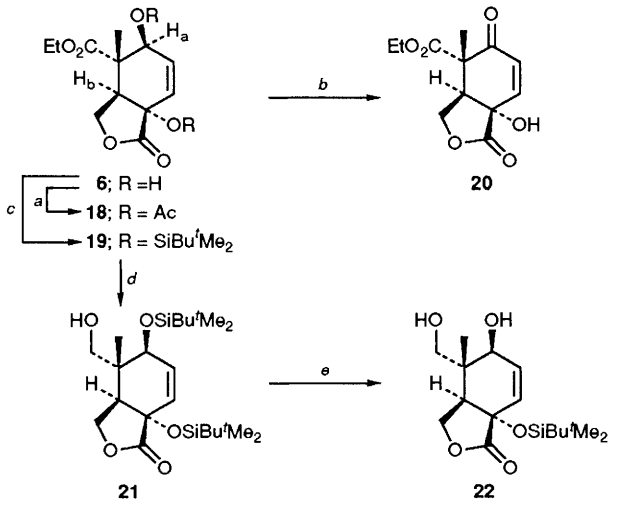
Scheme 1 *Reagents and conditions*: (*a*) 1.0 equiv. of $PhB(OH)_2$, PhH, 90 °C, 48 h; 1.0 equiv. of 2,2-dimethylpropane-1,3-diol, 25 °C, 30 min, 61%; (*b*) 2.5 equiv. of KH, 2.5 equiv. of $PhCH_2Br$, THF, 0.2 equiv. of Bu^n_4NI, 0 °C, 30 min then 25 °C, 1 h, 80%; (*c*) 5.0 equiv. of Red-Al, PhH–THF (9 : 1), reflux, 1 h, 90%; (*d*) excess of 2,2-dimethoxypropane, 0.1 equiv. of CSA, CH_2Cl_2, 100% (*e*) 10.0 equiv. of BH_3·THF, CH_2Cl_2, 25 °C, 1 h; excess of H_2O_2, excess of NaOH, 25 °C, 30 min, 60%; (*f*) excess of Ac_2O, 2.5 equiv. of DMAP, CH_2Cl_2, 25 °C, 30 min, 90%; (*g*) 0.2 equiv. of CSA, MeOH, 100%; (*h*) 2.4 equiv. of Bu^tMe_2SiOTf, 2.6 equiv. of 2,6-lutidine, CH_2Cl_2, 25 °C, 30 min, 90%; (*i*) excess of NaOMe, MeOH, 25 °C, 2 h, 95%; (*j*) 1.2 equiv. of $MeSO_2Cl$, 2.0 equiv. of DMAP, CH_2Cl_2, 0 °C, 2 h, 80%; (*k*) 5.0 equiv. of NaH, Et_2O, 45 °C, 12 h, 95%; (*l*) 3.0 equiv. of Bu^n_4NF, THF, 25 °C, 3 h, 90%. THF = tetrahydrofuran; DMAP = 4-dimethylaminopyridine; CSA = camphorsulfonic acid; Tf = CF_3SO_2.

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

§ *Selected data* for **6**: pale-yellow oil; R_f 0.25 (silica, 70% diethyl ether in light petroleum); IR (neat) ν_{max}/cm^{-1} 3441, 2979, 1777 and 1727; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.09 (dd, *J* 4.0, 10.0 Hz, 1 H, C*H*=CH), 5.82 (br d, *J* 10.0 Hz, 1 H, CH=C*H*), 4.63–4.58 [m, 2 H, C*H*–OH, –CH_2O–C(O)–], 4.45 [dd, *J* 8.2, 9.3 Hz, 1 H, –CH_2O–C(O)–], 4.18 (q, *J* 7.1 Hz, 2 H, CH_2CH$_3$), 3.70 (br, 1 H, OH), 3.10 [dd, *J* 7.7 Hz, 1 H, –C*H*CH$_2$O–C(O)–], 2.55 (br, 1 H, OH), 1.29 (s, 3 H, Me) and 1.26 (t, *J* 7.1 Hz, 3 H, CH$_2$C*H*$_3$): HRMS(FAB$^+$): Calcd for $C_{12}H_{16}O_6Cs$ (M$^+$ + Cs$^+$): 389.0001, found *m/z* 389.0005.

For **10**: amorphous foam; R_f 0.20 (silica, 50% diethyl ether in light petroleum); IR (neat) ν_{max}/cm^{-1} 3398, 2924, 1453, 1369, 1219 and 1063; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.28 (m, 10 H, ArH), 4.66 and 4.39 (AB quartet, *J* 11.8 Hz, 2 H, CH_2Ph), 4.64 and 4.56 (AB quartet, *J* 10.1 Hz, 2 H, CH_2Ph), 4.10 and 3.52 (AB quartet, br, *J* 12.0 Hz, 2 H, CH_2OH), 4.05 (dd, *J* 4.4, 12.6 Hz, 1 H, C*H*OH), 3.86 (dd, *J* 2.2, 12.3 Hz, 1 H, –CH_2OBn), 3.80 (dd, *J* 7.0, 12.3 Hz, 1 H, –CH_2OBn), 3.71 and 3.40 (AB quartet, *J* 11.6 Hz, 2 H, CH_2–O–), 3.07 (dd, *J* 4.1, 11.5 Hz, 1 H, –C*H*–O–), 2.47 (ddd, *J* 4.1, 4.4, 12.2 Hz, 1 H, CH_2), 1.85 (ddd, *J* 12.2 Hz, 1 H, CH_2), 1.72 (dd, *J* 2.2, 7.0 Hz, 1 H, C*H*–CH$_2$–OBn), 1.34 (s, 3 H, Me), 1.32 (s, 3 H, Me) and 1.15 (s, 3 H, Me); HRMS (FAB$^+$): Calcd for $C_{27}H_{36}O_6Cs$ (M + Cs$^+$): 589.1566, found *m/z* 589.1566.

For **17**: oil; R_f 0.40 (80% diethyl ether in light petroleum); IR (neat) ν_{max}/cm^{-1} 3450, 2980, 2870, 1465 and 1072; ^{1}H NMR (500 MHz, C_6D_6): δ 7.57–7.32 (m, 10 H, ArH), 5.09 (dd, *J* 3.2, 8.6 Hz, 1 H, C*H*O), 4.75 and 4.63 (AB quartet, *J* 7.5 Hz, 2 H, CH$_2$O), 4.70 and 4.55 (AB quartet, *J* 11.6 Hz, 2 H, benzylic), 4.70 and 4.54 (AB quartet, *J* 11.7 Hz, 2 H, benzylic), 3.94 and 3.64 (AB quartet, *J* 11.1 Hz, 2 H, CH$_2$O), 3.80 (dd, *J* 6.3, 10.7 Hz, 1 H, CHO), 3.70 (m, 2 H, CH$_2$O), 2.47 (t, *J* 5.9 Hz, 1 H, CH), 2.40 (m, 1 H, CH$_2$), 2.32 (m, 1 H, CH$_2$) and 1.36 (s, 3 H, Me); ^{13}C NMR (125 MHz, C_6D_6) δ 139.36, 138.88, 128.67, 128.59, 128.30, 127.91, 127.87, 127.63, 82.39, 80.73, 76.69, 75.17, 71.84, 66.43, 65.15, 59.62, 43.97, 42.02, 32.85 and 12.14; HRMS (FAB$^+$) Calcd for $C_{24}H_{30}O_5Cs$ (M$^+$ + Cs$^+$): 531.1148, found *m/z* 531.1164.



Scheme 2 *Reagents and conditions*: (*a*) excess of Ac_2O, 2.5 equiv. of DMAP, CH_2Cl_2, 25 °C, 10 min, 100%; (*b*) 1.2 equiv. of PDC, 4 Å MS, CH_2Cl_2 0 °C, 30 min then 25 °C, 30 min, 81%; (*c*) 5.0 equiv. of Bu^tMe_2SiOTf, 6.0 equiv. of 2,6-lutidine, 25 °C, 2.5 h, 67%; (*d*) 1.2 equiv. of $LiAlH_4$, Et_2O, 25 °C, 30 min, 87%; (*e*) 1.0 equiv. of CSA, CH_2Cl_2–MeOH (1:1), 25 °C, 20 min, 100%. PDC = pyridinium dichromate.

diol **10**§ in 60% yield. Acetylation of **10** followed by removal of the acetonide group and bis(silylation) gave derivative **13** *via* compounds **11** and **12** in 90 and 100% yields, respectively. Deacetylation of **13** under basic conditions resulted in the formation of diol **14** which was selectively converted to monomesylate **15** (80% yield) by the use of a slight excess of the requisite reagents (Scheme 1). Finally, treatment of **15** with NaH in diethyl ether at 45 °C for 12 h gave oxetane **16** (90% yield)[5] from which the silyl groups were removed by the action of Bu^n_4NF (92%) to afford compound **17**.§

The described chemistry may prove useful in studies directed toward the total synthesis of taxol **1** and analogues of it.

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