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A Convergent Carbohydrate Approach to the Synthesis of Taxol. Part 1. Ring A Subunit

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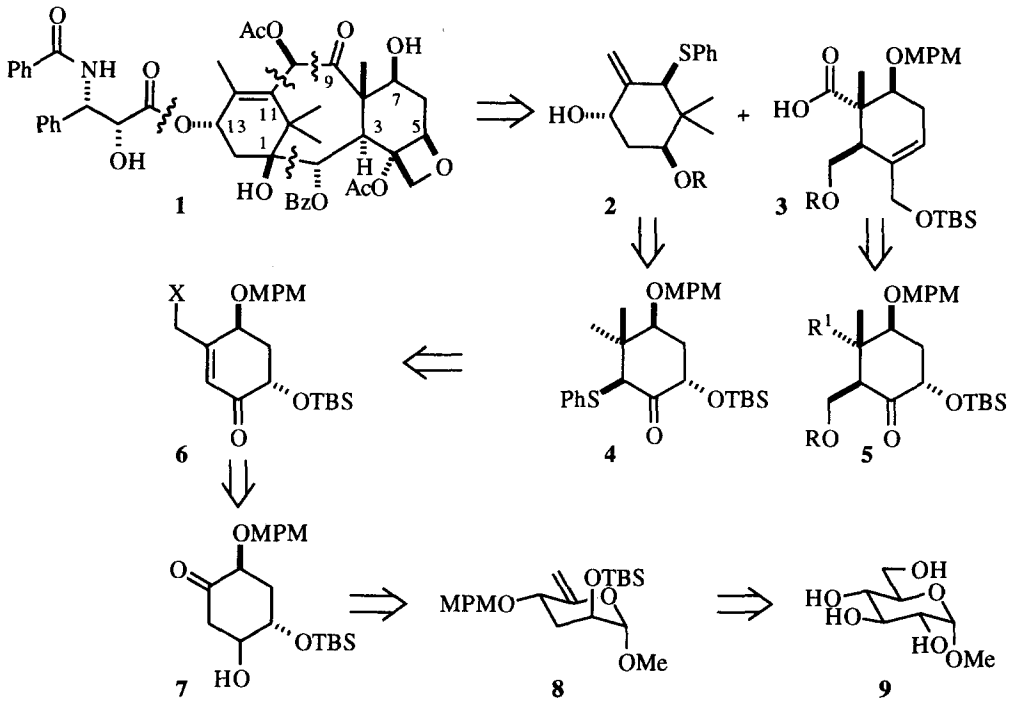
Abstract: *The synthesis of an advanced A-ring subunit of taxol has been performed from D-glucose.*

Ever since its isolation some twenty-five years ago, taxol **1** has attracted tremendous attention due to both its potent antitumour activity and its architecturally complex structure. A great variety of approaches towards the taxane diterpenes has been reported during the past years[1]. However, the total synthesis of taxol itself had remained an unattained goal until its recent independent completion by two research groups[2,3]. In this and the following papers we wish to disclose preliminary results in our quest for the total synthesis of taxol.

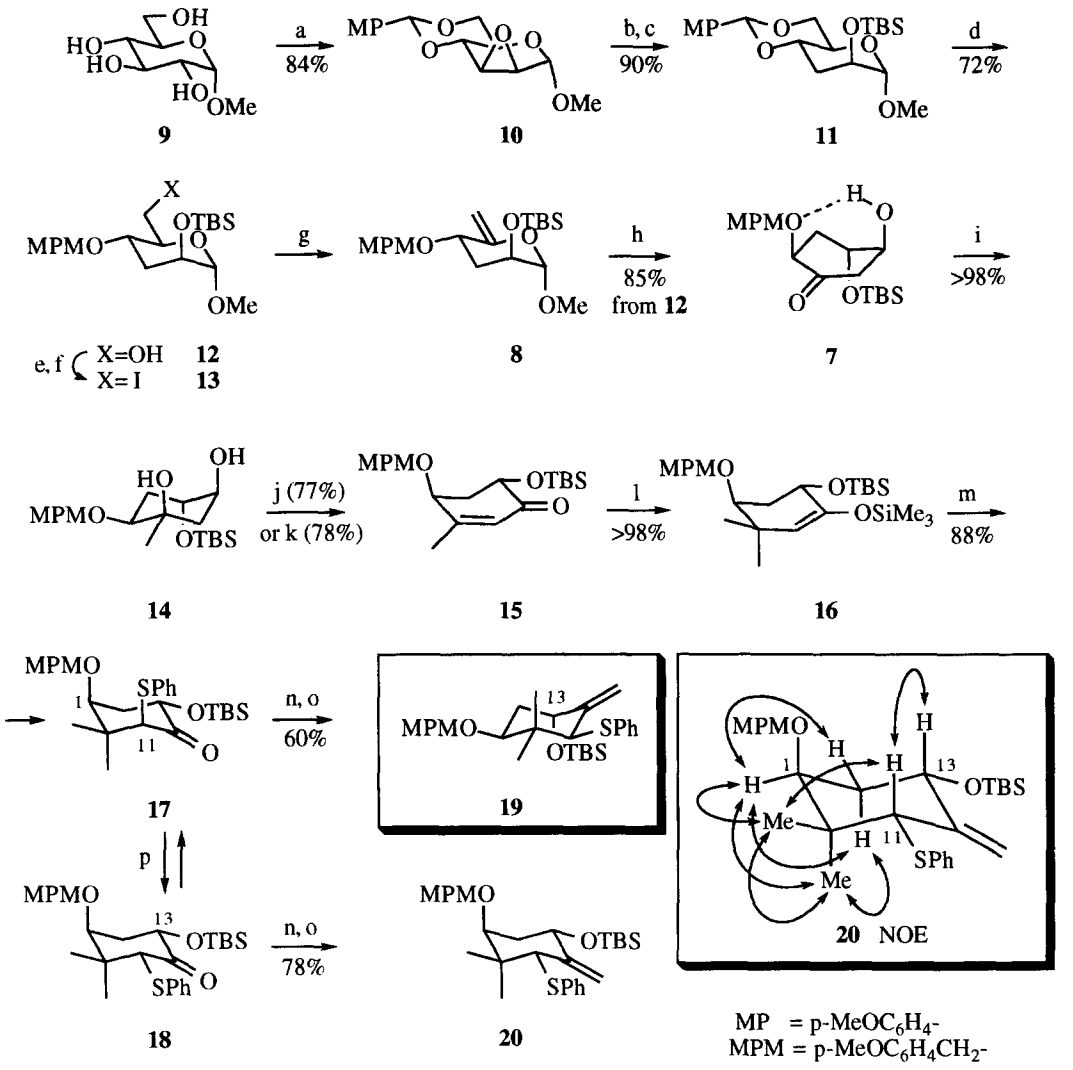
We were planning to design our synthetic scheme in a step-efficient divergentio-convergent mode taking advantage of a A + C→ABC approach which reveals hidden symmetry of the taxol molecule (Scheme 1). As a result of our retrosynthetic analysis, the A-(**2**) and C-ring (**3**) subunits have been selected as targets. Appropriately protected regiomeric allylic alcohol functions present therein can be generated from the very similar α–hydroxyketones **4** and **5** which might be available via tandem conjugate addition - α-functionalization to cyclohexenone(s) **6**.

With respect to the A-ring subunit **2**, the solution is quite clear since both the resident and the entering groups are methyls. The corresponding 3-substituted cyclohexenone **6** (X=H) is available in a two-step sequence from hydroxycyclohexanone **7**, the product of a Ferrier rearrangement of Δ^5-enopyranoside **8**[4]. The synthesis of the latter from D-glucose is based on well-documented schemes. As far as the synthesis of the C-ring is concerned, the situation is more complex. Whether the resident group in the starting substrate should be methyl also depends on the stereochemical outcome of the conjugate addition step. Although the factors controlling the stereochemistry of such an addition have been under investigation during the last thirty years[5], the predictions of the resulting configuration appear unreliable for complex substrates, particularly for the addition of a vinyl group[6] which we considered to be the most attractive precursor for the carboxyl function of the C-ring subunit **3**. In a favourable case, both A- and C-rings become available from the common enone **6** (X=H), otherwise the most promising precursor for the C-ring seems to be the protected 3-hydroxymethylcyclohexenone **6** (X=OR) accessible from the same hydroxycyclohexanone **7**. Our strategy, being relatively flexible, permits the creation of the correct configuration of the quaternary centre anyhow.



Scheme 1

Reduction of *manno*-epoxide **10**[7] with $LiAlH_4$ followed by protection of the resulting alcohol as TBS ether afforded **11** which was subjected to reductive p-methoxybenzylidene acetal ring cleavage. Among several reagents tried, the $SnCl_4$ - Et_3SiH system gave the best result with the formation of only one regiomer **12** in high yield. The product obtained was converted to Δ^5-enopyranoside **8** via elimination from the derived iodide **13** and then subjected to catalytic Ferrier rearrangement[8] to give the hydroxycyclohexanone **7** as an almost pure isomer at the carbinol centre[9]. Methyl Grignard addition to **7** followed by oxidation of the secondary hydroxyl group in the intermediate **14** and elimination of the tertiary alcohol via the derived mesylate or trifluoroacetate gave the α,β–unsaturated ketone **15**. Conjugate addition of lithium dimethylcuprate to enone **15** in the presence of TMSCl afforded silyl enol ether **16** which underwent electrophilic addition of phenylsulphenyl chloride[10] to give the kinetic phenylthio ketone **17** possessing its cyclohexane ring in a (distorted) conformation bearing the 13-silyloxy group (Taxol numbering) *equatorial*[11]. According to our strategy, the hydroxy group at C-13 of *axial* orientation is of crucial importance at the A- and C-ring connection step. Under mild basic conditions the ketone **17** underwent fast isomerization at C-11, without affecting the C-13 configuration, to give a readily separable mixture of **17** and its isomer **18** (**17** : **18** = 4 : 6 at equilibrium). Both were subjected to Peterson methylenation[12] affording respectively **19** and **20**. The product **20**, preserving the conformation of the cyclohexane ring of the starting ketone **18**, has its phenylthio group α–oriented, as evidenced by NOESY (Figure, Scheme 2) and ^{13}C NMR spectroscopy. On the contrary, olefination of **17** was accompanied by a conformational change as the C-13 silyloxy group of **19** has mainly the axial orientation. The cyclohexane ring conformation in **19** appears rather flexible as judged by strong signal broadenings in both its ^1H and ^{13}C NMR



a. p-$MeOC_6H_4CHO$, $(MeO)_3CH$, TsOH (cat)/DMF, then NaH, ImTs; b. $LiAlH_4$/THF, Δ; c. TBSCl, ImH/DMF, rt; d. Et_3SiH, $SnCl_4$ (2 eq)/CH_2Cl_2, -78°C; e. TsCl/Py, rt; f. LiI-HMPA/$PhCH_3$, Δ; g. t-BuOK/THF, rt; h. $Hg(OCOCF_3)_2$ (5 mol%)/acetone-H_2O (3:1); i. MeMgBr/Et_2O, -78°C to rt; j. Swern oxdation, then MsCl-Et_3N; k. TPAP (5 mol%), NMO, MS 4A/CH_3CN, rt, then $(CF_3CO)_2O$, Et_3N, DMAP (cat)/CH_2Cl_2, rt; l. Me_2CuLi, TMSCl, Et_3N, HMPA/THF, -78°C; m. PhSCl, Et_3N/CH_2Cl_2, rt; n. Me_3SiCH_2MgCl/THF; o. KH/THF ; p. saturated K_2CO_3/MeOH - MeOH (1 : 4). rt, 10 min.

Scheme 2

spectrum. The product **19**[13] represents the suitably protected A-ring subunit towards the stereoselective synthesis of taxol.

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7. Readily available from methyl α-D-glucopyranoside **9** in multigram quantities by a one-pot four-step reaction sequence in 84%+ yield; Ermolenko, M. S.; Shekharam, T. unpublished results.
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11. Given on the scheme are structure conformations which fit NMR spectroscopy and reflect the selectivity trends; see also the following Letter in this Issue.
12. For a review on the Peterson olefination see Ager, D. J. In *Organic Reactions*, vol. 38; Paquette, L. A. Ed.; John Wiley: New York, 1990; pp. 1-223.
13. All new compounds were characterized by analytical and spectroscopic methods. Specific rotations were measured in $CHCl_3$ solutions. Selected $[\alpha]_D$ data are given below:
12 : +66 (c 2.2); **7** : -72 (c 1.0); **14** : +9 (c 1.0); **15** : -56 (c 1.6); **17** : +3 (c 1.6); **18**: +29 (c 1.2).

19 : $[\alpha]_D$ +28 (c 1.4); ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.8-7.3 (m, 9H, Ar), 5.10 (br.s, 1H, =CH), 5.03 (br.s, 1H, =CH), 4.64 (m, 1H, H-13), 4.57 and 4.42 (2d, 2H, J_{gem}=11.5 Hz, AB of CH_2MP), 3.80 (s, 4H, OMe, H-11), 3.55 (dd, 1H, $J_{1,14ax}$=9.3 Hz, $J_{1,14eq}$=3.9 Hz, H-1), 1.94 (ddd, 1H, $J_{14ax,14eq}$=13.4 Hz, $J_{13,14eq}$=5.4 Hz, $J_{1,14eq}$=3.9 Hz, H-14eq), 1.71 (ddd, 1H, $J_{14ax,14eq}$=13.4 Hz, $J_{1,14ax}$=9.2 Hz, $J_{13,14ax}$=3.4 Hz, H-14ax), 1.24 (s, 3H, Me-eq), 0.96 (br.s, 3H, Me-ax), 0.90 (s, 9H, t-BuSi), 0.07 (s, 3H, MeSi), 0.02 (s, 3H, MeSi).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 159.3, 146.9, 138.2, 131.7, 130.1, 129.3, 128.7, 125.8, 113.9, 111.8 (br, =CH2), 81.0 (C-1), 71.7 (CH_2MP), 71.5 (br, C-13), 60.1 (br, C-11), 55.4 (OMe), 42.2 (C-15), 36.1 (C-14), 27.2 (Me-eq), 26.0 ($C(\underline{C}H_3)_3$), 18.3 ($\underline{C}(CH_3)_3$), 17.7 (br, Me-ax), -4.8 and -4.9 (Me_2Si).

20 : $[\alpha]_D$ +44 (c 1.0); mp 97-98.5° (from pentane); ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.8-7.3 (m, 9H, Ar), 5.48 (m, 1H, =CH), 5.37 (m, 1H, =CH), 4.58 and 4.39 (2d, 2H, J_{gem}=11.3 Hz, AB of CH_2MP), 4.43 (dd, 1H, $J_{13,14ax}$=11.2 Hz, $J_{13,14eq}$=4.9 Hz, H-13), 3.95 (s, 1H, H-11), 3.81 (s, 3H, OMe), 3.29 (m, 1H, H-1), 2.17 (ddd, 1H, $J_{14ax,14eq}$=13.4 Hz, $J_{13,14eq}$=4.9 Hz, $J_{1,14eq}$=3.2 Hz, H-14eq), 1.66 (ddd, 1H, $J_{14ax,14eq}$=13.4 Hz, $J_{13,14ax}$=11.2 Hz, $J_{1,14ax}$=2.4 Hz, H-14ax), 1.28 (s, 3H, Me-eq), 0.94 (s, 9H, t-Bu), 0.87 (s, 3H, Me-ax), 0.09 (s, 6H, Me_2Si).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 159.5, 147.9, 138.1, 130.9, 129.5, 128.7, 128.6, 125.3, 114.0, 109.8 ($=CH_2$), 83.6 (C-1), 71.9 (CH_2MP), 69.9 (C-13), 57.4 (C-11), 55.4 (OMe), 42.4 (C-15), 36.4 (C-14), 26.2 (Me-eq), 26.1 ($C(\underline{C}H_3)_3$), 21.8 (Me-ax), 18.6 ($\underline{C}(CH_3)_3$), -4.7 and -5.0 (Me_2Si).

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