Novel Chemistry of Taxol. Retrosynthetic and Synthetic Studies

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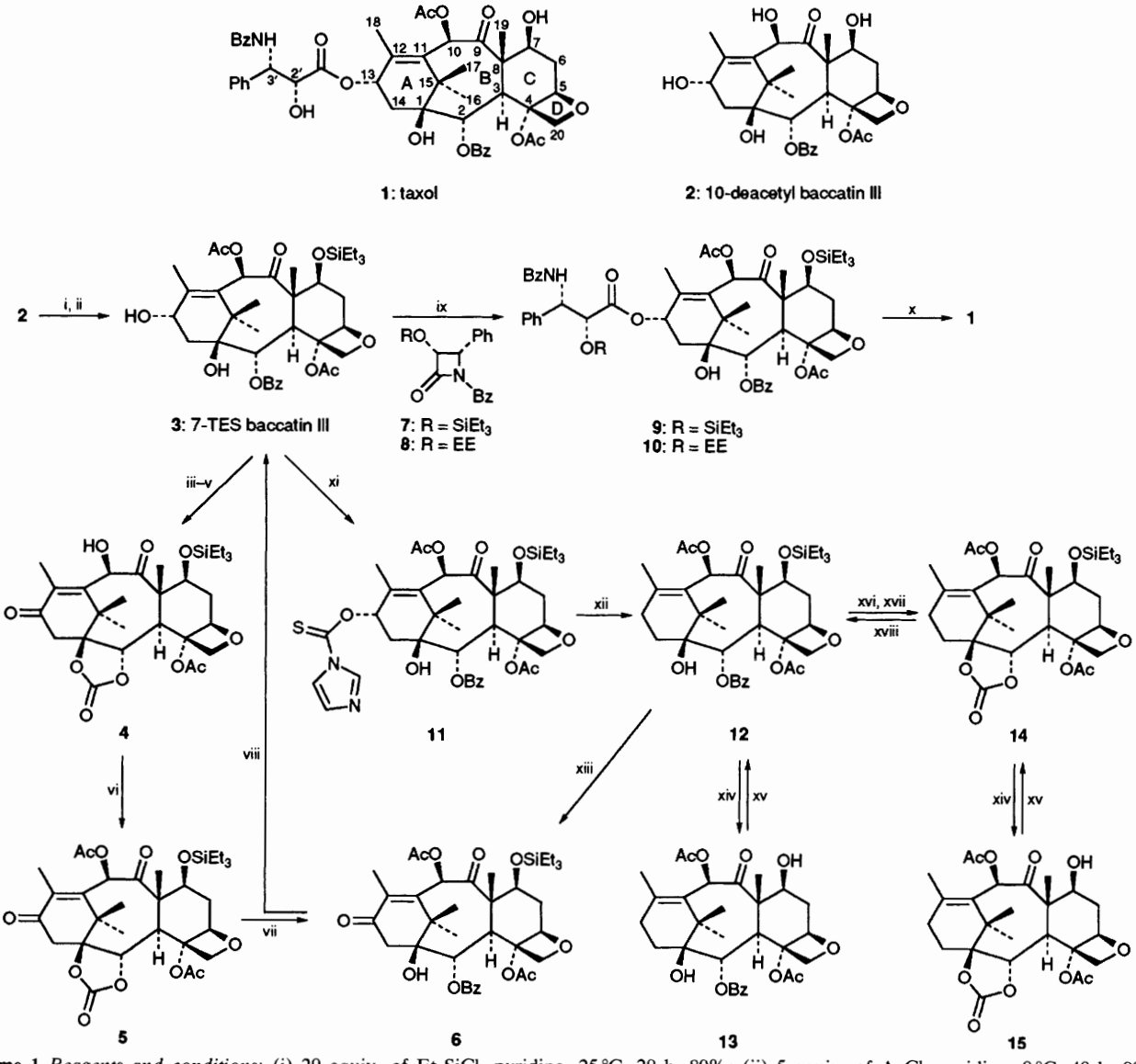
10-Deacetyl baccatin III **2** was used in the synthesis of compounds **4–6** and **11–15**, all of which were converted to Taxol **1** *via* efficient synthetic pathways

Taxol **1**, an important anticancer agent[1] isolated from the western yew, *Taxus brevifolia*,[2] was recently approved in the USA for treatment of ovarian cancer.[3] Furthermore, this agent and the related compound Taxotere, are showing promising properties against a variety of other tumours, including melanoma, breast, and lung cancers. In previous communications we described syntheses of *A*-ring systems,[4] *CD*-ring systems,[5] and *ABC* frameworks[6] of the taxoid family of compounds. For the purposes of paving the way for a total synthesis of Taxol **1** and for preparing novel Taxol analogues, we recently initiated a programme directed towards retrosynthetic and synthetic studies beginning with the naturally



Scheme 1 *Reagents and conditions*: (i) 20 equiv. of Et_3SiCl, pyridine, 25 °C, 20 h, 89%; (ii) 5 equiv. of AcCl, pyridine, 0 °C, 48 h, 90%; (iii) 0.05 equiv. of $(Pr^n)_4NRuO_4$, 1.5 equiv. of 4-morpholine *N*-oxide, 4 Å molecular sieves, acetonitrile, 30 min, 98%; (iv) K_2CO_3 cat., MeOH, H_2O, 0 °C, 9 h, 81%; (v) 10 equiv. of phosgene, pyridine, 25 °C, 30 min, 65%; (vi) 10 equiv. of Ac_2O, 20 equiv. of 4-dimethylaminopyridine, CH_2Cl_2, 30 min, 95%; (vii) 5 equiv. of PhLi, THF, −78 °C, 10 min, 70%, plus 10% 10-deacetyl **6**; (viii) 10 equiv. of $NaBH_4$, MeOH, 25 °C, 5 h, 83%; (ix) 3.5 equiv. of **7** or **8**, 3 equiv. of $NaN(SiMe_3)_2$, THF, 0 °C, 30 min, 87% based on 90% conversion; (x) HF·pyridine, THF, 25 °C, 1.25 h, 80% for **9**; EtOH, 0.5% HCl, 0 °C, 72 h 80% for **10**; (xi) 20 equiv. of thiocarbonyldiimidazole, 30 equiv. of 4-dimethylaminopyridine, THF, sealed tube, 75 °C, 18 h, 86%; (xii) 20 equiv. of Bu^n_3SnH, AIBN cat., toluene, 65 °C, 40%, plus 25% of C12–C13 alkene; (xiii) 30 equiv. of pyridiniumchlorochromate, NaOAc, Celite, benzene reflux, 75%; (xiv) HF·pyridine, THF, 1 h, 65% for **13**, 88% for **15**; (xv) 20 equiv. of Et_3SiCl, pyridine, 25 °C, 20 h, 85%; (xvi) K_2CO_3 cat., MeOH, H_2O, THF, 0 °C, 9 h, 85% based on 55% conversion; (xvii) 10 equiv. of phosgene, pyridine, 25 °C, 30 min, 95%; (xviii) 5 equiv. of PhLi, THF, −78 °C, 10 min, 80%. TES = $SiEt_3$, EE = ethoxyethyl.

occurring 10-deacetyl baccatin III **2**. Here we report the synthesis of a number of intermediates from compound **2** and their conversion to Taxol **1**.

Our initial goal was to prepare a C1–C2 vicinal diol in order to study the introduction of protecting groups at the C2 position and their conversion to the C1 hydroxy-C2 benzoate. To this end, 7-TES baccatin III **3** was prepared[7] from 10-deacetyl baccatin III **2** according to literature procedures[8] (Scheme 1).† All attempts to selectively deprotect the C2 and C10 hydroxy groups, including basic hydrolysis and metal hydride reductions, produced only low yields of the desired triol, a result which is in agreement with previously published studies.[9] It was assumed that oxidation of the C13 hydroxy group would remove a possible hydrogen bond between that hydroxy and the C4 acetate, thus rendering the C4 acetate less susceptible to hydrolysis or intramolecular attack from the C2 hydroxy group. Indeed TPAP oxidation[10] of **3** provided the corresponding C13 ketone, in 98% yield, which was readily hydrolysed under basic conditions to provide the corresponding C1–C2 vicinal diol (81% yield).

Preliminary model studies[6] in our synthetic programmme indicated the necessity for a cyclic protecting group for the C1–C2 diol in order to preorganize the molecular skeleton prior to ring closure to form the eight-membered ring. Furthermore, with the goal of selectively introducing the C2 benzoyl group in the synthetic direction, we envisioned the possibility of directly converting a C1–C2 carbonate into a C2 benzoate by addition of a nucleophilic reagent carrying a phenyl group. Treatment of the triol resulting from the oxidation–hydrolysis of **3** with phosgene in pyridine, did indeed provide the desired carbonate **4** in 65% yield. The acetate **5** was then prepared from **4** using standard acetylation conditions.

Treatment of the carbonate **5** with excess of PhLi at −78 °C for 10 min resulted in the regioselective formation of the benzoate **6** in 70% yield. A small amount (*ca.* 10%) of the 10-deacetyl product resulting from PhLi attack on the C10 acetate group was also observed, although treatment of the crude reaction mixture with Ac_2O in the presence of DMAP provided **6** as a single product, raising the yield of the **5** to **6** step to 80%. This chemistry provided a convenient protecting device for the C1–C2 diol group and opened direct access to the C1 hydroxy–C2 benzoate system of Taxol. The use of other nucleophilic reagents carrying other than phenyl groups to selectively open this carbonate ring should provide a variety of C2 esters, a class of derivatives which is otherwise difficult to obtain from naturally occurring taxoids. The remarkable resistance of the other four carbonyl functionalities in **5** towards PhLi is owing presumably to steric shielding of these sites. Enone **6** was converted back to Taxol **1** by regio- and stereo-selective reduction of the C13 carbonyl group with $NaBH_4$, giving 7-TES baccatin III **3** in 83% yield.[11] Attachment of the side chain onto intermediate **3** was accomplished using Ojima's method.[12] Thus, optically active β-lactams **7**[13] and **8**[13] were coupled[14] with **3** using $NaN(SiMe_3)_2$, to provide 2′,7-diprotected Taxol intermediates **9** and **10**, respectively. Deprotection of either of these compounds (**9** or **10**) using standard conditions provided Taxol **1** in *ca.* 70% overall yield from **3**.

Another possible step in a potential total synthesis of Taxol **1** is the oxidation of the C13 methylene to a ketone group. To test this hypothesis, the C13 deoxy compound **12** was prepared from **3**, *via* the thionoimidazolide **11**, using Barton's deoxygenation procedure (thiocarbonyldiimidazole–DMAP, heat 86%, followed by Bu^n_3SnH–AIBN, heat, 40%).[15] A substantial amount (*ca.* 25%) of the corresponding C12–C13 alkene was also isolated in this deoxygenation reaction. Enone **6** was then prepared from **12**, in 75% yield, using pyridinium chlorochromate (PCC) in refluxing benzene. In order to penetrate further into the projected synthetic scheme, the 7-hydroxy compound **13** was prepared from **12** by desilylation (HF·pyr, 65%). Conversion of **13** back to **12** was accomplished using Et_3SiCl in pyridine (85% yield). Compound **12** was also converted to carbonate **14** [(*a*) K_2CO_3, MeOH–H_2O–THF, 85% based on 55% conversion; (*b*) phosgene, pyridine, 95%] using similar chemistry as described for the synthesis of **4**. Desilylation of **14** (HF·pyr, 88%) led to the 7-hydroxy compound **15** which was converted back to **14** by silylation under standard conditions (Et_3SiCl-pyr, 85%). Nucleophilic addition of PhLi to the carbonate **14** gave the benzoate **12** in 80% yield.

The described chemsitry defines chemical pathways *via* which Taxol **1** and 10-deacetyl baccatin III **2** can be converted to a variety of intermediates including compounds **4–6** and **12–15**, all of which were converted back to Taxol **1**.

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Footnote

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

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