The Pinene Path to Taxanes. 6. A Concise Stereocontrolled Synthesis of Taxol

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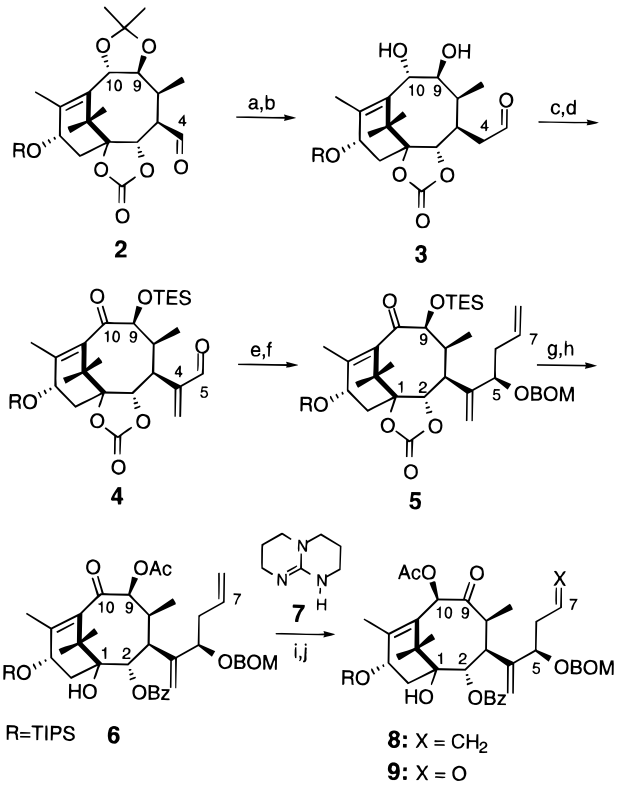
In the preceding communication,[1] we described the synthesis of a potentially general precursor (**2**, Scheme 1) of the highly promising chemotherapeutic agent Taxol[2] (**1**, Scheme 2) and its analogues. Our strategy for the elaboration of this AB-*bicyclic* precursor into the ABC-*tricyclic* core of the taxanes was predicated on the view[1b] that epimerization of the C7 center of Taxol[3] proceeds through the intermediacy of the AB-*bicyclic* enolaldehyde or its ketone isomer, leading to the intriguing possibility that the C-ring of Taxol could self-assemble under exceptionally mild conditions from a considerably less complex AB-*bicyclic* ketoaldehyde precursor (e.g., **9**). In this communication, the viability of this aldol cyclization strategy is demonstrated in a synthesis of Taxol (**1**), representing the shortest sequence yet reported for the preparation of this important natural product.[4,5]

The elaboration of our general taxane precursor (**2**, Scheme 1) into Taxol started with its homologation with $Ph_3PC(H)$-OMe (91%)[6] followed by a one-step hydrolysis of the enol ether and acetonide groups (HCl, NaI) to provide aldehyde **3** (94%).[7] Selective protection of the C9 hydroxyl was then accomplished in 92% yield with TESCl and pyridine. Dess−Martin periodinane oxidation[8] of the C10 alcohol and introduction of C20 with $[Me_2NCH_2]I$ ($\geq$0.1 M)[9] and Et_3N (excess) was conducted in one operation to produce enal **4** in 97% yield. The remaining carbons of the taxane skeleton were then introduced through

Scheme 1[a]



[a] (a) $Ph_3PCHOMe$, THF, −78 °C, 91%. (b) 1 N $HCl_{(aq)}$, NaI, dioxane, 94% at 90% conversion. (c) TESCl, pyr, CH_2Cl_2, −30 °C, 92%. (d) Dess−Martin periodinane, CH_2Cl_2; Et_3N, Eschenmoser's salt, 97%. (e) allyl-MgBr, $ZnCl_2$, THF, −78 °C, 89%. (f) BOMCl, $(i\text{-Pr})_2NEt$, 55 °C. (g) NH_4F, MeOH, rt, 93% over two steps. (h) PhLi, THF, −78 °C; Ac_2O, DMAP, pyr, 79%. (i) **7**, CH_2Cl_2, rt, 1 h, 80% at 63% conversion. (j) O_3, CH_2Cl_2, −78 °C; $P(OEt)_3$, 86%.

the addition of **4** to a solution of allylmagnesium bromide and $ZnCl_2$ (89%)[10] which after BOM (benzyloxymethyl) protection (*N*,*N*-diisopropylethylamine solvent) provided the ether **5** as a single diastereomer.[10c] The presence of $ZnCl_2$ in the former reaction completely suppressed addition of the Grignard reagent to the cyclic carbonate.

Removal of the C9 silyl group (NH_4F, MeOH)[11] provided an unstable hydroxyketone (93% over two steps) which was reacted immediately with PhLi[12] to form the C2 benzoate providing, after *in situ* acetylation, the acetate **6** in 79% yield. Transposition of the acetoxyketone under kinetic[5a] or equilibrating conditions (Et_2NH, KOAc, DMF)[13] resulted in limited success. However, when the guanidinium base **7**[14] was employed for this transposition, the desired acetoxyketone **8** and recyclable **6** were obtained in 80% as a 4:3 equilibrium mixture. The monosubstituted alkene in **8** was then cleaved through addition of an ozone solution to form aldehyde **9** in 86% yield.

The viability of the key aldol cyclization was addressed at this point. Previous studies in our laboratory[1b,15] showed that ketoaldehydes similar to **9** but incorporating a C1−C2 cyclic carbonate did *not* undergo aldol cyclization, preferring instead

(1) (a) Wender, P. A.; *et al. J. Am. Chem. Soc.* **1997**, *119*, 2755 (preceding paper). (b) For an overview of the pinene pathway, see ref 9 in the preceding paper.

(2) Taxol is the registered trademark for the molecule with the generic name paclitaxel. For reviews on Taxol, see refs 1a,b in the preceding paper.

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(4) For recent reviews of synthetic studies from over 35 groups, see ref 7 in the preceding paper.

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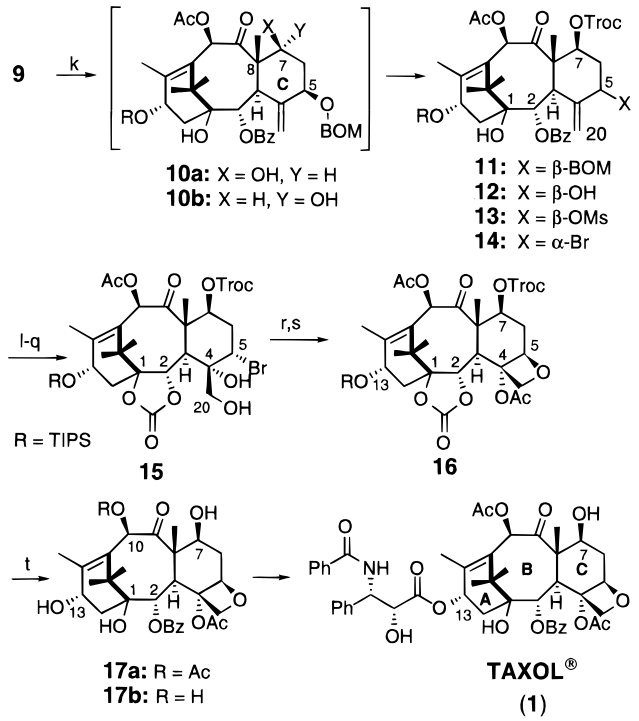
Scheme 2[a]



[a] (k) DMAP (xs), CH_2Cl_2; TrocCl, 62%. (l) NaI, $HCl_{(aq)}$, acetone, 97% at 67% conversion. (m) MsCl, pyr, DMAP, CH_2Cl_2, 83%. (n) LiBr, acetone, 79% at 94% conversion. (o) OsO_4, pyr, THF; $NaHSO_3$; imid, $CHCl_3$, 76% at 94% conversion. (p) triphosgene, pyr, CH_2Cl_2, 92%. (q) KCN, EtOH, 0 °C, 76% at 89% conversion. (r) $(i\text{-Pr})_2NEt$, toluene, 110 °C, 95% at 83% conversion. (s) Ac_2O, DMAP, 89%. (t) TASF, THF, 0 °C; PhLi, −78 °C, 46% 10-deacetylbaccatin III, 33% baccatin III.

to undergo elimination of the C5 ether through deprotonation of the aldehyde. However, a molecular modeling study (Macromodel, MM2* force field, Monte Carlo search) indicated that, by opening the C1−C2 cyclic carbonate to the hydroxybenzoate, the B-ring conformation would change, placing the C8 hydrogen in superior alignment with the C9 carbonyl for the desired deprotonation. In accord with this analysis, exposure of **9** (Scheme 2) to 4-pyrrolidinopyridine provided **10a** and its recyclable epimer **10b** (11:1, respectively) in a combined yield of 72%. This product ratio reflects a kinetic selectivity since neither **10a** nor **10b** epimerized when resubjected to the reaction conditions. Their interconversion can, however, be accomplished with $NaHCO_3$ in MeOH. Protection of the C7 hydroxyl of **10a** with TrocCl (2,2,2-trichloroethyl chloroformate) and pyridine gave **11** in quantitative yield. Conversion of **9** directly to **11** has also been accomplished in 62% yield by initiating cyclization of **9** with DMAP and adding TrocCl after complete conversion of starting material.

Introduction of the oxetane and final functionalization started with cleavage of the C5 BOM ether in **11** with HCl and NaI[7] to form alcohol **12** in 97% yield at 67% conversion. Higher conversion resulted in the formation of an undesired acid induced A-ring rearrangement product.[16] Difficulties encountered while attempting to form the oxetane through the displacement of a leaving group on C20 by the β-oriented C5 hydroxyl[17] prompted investigation of the complementary closure strategy (nucleophilic C20 hydroxyl, C5 leaving group). Toward this end, **12** was converted to the labile mesylate **13** (MsCl, DMAP, pyridine) which was reacted with LiBr to give bromide **14**. Stereoselective introduction of oxygen at C4 and C20 was accomplished with OsO_4.[5a] Direct closure of the resulting diol to form the oxetane was preempted by transfer of the C2 benzoate group to the C20 hydroxyl. Consequently, after osmylation, benzoyl migration was induced to proceed to completion with imidazole and the resulting C1−C2 diol was sequestered as a cyclic carbonate (triphosgene, pyridine) in 92% yield. The C20 benzoate was then removed with KCN[18] in ethanol to form diol **15**. Oxetane formation[17,19] proceeded smoothly with Hünig's base. Acetylation of the C4 hydroxyl was accomplished in 89% yield with Ac_2O and DMAP to give **16**. Removal of the TIPS group from C13 with TASF[5a] followed by addition of a solution of PhLi[12] produced in one operation baccatin III (**17a**, 33%) and 10-deacetylbaccatin III (**17b**, 46%). Alternatively, when the C13 alcohol was isolated (96% yield) and subsequently was reacted with PhLi, **17a** and **17b** (2:1, respectively) were obtained in a combined yield of 88%. Conversion of **17a** and **17b** to Taxol (**1**) has been achieved by employing the known three- or four-step sequences, respectively.[20]

In summary, this study introduces a new strategy for the elaboration of taxanes, with pinene providing the complete A- and key B-ring fragments and an aldol closure establishing the C-ring. This strategy provides Taxol in the correct enantiomeric form in 37 steps from verbenone, the air-oxidation product of pinene. This represents the shortest reported synthesis of Taxol and provides even more concise access to key analogues. Further development of this strategy and biological studies on analogues will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental procedures for the reported compounds (20 pages). See any current masthead page for ordering and Internet access information.

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