The Pinene Path to Taxanes. 5. Stereocontrolled Synthesis of a Versatile Taxane Precursor

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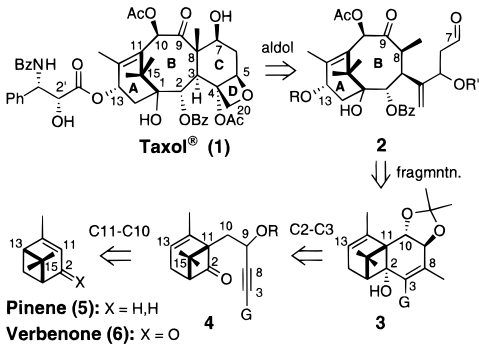
Taxol (**1**, Scheme 1)[1,2] has served over the past three decades as a stimulus for the development of fundamentally new advances in chemistry, biology, and medicine, resulting recently in its approval for the treatment of refractory ovarian[3] and metastatic breast cancers.[4] It is also in clinical trials for the treatment of lung, head and neck, and other cancers.[1,5] Crucial to the further development of this medicinal lead are efforts to improve the availability of Taxol and its precursors, to elucidate its novel mode of action at the molecular level,[1,6] and to identify clinically superior agents. Toward these ends, we describe herein an efficient stereocontrolled synthesis of a highly versatile taxane precursor which provides concise access to Taxol analogues and Taxol itself.[7,8]

Our synthesis strategy[9] derived from our recognition that pinene (**5**), an abundant component of pine trees and a major constituent of the industrial solvent turpentine, could supply 10 of the 20 carbons and the chirality of the taxane core. In this strategy, verbenone (**6**), the air oxidation product of pinene,[10] would be used as its dienolate for C11−C10 bond formation by alkylation or aldol procedures. The resultant product could then be rearranged to match the carbon connectivity of the taxane A-ring (**6** to **4**) through a variant of a photochemical process introduced by Hurst and Whitham in 1959.[11,12] Subsequent C2−C3 bond formation and fragmentation[12a−d] (**3** to **2**) would deliver the taxane AB-rings, thus setting the stage for C-ring formation through an aldol reaction (**2** to **1**).

Scheme 1



Implementation of this strategy started with C10−C11 bond formation which was accomplished on a large scale (1−3 mol) by treatment of verbenone (**6**, Scheme 2) with KO*t*-Bu followed by addition of prenyl bromide (**7**) to give the C11-alkylated product in 79% yield. Selective ozonolysis of the more electron-rich double bond of this product provided the aldehyde **8** in 85% yield. The carbon−carbon connectivity of the taxane A-ring was then established by photorearrangement[11,12] of **8** to the chrysanthenone derivative **9** (85% yield, >94% ee).[12c−e] The use of methanol in this reaction is essential for suppressing photoinduced racemization putatively involving fragmentation to and cyclization of a ketene.

Completion of the taxane B-ring involving introduction of a two-carbon connector between the C2 and C9 carbonyls of **9** was achieved in two steps. In the first step, the lithium salt of ethyl propiolate[13] was added selectively to the C9 carbonyl and the resultant alkoxide was trapped *in situ* with TMSCl to produce in 89% yield adducts **10**, as an inconsequential mixture of diastereomers. The C8 methyl group was then introduced by conjugate addition[14] of Me_2CuLi to **10**, which through generation of a C3 carbanion served additionally to effect intramolecular C2−C3 bond formation, thereby establishing in 97% yield the taxane B-ring in the form of the bicyclo[4.2.0]-octene subunit of **11**.

At this point in the synthesis, the conformational rigidity and stereochemical bias of tricycle **11** were exploited to selectively

(1) Taxol is the registered trademark for the molecule with the generic name paclitaxel. For reviews on Taxol, see: (a) *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995. (b) *Taxol Science and Applications*; Suffness, M., Ed.; CRC, Boca Raton, FL, 1995.

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(9) For an overview of the pinene pathway, see: Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Ohkuma, T.; Peschke, B.; Rawlins, D. B.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K.; Wessjohann, L. A. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M. Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995; pp 326−339. For part 4, see: Wender, P. A.; Glass, T. E.; Krauss, N. E.; Mühlebach, M.; Peschke, B.; Rawlins, D. B. *J. Org. Chem.* **1996**, *61*, 7662−7663.

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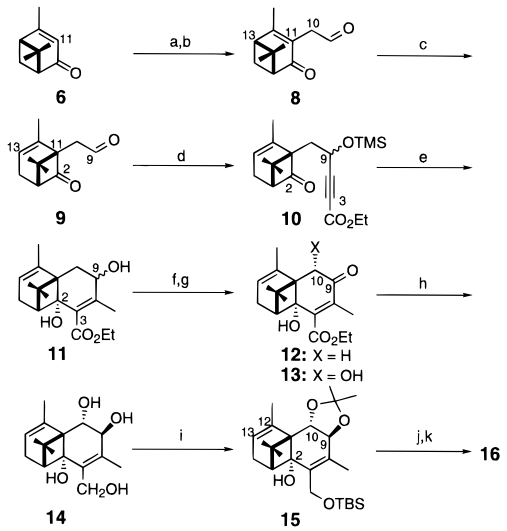
Scheme 2[a]



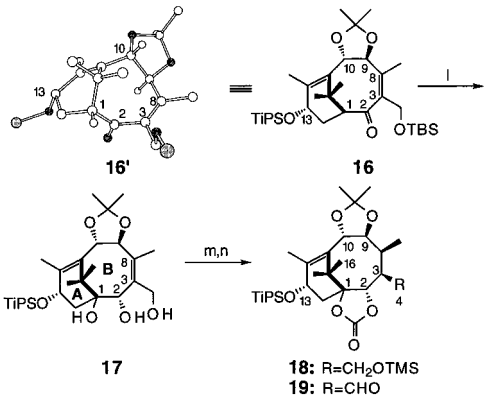
[a] (a) KO*t*-Bu, 1-bromo-3-methyl-2-butene (**7**), DME, −78 °C to room temperature (rt), 79% at 41% conversion. (b) O_3, CH_2Cl_2, MeOH, 85%. (c) *hν*, MeOH, 85%. (d) LDA, ethyl propiolate, THF, −78 °C; TMSCl, 89%. (e) Me_2CuLi, Et_2O, −78 °C to rt; AcOH, H_2O, 97%. (f) $RuCl_2(PPh_3)_3$, NMO, acetone, 97%. (g) KHMDS, Davis' oxaziridine, THF, −78 to −20 °C, 97% at 57% conversion. (h) $LiAlH_4$, Et_2O, 74%. (i) TBSCl, imid; PPTS, 2-methoxypropene, rt, 91%. (j) *m*-CPBA, Na_2CO_3, CH_2Cl_2. (k) DABCO (cat.), CH_2Cl_2, △; TIPSOTf, 2,6-lutidine, −78 °C, 85% over two steps.

introduce a C9−C10 acetonide, which was selected to control subsequent stereogenesis on the taxane B-ring. Toward this end, the alcohols **11** were oxidized with Dess−Martin periodinane (95%)[15] or with NMO and catalytic $(PPh_3)_3RuCl_2$ (97%) to give ketone **12**. Deprotonation of this ketone with KHMDS (1 equiv), followed by addition of Davis' oxaziridine[16a] (2 equiv) allowed for stereocontrolled introduction of the C10 oxygen from the less hindered enolate face, providing only the α-hydroxyketone **13** and unreacted **12**.[16b] Subsequent reduction of **13** with LAH (excess) stereoselectively gave the tetraol **14**. Treatment of this compound with imidazole and TBSCl followed by PPTS and 2-methoxypropene provided in one operation the acetonide **15** in 91% yield.

The taxane AB-ring system was next revealed by initial reaction of tricycle **15** with *m*-CPBA which resulted in chemoselective epoxidation of the trisubstituted alkene from its less encumbered α-face. DABCO induced fragmentation[12] of the resultant hydroxy-epoxide followed by *in situ* protection of the C13 alcohol provided the AB-bicycle **16** (Scheme **3**) in 85% yield.

The strategic role of the acetonide was now enlisted to control C1 oxidation and stereogenesis at C2, C3, and C8. Relative to other C9−C10 stereoisomers or analogues of **16** with noncyclic protecting groups, **16** (see partial structure **16′**)[17] is forced by the acetonide ring to assume a B-ring conformation in which the C2 carbonyl and C1 hydrogen are aligned for enolization as required to introduce the C1 hydroxyl of Taxol.[8,12c−d,18] The conformational influence of the acetonide was also expected to

Scheme 3[a]



[a] (l) KO*t*-Bu, O_2, $P(OEt)_3$, THF, −40 °C; NH_4Cl, MeOH, rt; $NaBH_4$, 91%. (m) H_2, Crabtree's catalyst, CH_2Cl_2, rt; TMS-Cl, pyridine, −78 °C; triphosgene, 0 °C, 98%. (n) PCC, 4 Å molecular sieves, CH_2Cl_2, 100%

control facial selectivity in the reduction of the C2 ketone and the hydrogenation of the C3−C8 alkene. In accord with this analysis, treatment of ketone **16** with KO*t*-Bu and $P(OEt)_3$ under an oxygen atmosphere, *in situ* removal of the TBS group with NH_4Cl/MeOH, and stereoselective reduction of the C2 ketone by addition of $NaBH_4$ gave in one operation the triol **17** (91%). Hydrogenation of the C3−C8 double bond of **17** from the desired α-face was accomplished with Crabtree's catalyst.[19] The product was protected *in situ* by treatment with TMSCl and pyridine followed by triphosgene to deliver the fully functionalized taxane AB-bicyclic system **18** in 98% yield. To provide a versatile handle for elaboration of the taxane C- and D-rings, the C4 center was oxidized with PCC to the aldehyde **19**. The success of these acetonide-controlled processes is contrasted by related reactions conducted on intermediates without the acetonide ring system which were hydrogenated from the undesired *β*-face of the C3−C8 alkene.

*Aldehyde **19**, a general taxane precursor, containing the complete carbon framework and oxygenation pattern of the A- and B-rings of Taxol, has been prepared from verbenone (**6**) in 14 steps.* It possesses fully differentiated functionalities allowing for the controlled introduction of side chains at C13, esters at C2, and a range of C-ring or *seco* C-ring variants at the C4 carbonyl as required to fully explore the structural determinants of biological and medicinal activity. In the following communication, the utility of this general purpose intermediate is demonstrated in the synthesis of Taxol (**1**).

Acknowledgment. This communication is dedicated to the late Matthew Suffness, a pioneer in the development of Taxol. The support of this work through a grant (CA 31845) provided by the National Institutes of Health is gratefully acknowledged. Exact mass analyses were performed by the University of California, San Francisco Regional Mass Spectrometry Facility. Fellowship support from the following institutions is also gratefully recognized: Eli Lilly and Roche (P.E.F.), National Science Foundation (T.E.G., T.P.M.), Swiss National Science Foundation (C.G., M.M.), ACS Division of Organic Chemistry and Pfizer (J.B.H.), Stiftung Stipendien-Fonds (J.J.), Bristol-Myers Squibb (D.L., M.G.N.), Syntex (D.L.), SERC/NATO (D.G.M., A.J.S.), Deutsche Forschungsgemein-schaft (H.P.), and Merck (R.E.T.).

Supporting Information Available: Spectroscopic data and experimental procedures for the reported compounds (18 pages). See any current masthead page for ordering and Internet access information.

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(17) MacroModel V4.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

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