First Total Synthesis of Taxol. 1. Functionalization of the B Ring

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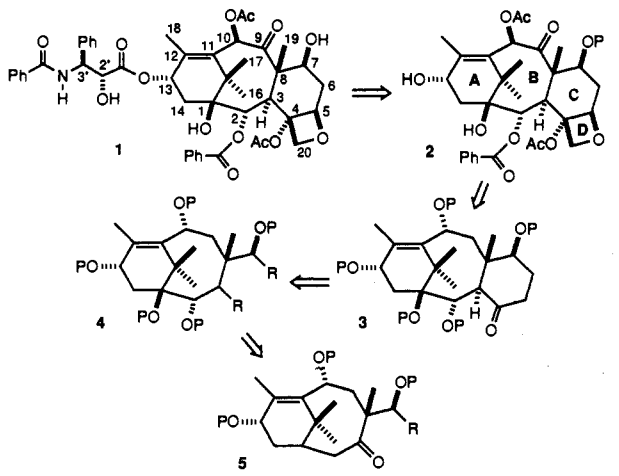
The total synthesis of the potent antitumor[1] agent taxol (**1**), isolated by Wall and Wani in 1971,[2] has stood for over 20 years as a major challenge for organic chemists. Taxol has been the subject of extensive chemical and biological studies, which have recently been summarized in several reviews,[3] and many synthetic approaches have been described.[3e,4]

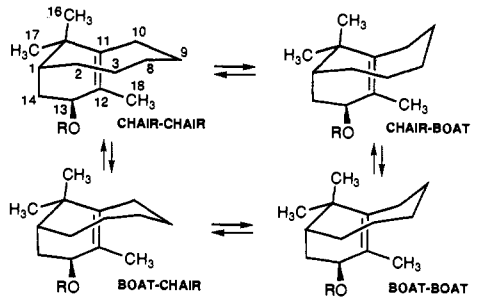
Until now, our taxane research program has produced a synthesis of the taxane ring system,[5] a total synthesis of taxusin,[6a] and a (now commercialized) semisynthesis of taxol.[7] Here and in the following communication we describe the first total synthesis of taxol.

The facile epimerization of taxol at C-7[8] is well documented,[3e] and we chose to pursue a synthetic strategy in which this stereocenter would be introduced at an early stage and carried throughout most of the synthesis in the absence of a C-9 carbonyl group. Thus, our route to taxol proceeds retrosynthetically through C-7 protected baccatin III (**2**) to the tricyclic ketone **3**, which arises from C ring closure of a precursor **4**, properly functionalized at C-1, C-2, C-3, C-7, and C-8. Synthesis of this precursor, made possible by conformational control of the eight-membered B ring, via the aldol product **5**, is described herein.



The fragmentation of bicyclic epoxy alcohols pioneered in our laboratory nine years ago,[5,9] known as the "epoxy alcohol fragmentation" and the cornerstone of our syntheses of the taxane skeleton, taxusin, and now taxol, has enabled the synthesis of a variety of molecules having the bicyclo[5.3.1] skeleton. Spectroscopic studies[10] of these compounds have demonstrated that there are *four distinct conformations of this eight-membered ring*, as shown in Scheme 1. For a given compound the equilibrium

Scheme I



will shift to favor conformations which orient substituents toward the periphery of the B ring to minimize nonbonded interactions.

Although the natural taxanes have a C-10β hydroxy or acyloxy substituent, the combination of a C-10β alkoxy group, a C-8β methyl group, and a C-3 ketone in this ring system shifts the equilibrium to strongly favor the chair-boat conformation. Our studies[10] have shown that a C-3 ketone in the chair-boat conformation does not undergo deprotonation at C-8α. Therefore, to enable C-8α deprotonation (and subsequent aldol condensation), we chose to utilize a C-10α silyloxy substituent as a conformational control element. Silylation (TESCl, pyridine) of **5a**,[6] a taxusin intermediate readily available from camphor in either enantiomeric form, gave **5b**, which then underwent epoxy alcohol fragmentation and protection at C-13 to give **6** in 93% overall yield. Although **6** was found to be in the chair-boat conformation, calculations indicate that, while the chair-boat conformer is lowest in energy, the chair-chair and boat-chair conformers are only ca. 2.5 kcal/mol less stable. Presumably deprotonation of one of these other conformers at C-8 is facile.

In the event, the magnesium enolate[11] of ketone **6** ($HN(iPr)_2$, THF, MeMgBr, 25 °C, 3 h, then **6**, 1.5 h) underwent aldol condensation with 4-pentenal (THF, −23 °C, 1.5 h), and the crude product was directly protected (Cl_2CO, pyridine, CH_2Cl_2, −10 °C, 0.5 h, then ethanol, 0.5 h) to give ethyl carbonate **7**, a ca. 6:1 mixture of chair-chair and boat-chair conformers ($CDCl_3$),[12] in 75% yield. Hydroxylation at C-2 (**7**, LDA, THF, −35 °C, 0.5 h, then −78 °C, 1.0 molar equiv of (+)-camphorsulfonyl oxaziridine (for the enantiomer leading to taxol; (−)-camphorsulfonyl oxaziridine for the enantiomer leading to *ent*-taxol), 0.5 h)[13] gave hydroxy carbonate **8** (chair-chair conformation) in 85% yield. Reduction of **8** from the periphery

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(5) Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731.

(6) (a) Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558. (b) Holton, R. A.; Juo, R.-R.; Lowenthal, R. E. U.S. Patent 4,876,399, 1989.

(7) See the following communication in this issue, ref 15.

(8) The taxane numbering system, as illustrated in **1**, is used throughout.

(9) (a) For application in the bicyclo[3.2.1] system, see ref 5. (b) For application in the bicyclo[2.2.1] system, see: Holton, R. A.; Kennedy, R. M. *Tetrahedron Lett.* **1984**, *25*, 4455. (c) For application in the bicyclo[3.1.1] system, see: Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878.

(10) Solution conformations have been determined by NOE difference spectroscopy at 500 MHz: Holton, R. A.; Somoza, C.; Kim, H. B.; Juo, R. R.; Williams, A. D.; Harusawa, S.; Takemoto, Y.; Smith, C. C.; Gentile, L. N.; Liang, F. Manuscript in preparation.

(11) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345.

(12) The ratio of conformers depended on the C-7 protecting group and the alkyl side chain.

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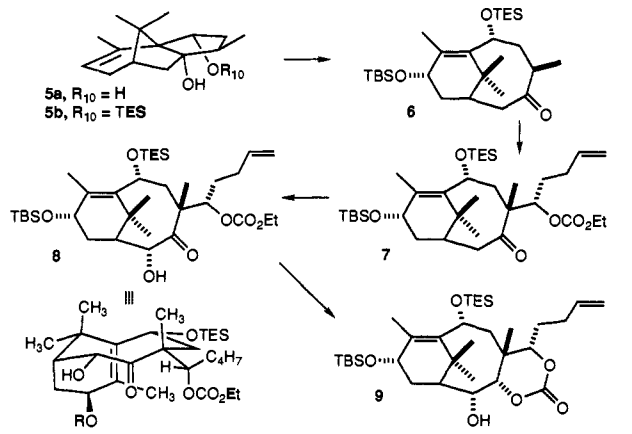
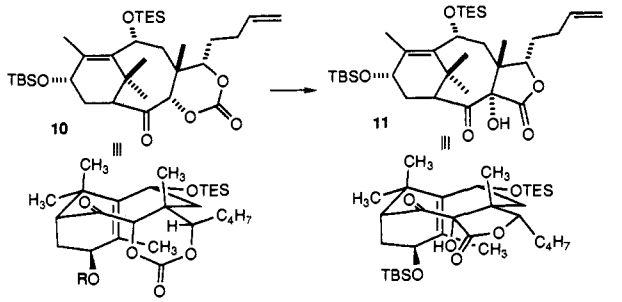
of the molecule[14] (20 molar equiv of Red-Al, toluene, −78 °C, 6 h, then warm to 25 °C over 6 h) gave a triol which, without isolation, was converted to carbonate **9** (Cl_2CO, pyridine, CH_2Cl_2, −78 to 25 °C, 1 h, 97%). Carbonate **9** could be obtained directly from Red-Al reduction of **8**, but complete reduction followed by regeneration of the cyclic carbonate was operationally easier and more efficient.

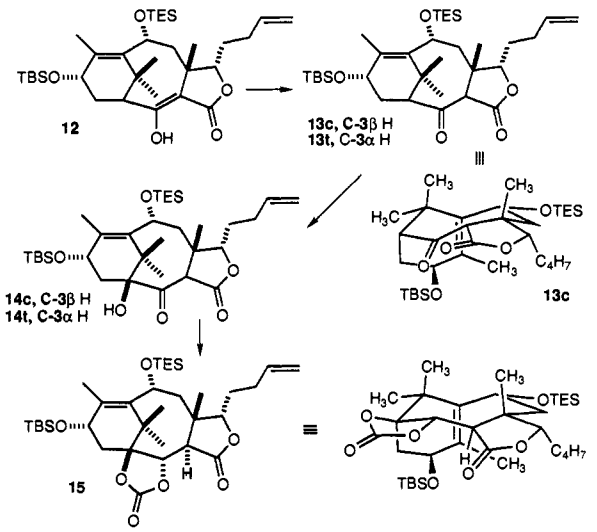


Synthesis of the C-1 through C-3 portion of taxol required introduction of a second conformational control element, a sufficiently large epimerizable substituent at C-3α, to shift the equilibrium in favor of the boat-chair conformation. This conformation was expected to permit generation of the C-1, C-2 enolate of a C-2 ketone, which would undergo hydroxylation at C-1 followed by hydride reduction of the C-2 carbonyl from the periphery to generate the C-2α alcohol. Finally, epimerization at C-3 would return the B ring to the chair-chair conformation.

Thus, **9** underwent Swern oxidation to give C-2 ketone **10** in 95% yield. That **10** was still in the chair-chair conformation (apparently the C-3α oxygen substituent is not bulky enough) was a matter of some concern. Treatment of **10** with 1.05 molar equiv of LTMP from −25 to −10 °C gave hydroxy lactone **11** in 90% yield. This remarkable result is analogous to the Chan rearrangement,[15] which, to our knowledge, has been used but once in synthesis.[16] The formation of **11** is the first example of this reaction in a cyclic system, and this is also the first indication that this can be a very stereoselective process.



The chair-chair conformation of **11** aligns the C-3α hydroxyl for facile reductive removal, and its samarium diiodide reduction led to the stable enol **12**, which, upon treatment with silica gel, was converted to a 6:1 mixture of cis- and trans-fused lactones **13**, from which the cis-fused lactone **13c** (boat-chair conformation) could be obtained by crystallization. Treatment of the trans-fused lactone **13t** with KOtBu in THF followed by quenching with acetic acid gave back **12**, and through this recycling **13c** was obtained in 91% yield from **11**. Attempts to generate and hydroxylate a dienolate from **12** were unsuccessful. Lactone **13t** was not deprotonated by LTMP at temperatures up to −10 °C and was recovered unchanged. However, treatment of **13c** with 4 molar equiv of LTMP at −10 °C followed by addition of (±)-camphorsulfonyl oxaziridine (5 molar equiv) to the enolate at −40 °C gave 88% of **14c** along with 8% of its trans-fused isomer **14t**, which was formed upon chromatographic separation of the small amount (3%) of unreacted **13c**. It is remarkable that *deprotonation of 13c with LTMP apparently occurs first, and perhaps only, at C-1*, even though the C-3 proton would normally be expected to be more acidic. Reduction of **14c** with Red-Al[14] (THF, −78 °C, 1.5 h) followed by a basic workup gave C-2α-hydroxy trans-fused lactone (88%) and 4% of **14t**, which could be converted to the C-2α-hydroxy trans-fused lactone almost quantitatively by samarium diiodide reduction.[17] The C-2α-hydroxy trans-fused lactone was quantitatively converted to carbonate **15**[18] by treatment with phosgene (10 molar equiv, pyridine, CH_2Cl_2, −23 °C, 0.5 h).



Therefore, as outlined here, **5a** can be transformed to lactone carbonate **15** in 12 steps and 40% overall yield. This series of reactions provides functionality at C-1, C-2, C-3, C-7, and C-8 as needed for a synthesis of taxol through careful conformational control of the bicyclo[5.3.1] eight-membered ring.

Conversion of **15** to taxol requires completion of the C ring, introduction of the D ring, and oxidation at C-9 along with adjustment of the C-9, C-10 regio- and stereochemistry. These efforts are the subject of the following communication.

Acknowledgment. We thank the National Cancer Institute (CA 42031, CA 55131) and private donors to the Taxol Research Fund for financial support of this work.

Supplementary Material Available: Experimental procedures and spectral data for compounds **5b** through **15** (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402.

(14) For a related example of carbonyl reduction in a taxane ring system, see: Shea, K. J.; Higby, R. G.; Gilman, J. W. *Tetrahedron Lett.* **1990**, *31*, 1221.

(15) Lee, S. D.; Chan, T. H.; Kwon, K. S. *Tetrahedron Lett.* **1984**, *25*, 3399.

(16) White, J. D.; Vedananda, T. R.; Kang, M.; Choudhry, S. C. *J. Am. Chem. Soc.* **1986**, *108*, 8105.

(17) For an example of reduction of a remotely related C-2 ketone with sodium, see ref **9c**.

(18) The C-1, C-2 cyclic carbonate has been found to be an excellent protecting group; it offers some resistance to acid-promoted rearrangement and can be readily converted to the C-2 benzoate. Holton, R. A.; Kim, S.; Tao, C. Manuscript in preparation.