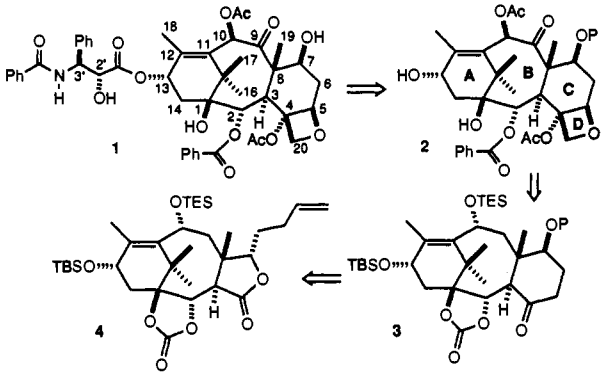
First Total Synthesis of Taxol. 2. Completion of the C and D Rings

Robert A. Holton,* Hyeong-Baik Kim, Carmen Somoza, Feng Liang, Ronald J. Biediger, P. Douglas Boatman, Mitsuru Shindo, Chase C. Smith, Soekchan Kim, Hossain Nadizadeh, Yukio Suzuki, Chunlin Tao, Phong Vu, Suhan Tang, Pingsheng Zhang, Krishna K. Murthi, Lisa N. Gentile, and Jyanwei H. Liu

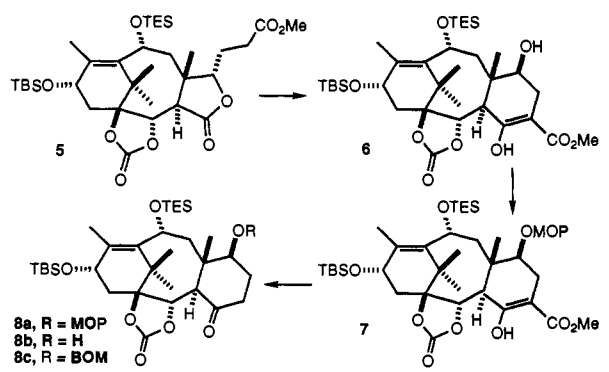
Dittmer Laboratory of Chemistry
Florida State University, Tallahassee, Florida 32306

Received December 21, 1993

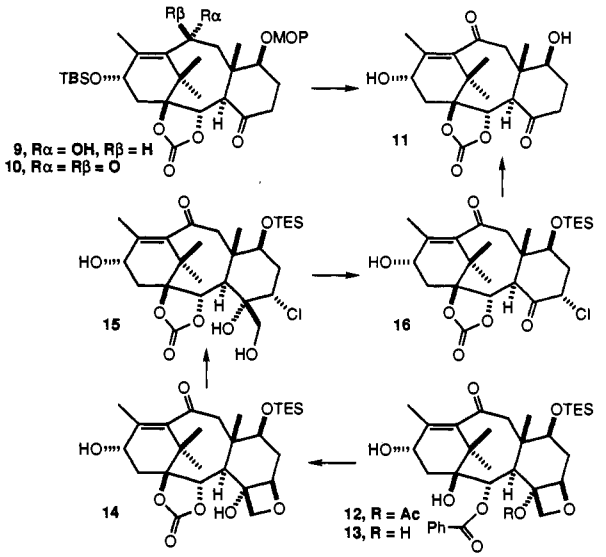
The synthesis of lactone **4**, a taxol intermediate in which the regio- and stereochemistry of C-1, C-2, C-3, C-7, C-8, C-13, and the A ring double bond were established, was the subject of the preceding communication.[1] We now describe the conversion of **4** to taxol (**1**)[2] through cyclization of the C ring, introduction of the oxetane D ring, and, finally, oxidation at C-9 followed by adjustment of the regio- and stereochemistry at C-9 and C-10.



Oxidative cleavage of the terminal olefin of **4** was carried out by ozonolysis in the presence of methanol and sodium hydroxide,[3] or, in somewhat higher yield (93%), by first ozonolysis to the aldehyde followed by oxidation to the acid ($KMnO_4$, KH_2PO_4)[4] and esterification with diazomethane to produce methyl ester **5**. Dieckmann cyclization of **5**, following the protocol recently developed in our laboratory (LDA, THF, –78 °C, 0.5 h, then HOAc, THF),[5] gave the enol ester **6** in 93% yield at 90% conversion. Attempted decarbomethoxylation of **6** resulted in at least partial reversion to **5**, and **6** was therefore temporarily protected (pTsOH, 2-methoxypropene, 100%) to give **7**, which smoothly underwent decarbomethoxylation (PhSK, DMF, 86 °C, 3 h) to provide **8a**, or, if an acidic workup was employed, hydroxy ketone **8b**, in 92% yield.



To secure completely unambiguous structure confirmation, **8a** was converted to diol carbonate **11**, which was independently synthesized from baccatin III (**2**, P = H). Selective deprotection of **8a** with TBAF (1 molar equiv, THF, –10 °C, 6 h) gave alcohol **9**, which was then oxidized with tetrapropylammonium perruthenate[6] (TPAP (cat.), NMO, molecular sieves, CH_2Cl_2, 25 °C, 1.5 h) to ketone **10** in 86% overall yield from **8a**. Deprotection (HF, pyridine, CH_3CN, 96%) of **10** provided diol carbonate **11**. Alternatively, hydroxy ketone **12**, readily available from baccatin III,[7] quantitatively underwent selective cleavage of the C-4 acetate with Super-Hydride (THF, –78 °C, 1 h) to give **13**, which underwent solvolysis of the C-2 benzoate (NaOMe), with formation of varying amounts of the C-2, C-20 tetrahydrofuran.[8] The resulting tetraol was converted to the C-1, C-2 cyclic carbonate (Cl_2CO, pyridine, CH_2Cl_2, –78 to –10 °C, 1 h) **14** in 70% yield from **13**. Cleavage of the oxetane with TMSCl[9] (CH_2Cl_2, 25 °C, 1 h) provided C-5α-chloro triol **15**, which was converted to keto carbonate **16** with lead tetraacetate[10] (benzene, 25 °C, 10 min) in 90% yield from **14**. Finally, **16** underwent samarium diiodide reduction (THF, –78 °C, 5 min) followed by removal of the C-7 TES protecting group (HF, pyridine, acetonitrile, 25 °C, 3 h) to give **11** in 70% yield from **16**. With the structure of **8** securely established, the remaining issues of the conversion of **8** to taxol were addressed.



Synthesis of the acetoxy oxetane proved to be unusually difficult. Although we had already established an effective protocol for closure of the oxetane[9a] from a halo diol like **15**, the C-4 carbonyl

(1) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Isolation: Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. For references to the chemistry and biology of taxol, see ref 1.

(3) (a) Sundaraman, P.; Walker, E. C.; Djerassi, C. *Tetrahedron Lett.* **1978**, 1627. (b) Marshall, J. A.; Garofalo, A. W.; Sedrani, R. C. *Synlett* **1992**, *8*, 643.

(4) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

(5) (a) For a similar cyclization reported to proceed in 13% yield, see: Gardner, P. D.; Haynes, G. R.; Brandon, R. L. *J. Org. Chem.* **1957**, *22*, 1206. (b) Holton, R. A.; Boatman, P. D.; Kim, H. B.; Murthi, K. K. Manuscript in preparation.

(6) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(7) Holton, R. A.; Somoza, C.; Smith, C. C.; Suzuki, Y. Manuscripts in preparation.

(8) (a) Farina, V.; Huang, S. *Tetrahedron Lett.* **1992**, *33*, 3979. (b) Wahl, A.; Gueritte-Voegelein, F.; Guenard, D.; Le Goff, M. T.; Potier, P. *Tetrahedron* **1992**, *48*, 6965.

(9) (a) Holton, R. A.; Tao, C.; Shindo, M. Manuscript in preparation. (b) See ref 10 for skeletal rearrangement of baccatin derivatives under similar conditions.

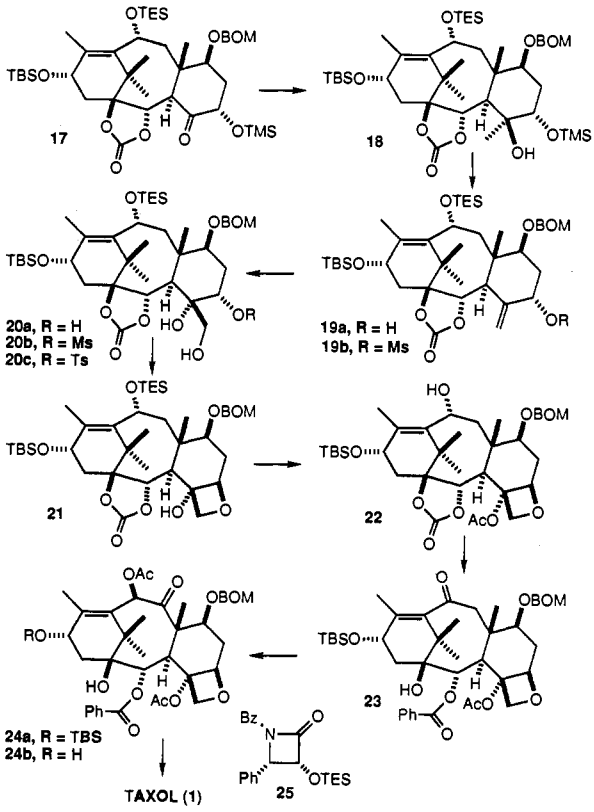
(10) Chen, S. H.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805.

0002-7863/94/1516-1599$04.50/0

group of **8** was very hindered, and addition of C-20 to it in the presence of the carbonate failed with most nucleophilic reagents. For example, although the enol triflate could be prepared in high yield, it was completely resistant to oxidative addition to a transition metal (e.g., Pd(0)). Furthermore, all reagents that successfully underwent addition to C-4 did so from the α face, thus requiring introduction of C-20 in the β configuration by indirect means. A robust protecting group at C-7 which would survive the remainder of the synthesis was desired, and **8b** reacted with BOM chloride ($EtN(iPr)_2$, CH_2Cl_2, $(Bu)_4NI$, reflux, 32 h) to give C-7 BOM derivative **8c** in 92% yield. The TMS enol ether of **8c** (LDA, THF, TMSCl, –78 °C) underwent oxidation with mCPBA (hexane, 25 °C, 5 h) to C-5α (trimethylsilyl)oxy ketone **17** in 86% yield at 86% conversion. Addition of methylmagnesium bromide to **17**, a low-yield (30–60%) reaction in ethereal or hydrocarbon solvents, proceeded well in methylene chloride solution (–45 °C, 15 h, 10 molar equiv of MeMgBr) to give tertiary alcohol **18** in 95% yield. Elimination of **18** was carried out with Burgess' reagent,[11] and acidic workup then provided allylic alcohol **19a** in 63% yield.

Alcohol **19a** was converted to oxetane **21** through either C-5α mesylate **20b** or C-5α tosylate **20c**. Mesylate **19b** was generated quantitatively (MsCl, pyridine) from alcohol **19a**, and osmylation of **19b** gave **20b** in 60–65% yield. Alternatively, osmylation (ether/pyridine, 0 °C, 12 h) of **19a** gave triol **20a** in 80% yield at 91% conversion. Triol **20a** was converted to tosylate **20c** through temporary protection of the C-20 hydroxyl group as the TMS ether (TMSCl, Et_3N, –78 °C), formation of C-5α tosylate, and cleavage of the temporary TMS protecting group (LDA, TsCl, –35 °C, 3 h, then HOAc, 0 °C, 14 h) in 85% overall yield at 94% conversion without isolation of intermediates. Either **20b** or **20c** underwent cyclization[9a,12] to oxetanol **21** (DBU, toluene, 105 °C, 2 h) in 80–85% yield. Acetylation of **21** (Ac_2O, pyridine, DMAP, 24 h, 25 °C) was difficult and proceeded in only 70–75% yield, but was followed by quantitative removal of the C-10 TES group (HF pyridine complex, CH_3CN, 0 °C, 11 h) to give **22**. Addition of phenyllithium[13] (2.1 molar equiv, THF, –78 °C, 10 min) to **22** to provide the C-2 benzoate was followed by TPAP oxidation (NMO, molecular sieves, CH_2Cl_2, 25 °C, 15 min), giving ketone **23** in 85% yield.

Oxidation at C-9 and rearrangement to the taxol C-9, C-10 regio- and stereochemistry, following the protocol established in our previous studies,[7] proceeded nicely. A THF solution of the enolate of **23** (4 molar equiv of KOtBu, THF, –78 to 0 °C, 0.5 h) was added to a suspension of benzeneseleninic anhydride (8 molar equiv, THF, 0 °C, 40 min), and the product was directly treated further with KOtBu (4 molar equiv, THF, –78 °C, 10 min). Direct acetylation of the product (Ac_2O, pyridine, DMAP, 20 h, 25 °C) provided 7-BOM-13-TBS baccatin III (**24a**) quantitatively.



As the difficult acetylation of the C-4 hydroxyl group had already shown, the underside of the molecule was quite crowded, and removal of the C-13 TBS group was almost a problem. Treatment of **24a** with TBAF led to cleavage of the C-2 benzoate prior to removal of the TBS group. The TBS group could be removed with HF (pyridine, 90 °C, 12 h) to give **24b** in 65% yield along with several rearrangement products. Finally it was found that with TASF[14] (THF, 25 °C, 1 h) 7-BOM baccatin III (**24b**) was produced in 94% yield. Attachment of the C-13 side chain[15] proceeded uneventfully: the lithium alkoxide of **24b** (LHMDS, THF) was treated with β-lactam **25** (THF, 0 °C, 1 h), the product was desilylated (HF, pyridine, CH_3CN, 0 °C, 1 h) and, finally, the C-7 BOM group was removed by hydrogenolysis (H_2, Pd/C, EtOH, reflux, 1 h) to give taxol in 93% yield from **24b**.

In this and the preceding communication we have described the first total synthesis of the antitumor agent taxol. It illustrates the use of conformational control in synthesis and has provided a variety of uniquely challenging and interesting situations, many of which are subjects of ongoing investigations in our laboratory. The synthesis produces (–)-taxol[16a] from (–)-borneol, and *ent*-(+)-taxol[16b] from (–)-patchino.[16c] The overall yield of taxol from diol **5a**[1] is ca. 4–5%.

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 **5** through taxol (24 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.

(11) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(12) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823.

(13) Holton, R. A.; Kim, S.; Tao, C. Manuscript in preparation.

(14) (a) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (b) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106.

(15) (a) Holton, R. A. Advances in Taxane Synthesis. Midwestern Regional ACS Meeting, Cleveland, OH, June 1989. (b) Holton, R. A. Progress in Taxol Synthesis. *Abstracts of Papers*, 203rd National Meeting of the American Chemical Society, San Francisco, CA; American Chemical Society: Washington, DC, 1992. U.S. Patent 5,015,744, 1991; European Patent 0 400 971, 1990. (d) Holton, R. A. U.S. Patent 5,136,060, 1992. (e) Holton, R. A. U.S. Patent 5,175,315, 1992. (f) Holton, R. A. PCT Patent Application International Publication Number WO 93/06079, 1993. (g) Holton, R. A. U.S. Patent 5,229,526, 1993. (h) Other patents pending. (i) Subsequent to these disclosures, similar findings have been reported; see: Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149 and references therein. (j) For an alternate approach, see: Commercon, A.; Bezard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185 and references therein.

(16) (a) Identical in all respects with an authentic sample of natural taxol provided by Bristol-Myers Squibb Company. (b) $[\alpha]^{23}_D$ = +47° (*c* 0.19, MeOH); identical in all other respects with an authentic sample of natural taxol. (c) Reference 6a in the preceding paper in this issue.