Total Synthesis of Taxol. 1. Retrosynthesis, Degradation, and Reconstitution

K. C. Nicolaou,* P. G. Nantermet, H. Ueno, R. K. Guy, E. A. Couladouros, and E. J. Sorensen

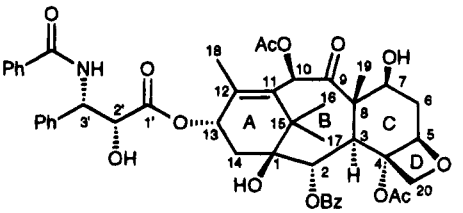
Contribution from the Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

Received July 7, 1994[⊗]

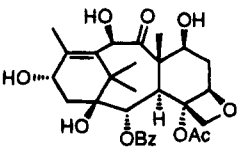
Abstract: A successful strategy for the enantioselective synthesis of the natural stereoisomer of Taxol (**1**) has been developed. This strategy utilized the convergent assembly of Taxol's central eight-membered B ring from preformed synthons for rings A (**10**) and C (**9**) followed by late introduction of the D ring and side chain. Degradative studies confirmed the viability of certain crucial manipulations including oxidation of the C13 position (**35** → **3**) and regioselective introduction of the C1-hydroxyl, C2-benzoyloxy moiety (**29** → **31**). Additionally, a convenient method for the large-scale production of **29**, a derivative useful for C2 analog production, was developed.

Introduction

Taxol (Figure 1, **1**),[1,2] a diterpene produced by several plants of the genus *Taxus*,[3] was isolated from the cytotoxic methanolic extract of the bark of *T. brevifolia*.[4] Taxol interacts with microtubules, important cellular structural proteins,[5] in a manner that catalyzes their formation from tubulin and stabilizes the resulting structures.[6] In cells this phenomenon leads to an altered morphology with the microtubules forming stable bundles and the cell being unable to assemble a normal mitotic spindle.[7] Cells treated with Taxol normally arrest at the transition between interphase and mitosis and die. The elucidation of this unique mechanism of action during the late 1970s and early 1980s sped Taxol's development as an anticancer drug. Since that time, Taxol has revealed unusual efficacy as a clinical agent,[8] experiencing rapid development for the treatment of breast,[9] ovarian,[10] skin,[11] lung,[12] and head and neck[13] cancers.



1: Taxol



2: 10-deacetylbaccatin III

Figure 1. Structure of Taxol (**1**) and 10-deacetylbaccatin III (**2**).

In 1993, Taxol was approved by the FDA for use in the U.S. for treatment of breast and ovarian cancers.

Taxol's development as a therapeutic agent precipitated a fundamental problem with its production: the original source of its isolation, *T. brevifolia*, was a slowly growing and rare tree whose content of Taxol could not possibly meet the demand.[14] The public's perception of the ecological disaster involved in harvesting these trees from the last remaining old growth forests of the Pacific Northwest caused an ongoing debate about the ethics of producing Taxol.[15] A wide range of research was carried out to solve this problem, including plantation farming, cellular culture, semisynthesis, and total synthesis.[14] A semisynthetic process utilizing 10-deacetylbaccatin III (**2**, Figure 1), derived from the common *T. baccata* shrub, as the starting material has, at least temporarily, resolved this dilemma.[14] Over the past two decades some 30 synthetic

* Address correspondence to this author at The Scripps Research Institute or the University of California.

⊗ Abstract published in *Advance ACS Abstracts,* December 15, 1994.

(1) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.

(2) Kingston, D. G. I. *Fortschr. Chem. Org. Naturst.* **1993**, *61*, 1.

(3) Appendino, G. *Fitoterapia* **1993**, *54*, *Suppl. NI*, 5.

(4) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggen, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(5) (a) Mandelkow, E.; Mundelkow, E.-M. *Curr. Opin. Struct. Biol.* **1994**, *4*, 171. (b) Avila, J. *Life Sci.* **1991**, *50*, 327.

(6) Manfredi, J. J.; Horwitz, S. B. *Pharmacol. Ther.* **1984**, *25*, 83. Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.

(7) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561.

(8) Lavelle, F. *Curr. Opin. Invest. Drugs* **1993**, *2*, 627. Rowinsky, E. K.; Onetto, N.; Canetta, R. M.; Arbuck, S. G. *Semin. Oncol.* **1992**, *19*, 646.

(9) Holmes, F. A.; Waters, R. J.; Theriault, R. I.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. *J. Natl. Cancer Inst. U.S.A.* **1991**, *83*, 1797.

(10) McGuire, W. P.; Rowinsky, E. K.; Rosenshein, N. B.; Grumbine, F. C.; Ettinger, D. S.; Armstrong, D. K.; Donehower, R. C. *Ann. Intern. Med.* **1989**, *111*, 273. Einzig, A. I.; Wiernik, P. H.; Sasloff, J.; Garl, S.; Runowicz, C.; O'Hanlan, K. A.; Goldberg, G. *Proc. Am. Assoc. Cancer Res.* **1990**, *31*, 187 (Abstract 1114). Pazdur, R.; Ho, D. H.; Lassere, Y.; Bready, B.; Kvakoff, I. H.; Raber, M. N. *Proc. Am. Soc. Clin. Oncol.* **1992**, *11*, 111 (Abstract 265). Caldas, C.; McGuire, W. P., III. *Semin. Oncol.* **1993**, *20* (4 Suppl. 3), 50.

(11) Einzig, A. I.; Hochster, H.; Wiernik, P. H.; Trump, D. L.; Dutcher, J. P.; Garowski, E.; Sasloff, J.; Smith, T. J. *Invest. New Drugs* **1991**, *9*, 59. Legha, S. S.; Ring, S.; Papadopoulos, N.; Raber, M. N.; Benjamin, R. *Cancer* **1990**, *65*, 2478.

(12) Chang, A.; Kim, K.; Glick, J.; Anderson, T.; Karp, D.; Johnson, D. *J. Natl. Cancer Inst. U.S.A.* **1993**, *85*, 388. Murphey, W. K.; Winn, R. J.; Fossella, F. V.; Shin, D. M.; Hynes, H. E.; Gross, H. M.; Davila, E.; Leimert, J. T.; Dhinga, H. M.; Raber, M. N.; Krakoff, I. H.; Hong, W. K. *Proc. Am. Soc. Clin. Oncol.* **1993**, *85*, 384. Ettinger, D. S. *Semin. Oncol.* **1993**, *20* (4 Suppl. 3), 46.

(13) Forastiere, A. A. *Semin. Oncol.* **1993**, *20* (4 Suppl. 3), 56.

(14) Borman, S. *Chem. Eng. News* **1991**, Sept 2, 11.

(15) Hartzell, H. *The Yew Tree, A Thousand Whispers*; Hulogosi: Eugene, OR, 1991.

0002-7863/95/1517-0624$09.00/0

groups, attracted by the molecule's challenging architecture and importance in medicine, undertook the task of the total synthesis of Taxol.[1,2] Herein and in the following articles[16-18] we report the total synthesis of Taxol (**1**).[19]

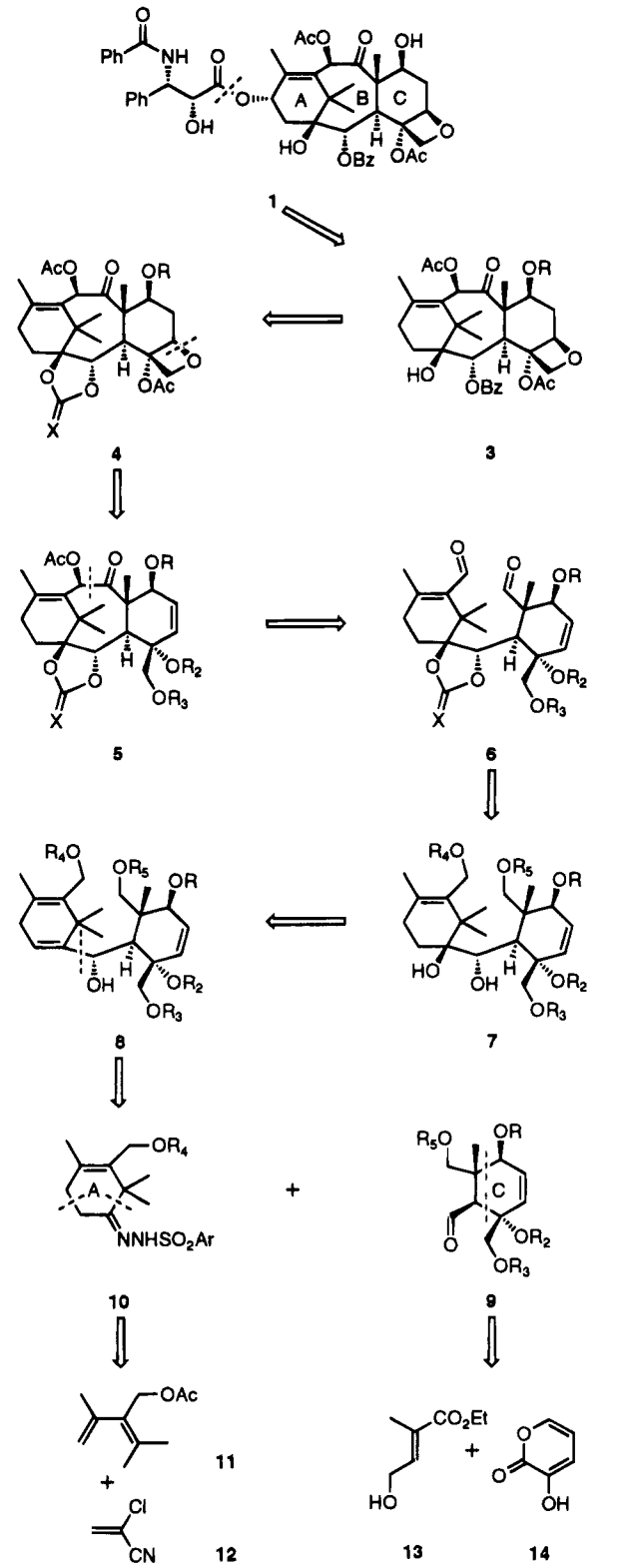
Retrosynthetic Analysis and Strategy

The retrosynthetic analysis and final synthetic strategy discussed below emerged after considering several options and examining information gathered during preliminary studies in this program. Aspects of alternative plans originally considered will be discussed in the context of the overall story as revealed in this and the following papers in this series.

In considering a strategy for the total synthesis of Taxol (**1**), we set the following postulate as a condition: the route should be short and flexible to allow for the eventuality of producing the natural product and a variety of its analogs in a practical way and to deliver the target molecule in its enantiomerically pure and correct form. To best fulfill this criteria, a convergent sequence was chosen in which rings A and C were to be constructed separately and then brought together to form the 8-membered ring B. Examples already in the literature and knowledge derived from our own experience led us to conclude that we could leave for the final stages the attachment of the side chain,[20,21] the oxygenation of the C13 position,[22] and the formation of the oxetane ring.[23-25]

Scheme 1 shows the retrosynthetic analysis of Taxol (**1**) on which the synthetic strategy was based. Thus, appropriate protection, removal of the side chain, and deoxygenation transforms at C13 led, retrosynthetically, to the baccatin derivative **3**. Functional group manipulation at C1 and C2 led to the 5-membered ring derivative **4** which was envisioned as a precursor to the 1-hydroxy-2-benzoate system of Taxol. Retrosynthetic disassembly of the oxetane ring in **4** and introduction of a double bond in ring C allowed the generation of intermediate **5** as a possible precursor. The carbocyclic ABC taxoid core **5** was then retrosynthetically broken by standard functional group manipulations and disconnection of the C9–C10 bond leading to dialdehyde **6**. The latter was considered as a good candidate to afford, in the synthetic direction, compound **5** via a McMurry pinacol coupling.[26] Continuing with the simplification of structure, intermediate **6** was traced back to diol **7** and then to allylic alcohol **8** as potential progenitors. Finally, disconnection of **8** via a Shapiro[27] transform led to hydrazone **10** representing ring A and aldehyde

Scheme 1. Retrosynthetic Analysis of Taxol (**1**)[a]



[a] Bz = COPh; R, R_1, R_2, R_3, R_4, R_5 = protecting groups.

(16) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634.

(17) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, xxx.

(18) Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, xxx.

(19) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630. Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F. 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.* **1994**, *116*, 1597. Holton, R. A.; Kim, H. B.; Somoza, C.; 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.* **1994**, *116*, 1599.

(20) Holton, R. A. Workshop on Taxol and Taxus, 1991. Holton, R. A. Eur. Pat. Appl. EP400,971 1990; *Chem. Abstr.* **1990**, *114*, 164568q.

(21) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681. Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985. Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. M.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149.

(22) Ulman Page, P. C.; McCarthy, T. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., FRS, Eds.; Pergamon Press: New York, 1991; Vol. 7, p 99.

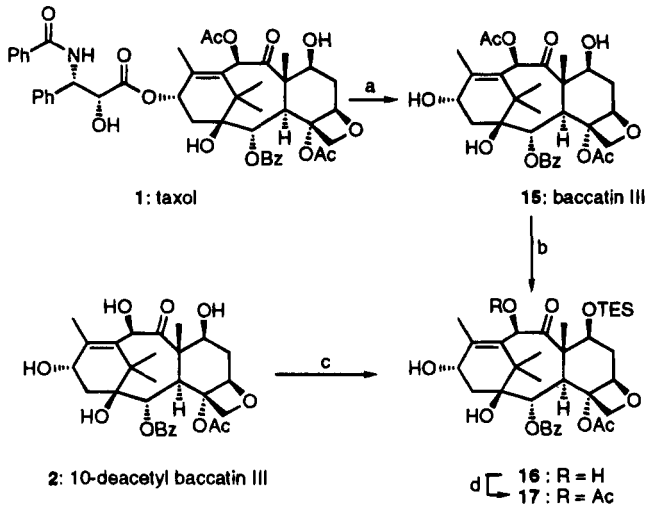
(23) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823.

(24) Magee, T. V.; Bornmann, W. G.; Isaccs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274.

(25) Nicolaou, K. C.; Liu, J.-J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1118.

(26) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405. Lenoir, D. *Synthesis* **1989**, 883.

Scheme 2. Preparation of 7-TES-baccatin III (**17**)[a]



[a] Reagents and conditions: (a) excess n-Bu_4NBH_4, CH_2Cl_2, 25 °C, 7 h, then AcOH, 77%; (b) 30 equiv of Et_3SiCl, pyridine, 25 °C, 24 h, 85%; (c) 20 equiv of Et_3SiCl, pyridine, 25 °C, 17 h, 91%; (d) 5 equiv of AcCl, pyridine, 0 °C, 48 h, 82%. TES = $SiEt_3$, Bz = COPh.

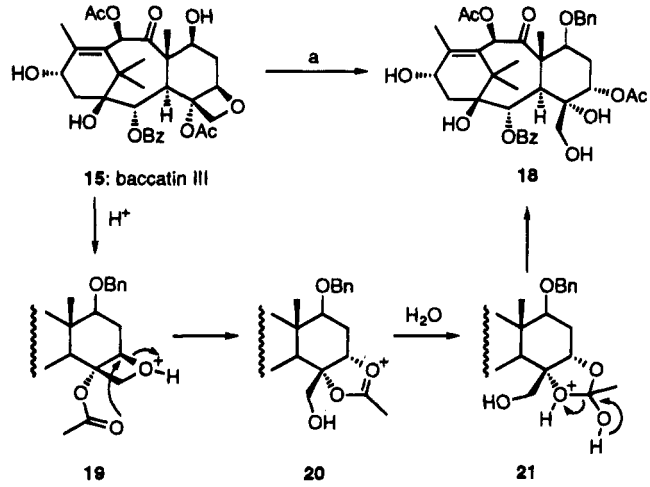
9 representing ring C. The cyclohexene derivatives **10** and **9** were then disassembled by Diels–Alder transforms to afford olefins **11–14** as potential starting materials.

The synthetic strategy derived from the analysis discussed above included a number of sensitive and rather daring steps in its final stages. In order to explore these final steps and establish their viability, we embarked, in parallel with the forward execution of the scheme, on degradation studies starting with Taxol (**1**) and 10-deacetylbaccatin III (**2**).[28] Included amongst our goals in this program were the following: deoxygenation of the C13 position and exploration of its allylic oxidation, establishment of a suitable cyclic protecting group for the C1 and C2 hydroxyl groups and its regioselective conversion to the requisite C1 hydroxy, C2 benzoate functionality, and cleavage of the C9–C10 bond in order to obtain intermediates suitable for exploring the McMurry pinacol coupling as a means to construct the 8-membered ring of Taxol.

Preparation of 7-TES-baccatin III

Since 7-benzyl and 7-triethylsilyl (TES) baccatin III were projected as advanced intermediates in our synthesis, one of our early objectives was to prepare these compounds from the naturally occurring Taxol (**1**) and 10-deacetylbaccatin III (**2**). While the former natural product is found in the bark of the Pacific Yew tree (*T. Brevifolia*) in rather limited amounts, the latter compound is readily available from the needles of the European Yew tree (*T. baccata*). Scheme 2 summarizes the chemistry that led to the preparation of **17** from **1** and **2**. Thus removal of the side chain from Taxol (**1**) via reduction of the C13 ester linkage proceeded according to Kingston's method (n-Bu_4NBH_4)[29] to afford baccatin III (**15**) in 77% yield. Our synthetic strategy was best served by a 7-benzyl derivative and we, therefore, first considered the preparation of such an intermediate. Basic conditions were, however, unacceptable because of the well-documented epimerization at C7 via a retroaldol/aldol sequence.[2,30,31] Acidic conditions (benzyl trichloroacetimidate/triflic acid),[32] also proved too destructive: giving opening of the oxetane ring[30] and leading to compound **18** (Scheme 3) as a major product (C7 stereochemistry not defined, acid-catalyzed epimerization at this position has also been reported).[31] This compound was presumably formed via intermediates **19–21** as shown in Scheme 3 by a mechanism similar to that proposed by Kingston in his oxetane opening reaction induced by Meerwein's reagent.[31]

Scheme 3. Benzylation of the C7 Position and Oxetane Ring Opening[a]



[a] Reagents and conditions: (a) 20 equiv of benzyl trichloroacetimidate, 1.0 equiv of triflic acid, CH_2Cl_2, 25 °C, 40 h, 50%. Bz = COPh, Bn = CH_2Ph.

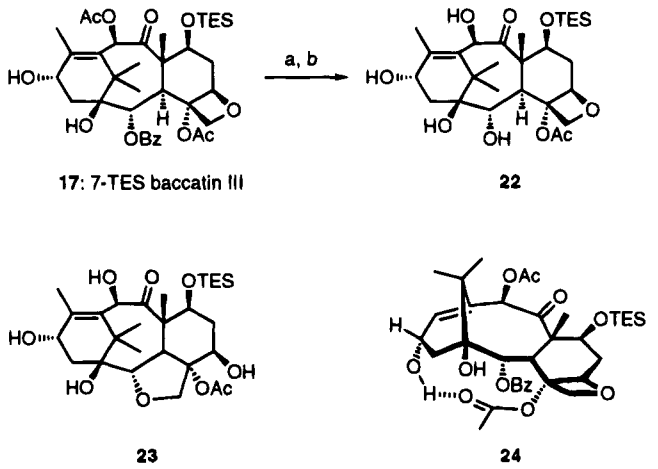
Failing to introduce a benzyl group at the C7 hydroxyl, we then turned to a silyl group. In agreement with Greene,[34] we observed that a *tert*-butyldimethylsilyl (TBS) group could not be efficiently introduced. Installation of a triethylsilyl (TES) group at C7, however, was smoothly accomplished with TESCl in pyridine[34] (85% yield) to afford 7-TES-baccatin III (**17**). The same compound was obtained from 10-deacetylbaccatin III (**2**) following Greene's procedure[34] involving selective silylation at the C7 hydroxyl group followed by acetylation of the C10 hydroxyl group. The latter step (AcCl, pyridine, 0 °C) proved rather capricious on a larger scale, presumably due to the oxetane opening and ring A skeletal rearrangements—although the byproducts were not isolated.[31,33,35–37] As we will see later in this discussion, however, a more reliable method for this transformation was discovered and utilized.

Formation of the 1,2-Carbonate Ring and Reconversion to the 1-Hydroxy, 2-Benzoate System

With 7-TES-baccatin III (**17**) in hand, we then turned our attention to the hydrolysis of the C2-benzoate and the C10-acetate in order to gain access to further degradation products (Scheme 4). Early trials using hydrolysis, methanolysis, or

(27) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1.
(28) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1994**, 295.
(29) Magri, N. F.; Kingston, D. G. I.; Jitrangsri, C.; Piccariello, T. *J. Org. Chem.* **1986**, *51*, 3239.
(30) Kingston, D. G. I. *Pharmacol. Ther.* **1991**, *52*, 1.
(31) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114.
(32) Iversen, T.; Bundle, K. R.; *J. Chem. Soc., Chem. Commun.* **1981**, 1240. White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.* **1988**, *110*, 1624. Widmer, U. *Synthesis* **1987**, 568.
(33) Wahl, A.; Guéritte-Voegelein, F.; Guénard, D.; Le Goff, M.-T.; Potier, P. *Tetrahedron* **1992**, *48*, 6965.
(34) Denis, J. N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917.
(35) Appendino, G.; Ozen, H. C.; Gariboldi, P.; Torregiani, E.; Gabetta, B.; Nizzola, R.; Bombardelli, E. *J. Chem. Soc. Perkin Trans. I* **1993**, 1563.
(36) Kingston, D. G. I.; Samaranayake, G.; Ivey, C. A. *J. Nat. Prod.* **1990**, *53*, 1.
(37) Guéritte-Voegelein, F.; Guénard, D.; Potier, P. *J. Nat. Prod.* **1987**, *50*, 9.

Scheme 4. Early Attempts at C2 and C10 Hydrolysis[a]



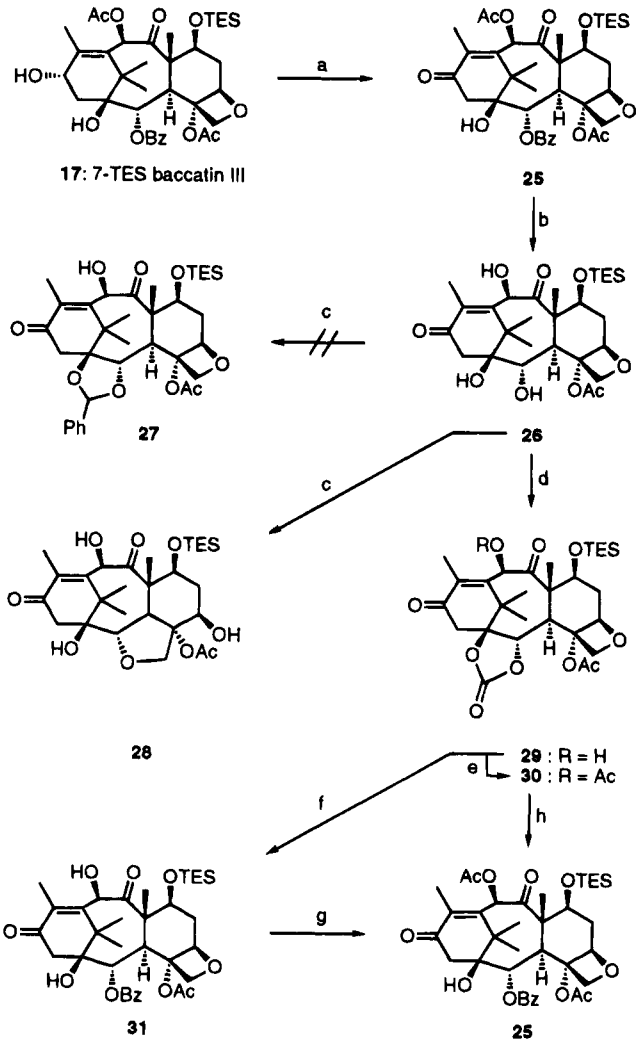
[a] Reagents and conditions: (a) excess $LiAlH_4$, THF, −78 °C or −30 °C, 1−5 h; (b) excess K_2CO_3, MeOH, H_2O, 0 °C or 25 °C, 1−5 h. TES = $SiEt_3$, Bz = COPh.

metal hydride reductions gave poor yields of tetrol **22**, in agreement with previous observations.[33,38,39] The principal byproducts seemed to result from deacetylation at C4 and various intramolecular reactions such as the opening of the oxetane ring by the newly liberated C2 hydroxyl group to form compound **23** (Scheme 4). The intramolecular engagement of the C4 acetate and C13 hydroxyl in a hydrogen-bonding arrangement (structure **24**, Scheme 4) is presumably responsible for the ease of deacetylation of the C4 oxygen. Similar structures have previously been invoked to explain deacetylation of C4 in analogous situations.[2,30,33] It was, therefore, decided to remove any possible interference from the C13 hydroxyl group by either oxidizing it to the enone or removing it altogether. Such manipulations would also further our exploration of degradative and synthetic chemistry.

Oxidation of C13 was projected not only as a means to remove the troublesome hydroxyl group but also as a way to change the conformation of the molecule to the extent that might affect the rate of hydrolysis of the C4 acetate and prevent attack of the C2 alkoxide on the oxetane ring. This operation[40,41] (**17** → **25**, Scheme 5) was smoothly carried out in 98% yield using Ley's TPAP/NMO system.[42] As hoped, enone **25** was readily hydrolyzed in basic conditions (K_2CO_3, MeOH, H_2O, 0 °C) to provide triol **26** in 91% yield. Contrary to the previously accepted order of ester reactivity in taxoids (C9, C10 > C2),[2] it was observed that, if so desired, the C10-acetate of compound **26** could be partially retained, as it reacts more slowly than the C2-benzoate under the above conditions.

Initial attempts to introduce a benzylidene,[43] a potential precursor to the C1-hydroxy, C2-benzoate system,[44] or an acetonide[45] protecting group at the C1−C2 site met with failure,

Scheme 5. Preparation of Carbonate **30** from 7-TES-baccatin III (**17**) and Its Transformation to Enone **25**[a]



[a] Reagents and conditions: (a) 1.5 equiv of 4-methylmorpholine *N*-oxide (NMO), 0.05 equiv of tetrapropylammonium perruthenate (TPAP), CH_3CN, 25 °C, 1.5 h, 98%; (b) excess K_2CO_3, MeOH, H_2O, 0 °C, 4 h, 91%; (c) 0.05 equiv of camphorsulfonic acid (CSA), 1.0 equiv of benzaldehyde dimethyl acetal or excess 2,2-dimethoxypropane, CH_2Cl_2, 25 °C, 20 h; (d) 10 equiv of phosgene, pyridine, 0 °C, 0.5 h, 85% or 6 equiv of carbonyldiimidazole, THF, 40 °C, 0.5 h, then 1 N aqueous HCl, THF, 25 °C, 15 min, 93%; (e) 4.5 equiv of Ac_2O, 9 equiv of 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 25 °C, 0.5 h, 95%; (f) 10 equiv of PhLi, THF, −78 °C, 0.5 h, 85%; (g) 10 equiv of Ac_2O, 5 equiv of DMAP, CH_2Cl_2, 25 °C, 2.5 h, 95%; (h) 5 equiv of PhLi, THF, −78 °C, 15 min, 70% plus 10% of **31**. TES = $SiEt_3$, Bz = COPh.

as the C2-hydroxyl group opened the oxetane ring under the acidic conditions used. In both instances the resulting product was the tetrahydrofuran derivative **28** (Scheme 5).[33,38,46] Attention then focused on constructing a carbonate ring at the C1−C2 site, an operation that required basic rather than acidic conditions. Despite the scarcity of reports of nucleophilic additions to carbonates to form esters,[47,48] we entertained the possibility of converting such functionality directly to the desired 1,2-hydroxybenzoate of Taxol (**1**) in the synthetic direction, by addition of nucleophilic phenyl species (Scheme 5). Even though the regiospecificity of such an opening was questionable,

(38) Klein, L. L. *Tetrahedron Lett.* **1993**, *34*, 2047.
(39) Chen, S.-H.; Wei, J.-M.; Farina, V. *Tetrahedron Lett.* **1993**, *34*, 3205.
(40) Harrison, J. W.; Scrowsten, R. M.; Lythgoe, B. *J. Chem. Soc. C* **1966**, 1932.
(41) Senilh, V.; Guéritte, F.; Guénard, D.; Colin, M.; Potier, P. *C. R. Acad. Sci. Paris* **1984**, *299*, 1039.
(42) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.
(43) Albert, R.; Dax, K.; Pleschko, R.; Stutz, K. *Carbohydr. Res.* **1985**, *137*, 282. Yamanoi, T.; Akiyama, E.; Inazu, T. *Chem. Lett.* **1989**, 335. Crimmins, M. T.; Hollis, W. G., Jr.; Lever, G. J. *Tetrahedron Lett.* **1987**, *28*, 3647.
(44) Binkley, R. W.; Goewey, G. S.; Johnston, J. C. *J. Org. Chem.* **1984**, *49*, 992.
(45) Evans, M. E.; Parrish, F. W.; Long, L., Jr. *Carbohydr. Res.* **1967**, *3*, 453. Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495.
(46) Farina, V.; Huang, S. *Tetrahedron Lett.* **1992**, *33*, 3979.
(47) Satyanarayana, G.; Sivaram, S. *Synth. Commun.* **1990**, *20*, 3273.
(48) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957.

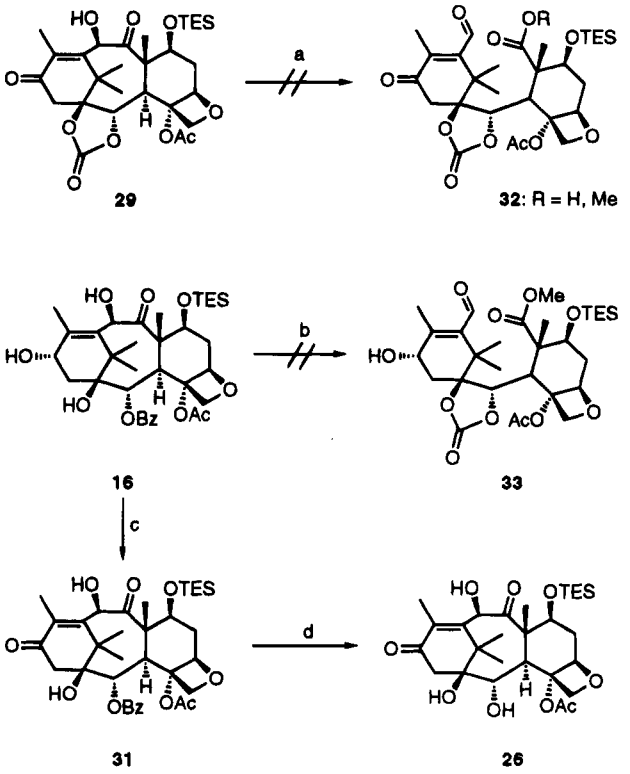
we expected the distinctly different steric environment of the two positions to favor the less crowded C2 regioisomer. Treatment of triol **26** with phosgene in pyridine provided the desired carbonate **29** in 85% yield.[49] It was later discovered that the carbonate **29** could be obtained in 93% yield by using carbonyldiimidazole[50] and 4-(dimethylamino)pyridine (DMAP) in THF followed by acidic hydrolysis of the imidazole carbamate at C10.

With a practical preparation of carbonate **29** secured, we then proceeded to investigate the anhydrous nucleophilic opening of the carbonate ring with organometallic species—a rather daring proposition considering the presence of four additional carbonyl groups within the molecule. To our pleasant surprise, exposure of **29** to excess phenyllithium in THF at −78 °C for 0.5 h resulted in the regioselective formation of the C2-benzoate **31** in 85% yield. This product was readily acetylated (95% yield) at the C10 hydroxyl position to afford compound **25**. The carbonate ring opening was also performed on the C10-acetate derivative **30**, resulting in the formation of a mixture of **25** (70%) and the corresponding 10-deacetyl derivative **31** (10%). Acetylation of the crude reaction mixture under standard conditions followed by chromatographic purification afforded **25** in 80% overall yield from **30**. The resistance of the other carbonyl moieties in these substrates to phenyllithium attack is, presumably, due to their steric shielding by the surrounding groups. In addition to providing a clear path for some of the final steps in the projected synthesis of Taxol (**1**), this chemistry was exploited to deliver a variety of C2 analogs of the natural product.[51,52]

Attempts To Cleave the C9−C10 Bond of the Taxol Skeleton. Preparation of Enone 26

With the C1−C2 diol system protected and the C9−C10 site free as a hydroxy ketone, as in compound **29** (Scheme 6), we attempted the cleavage of the C9−C10 bond under a variety of oxidative conditions. Unfortunately, however, none of these methods (including $Pb(OAc)_4$, $NaIO_4$,[53] and Baeyer−Villiger/hydrolysis[54]) led to the expected aldehyde **32** (Scheme 6) or any other cleavage product. Steric crowding is presumably again responsible for this inertness. This phenomenon also manifested itself in the reluctance of 7-TES-10-deacetylbaccatin III (**16**) to enter in any cleavage process to afford **33** (Scheme 6) under similar conditions. In the reaction of **16** with $Pb(OAc)_4$, it was surprising to observe a 20% yield of the C13-oxidized product, namely enone **31** (Scheme 6), in addition to recovered starting material (60%). This selective oxidation (**16** → **31**) could be carried out more efficiently with TPAP−NMO[42] in methylene chloride (96% yield). Subsequent hydrolysis (K_2CO_3, MeOH, H_2O, 0 °C) of the C2-benzoate from **31** provided triol **26** in 93% yield. This sequence allows the conversion of naturally occurring 10-deacetylbaccatin III (**2**) to compound **26** in three steps and in 81% overall yield, avoiding the problematic acetylation at C10.

Scheme 6. Selective Oxidation of the C13 Hydroxyl Group and Preparation of Enone **26**[a]



[a] Reagents and conditions: (a) 15 equiv of $Pb(OAc)_4$, MeOH, benzene, 0 → 50 °C; or excess of $NaIO_4$, MeOH, H_2O, 25 °C; or 2 equiv of H_2O_2, 8 equiv of NaOH, MeOH, H_2O, 0 °C, 1.25 h; (b) 15 equiv of $Pb(OAc)_4$, MeOH, benzene, 50 °C, 24 h; (c) 1.0 equiv of 4-methylmorpholine *N*-oxide (NMO), 0.05 equiv of tetrapropylammonium perruthenate (TPAP), CH_2Cl_2, 25 °C, 2 h, 96%; (d) 10 equiv of K_2CO_3, MeOH, H_2O, 0 °C, 2.5 h, 93% based on 81% conversion. TES = $SiEt_3$, Bz = COPh.

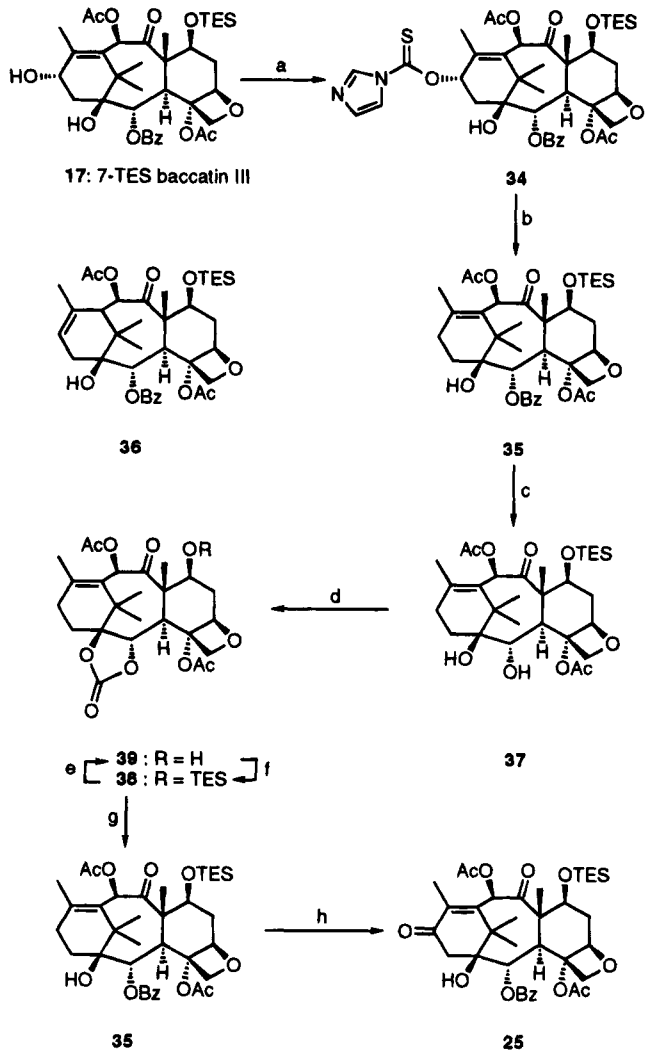
C13 Deoxygenation, Reoxygenation, and Side-Chain Attachment

In order to delve further into our planned synthetic strategy, we focused our efforts on the deoxygenation of the C13 position and on its subsequent reoxygenation. The first objective proved rather problematic as initial attempts of Wolf−Kishner reduction[55] of enone **25** (Scheme 5) and thioacetal formation/reduction[56] of the same compound failed. A Barton deoxygenation[57] was then considered. Although a C13 xanthate could not be produced, strenuous conditions (excess (thiocarbonyl)-diimidazole and DMAP, 75 °C, 18 h) allowed the conversion of 7-TES-baccatin III (**17**) to thiocarbamate **34** (Scheme 7) in 86% yield. Treatment of **34** with excess *n*-Bu_3SnH in toluene at 85 °C in the presence of a catalytic amount of AIBN provided the desired C13 deoxy derivative **35** in 59% yield, together with its $\Delta^{12,13}$ regioisomer **36** (17% yield). Increasing the concentration of *n*-Bu_3SnH in an attempt to trap the initially formed C13 radical before it rearranges to its C11 isomer, responsible for the formation of the byproduct **36**, did not change the ratio of the two products.

The desired oxidation of the C13 allylic position[22] to a carbonyl function was demonstrated on intermediate **35** by

(49) Haworth, W. N.; Porter, C. R. *J. Chem. Soc.* **1930**, 151.
(50) Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975**, *5*, 47.
(51) Nicolaou, K. C.; Couladouros, E. A.; Nantermet, P. G.; Renaud, J.; Guy, R. K.; Wrasidlo, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1581.
(52) Nicolaou, K. C.; Renaud, J.; Nantermet, P. G.; Guy, R. K.; Couladouros, E. A.; Wrasidlo, W. Submitted.
(53) Shing, T. K. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., FRS, Eds.; Pergamon Press: New York, 1991; Vol. 7, p 708. Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3146.
(54) Krow, G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., FRS, Eds.; Pergamon Press: New York, 1991; Vol. 7, p 671. Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* **1977**, *42*, 4061.
(55) Todd. *Org. React.* **1962**, *12*, 356.
(56) Van Tamelen. *Org. React.* **1948**, *4*, 378. Dailey, O. D., Jr. *J. Org. Chem.* **1987**, *52*, 1984. Corey, E. J.; Shimoji. *Tetrahedron Lett.* **1983**, *24*, 169.
(57) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574. Barton, D. H. R.; Dorchak, J.; Jaszberenyi *Tetrahedron* **1992**, *48*, 7435. Hartwig *Tetrahedron* **1983**, *39*, 2609.

Scheme 7. C13 Deoxygenation and Oxygenation[a]



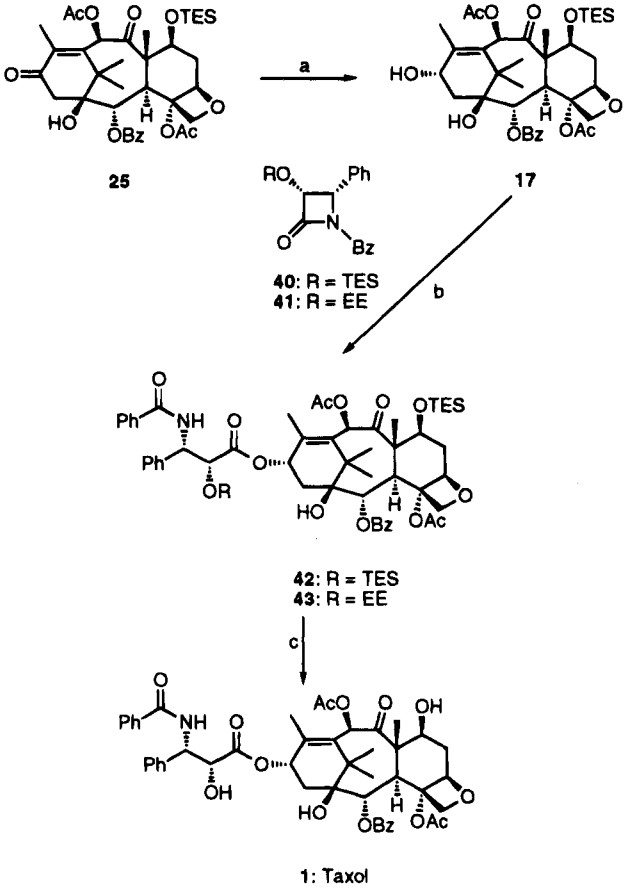
[a] Reagents and conditions: (a) 20 equiv of (thiocarbonyl)diimidazole, 30 equiv of 4-(dimethylamino)pyridine (DMAP), THF, 75 °C, sealed tube, 18 h, 86%; (b) 10 equiv of *n*-Bu_3SnH, 0.1 equiv of azobis(isobutyronitile) (AIBN), toluene, 85 °C, 2 h, 59% of **35** plus 17% of **36**; (c) 20 equiv of K_2CO_3, MeOH, THF, H_2O, 0 °C, 6 h, then −20 °C, 10 h, 94% based on 62% conversion; (d) 10 equiv of phosgene, pyridine, 25 °C, 15 min, 86%; (e) HF·pyridine, THF, 25 °C, 2 h, 88%; (f) 50 equiv of Et_3SiCl, pyridine, 25 °C, 24 h, 85%; (g) 5 equiv of PhLi, THF, −78 °C, 15 min, 80%; (h) 30 equiv of pyridinium chlorochromate (PCC), 30 equiv of NaOAc, Celite, benzene reflux, 1 h, 75%. TES = $SiEt_3$, Bz = COPh.

exposure to pyridinium chlorochromate (PCC)[58] in the presence of NaOAc and Celite in refluxing benzene to afford, in 75% yield, enone **25** (Scheme 7).

The C13 deoxy intermediate **35** was converted to the corresponding diol **37** (Scheme 7) via selective benzoate hydrolysis (K_2CO_3, MeOH, H_2O, THF, 0 °C, 94% yield based on 62% conversion). The carbonate ring was installed at the C1−C2 positions of the latter compound by the phosgene−pyridine method,[49] furnishing intermediate **38** in 86% yield. Desilylation of the C7 hydroxyl group by exposure to HF·pyridine[59] led to **39**, in 88% yield, a compound that was projected as an advanced intermediate in our synthetic scheme.

Using the key intermediate **39** (Scheme 7), obtained from 10-deacetylbaccatin III (**2**) as described above, a sequence was

Scheme 8. Taxol's Side-Chain Attachment[a]



[a] Reagents and conditions: (a) excess $NaBH_4$, MeOH, 25 °C, 3 h, 94% based on 88% conversion; (b) for **42**, 3 equiv of $NaN(SiMe_3)_2$, 3.5 equiv of β-lactam **40**, THF, 0 °C, 0.5 h, 86% based on 89% conversion; for **43**, 2.5 equiv of $NaN(SiMe_3)_2$, 1.2 equiv of β-lactam **41**, THF, 0 °C, 20 min, 80% based on 54% conversion; (c) for **42**, HF·pyridine, THF, 25 °C, 1.25 h, 80%; for **43**, EtOH, 0.5% aqueous HCl, 0 °C, 72 h, 80%. TES = $SiEt_3$, Bz = COPh, EE = ethoxyethyl.

established toward Taxol (**1**) as follows: (a) silylation with TESCl under standard conditions[34,60] to afford **38** (85% yield); (b) carbonate ring opening with phenyllithium, as described above, to convert **38** to **35** (80% yield, Scheme 7); (c) allylic oxidation (75%); (d) stereoselective reduction of the enone carbonyl of **25** with $NaBH_4$ according to Potier's method[29,41] to provide 7-TES-baccatin III (**17**, Scheme 8) in 94% yield, based on 88% conversion; and finally (e) attachment of the side chain onto **17** using the Ojima−Holton β-lactam method[20,21] (Scheme 8). To the latter end, both optically active β-lactams **40** and **41** were prepared according to Ojima's procedure and coupled to **17** using $NaN(SiMe_3)_2$ to provide the 2′,7-diprotected Taxol derivatives **42** and **43**, respectively. Deprotection of **42** with HF·pyridine[59] in THF furnished Taxol (**1**) in 80% yield, whereas exposure of **43** to dilute HCl in EtOH[61] led to the same target (**1**) in a similar fashion (80%).

Conclusion

The chemistry described in this article shed light on the chemical properties of Taxol (**1**) and its derivatives and opened

(58) Parish, E. J.; Wei, T. Y. *Synth. Commun.* **1987**, *17*, 1227. Rathore, R.; Saxena, N.; Chadrasekaran *Synth. Commun.* **1986**, *16*, 1493.
(59) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.
(60) Hart, T. W.; Metcalfe, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156. Roush, W. R.; Russo-Rodrigez, S. *J. Org. Chem.* **1987**, *52*, 598.
(61) Ogilvie, K. K.; Thompson, E. A.; Quiliam, M. A.; Westmore, J. B. *Tetrahedron Lett.* **1974**, 2865.

access to a number of valuable taxoid intermediates. Specifically, it allowed the definition of a series of key intermediates and of a track along which our total synthesis was to follow (**39** → **38** → **35** → **25** → **17** → **1**). Furthermore, the easy access to the 5-membered ring carbonate intermediate **29** developed in this program was crucial to providing a practical entry into a plethora of C2 analogs of Taxol (**1**) via nucleophilic opening of the carbonate ring with a variety of reagents. The following papers in this series describe the total synthesis[16-18] of Taxol (**1**) and a variety of its analogs.[51,52]

Experimental Section

General Techniques. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and ethyl ether (Et_2O) were distilled from sodium–benzophenone, and methylene chloride (CH_2Cl_2), benzene (PhH), and toluene from calcium hydride. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. All solutions used in workup procedures are saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.[62] Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254).

NMR spectra were recorded on Brucker AMX-500 or AM-300 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. The carbon numbering of Taxol (**1**) was used to assign protons. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Melting points (mp) are uncorrected, recorded on a Thomas Hoover capillary melting point apparatus.

Experimental techniques and data for compounds **15**, **16**, **18**, and **28** may be found in the supplementary material.

7-TES-baccatin III (17). A. Silylation of 15 to 17. To a solution of baccatin III (**15**, 165 mg, 0.28 mmol) in pyridine (14 mL) was added chlorotriethylsilane (1.42 mL, 8.45 mmol) dropwise. The solution was stirred at 25 °C for 24 h. After dilution with Et_2O (100 mL), the solution was washed with aqueous $CuSO_4$ (3 × 20 mL) and brine (20 mL). The organic extract was dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 35 → 50% EtOAc in petroleum ether) to give **17** (168 mg, 85%) as a white solid.

B. Acetylation of 16 to 17. To a solution of 7-TES-10-deacetylbaccatin III (**16**, 0.21 g, 0.318 mmol) in pyridine (8 mL) at 0 °C was added acetyl chloride (0.113 mL, 1.59 mmol) dropwise. The solution was stirred at 0 °C for 48 h. After dilution with Et_2O (20 mL), the reaction was quenched with aqueous $NaHCO_3$ (10 mL). The organic layer was separated, washed with aqueous $CuSO_4$ (2 × 10 mL) and brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 25 → 50% EtOAc in petroleum ether) to give 7-TES-baccatin III (**17**, 183 mg, 82%) as a white solid.

C. Reduction of Enone 25 to 17. A solution of enone **25** (10 mg, 0.014 mmol) in MeOH (2 mL) was treated with an excess of $NaBH_4$ for 3 h at 25 °C. The reaction was quenched with aqueous NH_4Cl (1 mL), and the resulting mixture was stirred at 25 °C for 15 min. After dilution with water (5 mL), the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 25 → 50% EtOAc in petroleum ether) to give starting enone **25** (1.2 mg, 12%) and 7-TES-baccatin III (**17**, 8.3 mg, 94% based on 88% conversion) as a white powder: R_f = 0.43 (silica, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ −49 (*c* 0.4, MeOH); IR (thin film) ν_{max} 3518, 2914, 1723, 1448, 1237 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.5 Hz, 2 H, Bz), 7.58 (t, *J* = 7.4 Hz, 1 H, Bz), 7.46 (t, *J* = 7.4 Hz, 2 H, Bz), 6.44 (s, 1 H, 10-H), 5.61 (d, *J* = 7.0 Hz, 1 H, 2-H), 4.94 (d, *J* = 9.5 Hz, 1 H, 5-H), 4.82 (m, 1 H, 13-H), 4.47 (dd, *J* = 10.5, 6.8 Hz, 1 H, 7-H), 4.28 (A of AB, d, *J* = 8.3 Hz, 1 H, 20-H), 4.12 (B of AB, d, *J* = 8.3 Hz, 1 H, 20-H), 3.86 (d, *J* = 7.0 Hz, 1 H, 3-H), 2.51 (m, 1 H, 6-H), 2.27 (s, 3 H, OAc), 2.25 (m, 1 H, 14-H), 2.17 (s, 3 H, OAc), 2.16 (s, 3 H, 18-CH_3), 2.05 (m, 1 H, 14-H), 1.85 (m, 1 H, 6-H), 1.55 (s, 3 H, 19-CH_3), 1.17 (s, 3 H, 16-CH_3), 1.02 (s, 3 H, 17-CH_3), 0.90 (t, *J* = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.62–0.50 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 171.0, 169.4, 167.1, 143.9, 133.6, 132.6, 130.1, 129.4, 128.6, 84.2, 80.8, 78.7, 76.5, 75.8, 74.7, 72.3, 67.9, 58.6, 47.2, 42.7, 38.2, 37.2, 26.8, 22.7, 21.0, 20.1, 15.0, 9.9, 6.7, 5.2; FAB HRMS (NBA/CsI) *m/e* 833.2339, M + Cs^+ calcd for $C_{37}H_{52}O_{11}Si$ 833.2333.

Enone 25. A. Oxidation of Alcohol 17 to 25. To a solution of 7-TES-baccatin III (**17**, 30 mg, 0.043 mmol) and 4-methylmorpholine *N*-oxide (NMO, 7.5 mg, 0.064 mmol) in acetonitrile (5 mL) was added 4-Å molecular sieves (20 mg), and the suspension was stirred at 25 °C for 5 min. A catalytic amount of tetrapropylammonium perruthenate (TPAP) was added, and the reaction mixture was stirred at 25 °C for 1.5 h. The reaction mixture was concentrated, suspended in CH_2Cl_2 (20 mL), and filtered through silica gel. Elution with CH_2Cl_2 (20 mL) and 50% EtOAc in hexanes (20 mL), followed by concentration, gave enone **25** (29 mg, 98%) as a white solid.

B. Conversion of Carbonate 30 to 25. A solution of carbonate **30** (17.6 mg, 0.028 mmol) in THF (2 mL) at −78 °C was treated with PhLi (0.070 mL, 2 M in cyclohexane, 0.14 mmol) and stirred at −78 °C for 15 min. The reaction was quenched with aqueous NH_4Cl (1 mL), and the resulting mixture was allowed to warm to 25 °C. After dilution with Et_2O (10 mL), the organic layer was separated, dried ($MgSO_4$), and concentrated to give hydroxy benzoate **25** containing ca. 10% of the 10-deacetylated compound (^1H NMR). The crude mixture was dissolved in CH_2Cl_2 (1.5 mL), treated with 4-(dimethylamino)pyridine (DMAP, 61.0 mg, 0.50 mmol) and acetic anhydride (0.024 mL, 0.25 mmol), and stirred at 25 °C for 1 h. The reaction mixture was diluted with Et_2O (10 mL), washed with 10% aqueous HCl (5 mL), 10% aqueous NaOH (5 mL), and brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 25 → 50% EtOAc in petroleum ether) to give hydroxy benzoate **25** (15.9 mg, 80%) as a white solid.

C. Acetylation of Alcohol 31 to 25. To a solution of alcohol **31** (650 mg, 0.989 mmol) in CH_2Cl_2 (50 mL) were added 4-(dimethylamino)pyridine (DMAP, 600 mg, 4.9 mmol) and acetic anhydride (0.9 mL, 9.89 mmol). The solution was stirred at 25 °C for 2.5 h, the reaction was quenched with aqueous $NaHCO_3$ (10 mL), and the resulting mixture was diluted with Et_2O (100 mL), washed with 10% aqueous HCl (50 mL), 10% aqueous NaOH (50 mL), and brine (30 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 35% EtOAc in petroleum ether) to give acetate **25** (657 mg, 95%) as a white solid.

D. Allylic Oxidation of 35 to 25. A solution of **35** (1.3 mg, 0.0019 mmol) in benzene (0.5 mL) was treated with anhydrous NaOAc (4.7 mg, 0.057 mmol), anhydrous Celite (12.0 mg), and pyridinium chlorochromate (12.0 mg, 0.056 mmol) and stirred at reflux for 1 h. The reaction mixture was filtered through silica gel, eluted with Et_2O (20 mL), concentrated, and purified by preparative TLC (silica, 30% Et_2O in benzene) to give enone **25** (1.0 mg, 75%) as a film: R_f = 0.5 (silica, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ − 19.8 (*c* 0.85, $CHCl_3$); IR (thin film) ν_{max} 3499, 2956, 1758, 1732, 1673, 1657, 1604 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.3 Hz, 2 H, Bz), 7.61 (t, *J* = 7.5 Hz, 1 H, Bz), 7.47 (t, *J* = 7.8 Hz, 2 H, Bz), 6.57 (s, 1 H, 10-H), 5.67 (d, *J* = 6.7 Hz, 1 H, 2-H), 4.90 (d, *J* = 8.4 Hz, 1 H, 5-H), 4.46 (dd, *J* = 10.4, 6.8 Hz, 1 H, 7-H), 4.31 (A of AB, d, *J* = 8.5 Hz, 1 H, 20-H), 4.09 (B of AB, d, *J* = 8.5 Hz, 1 H, 20-H), 3.89 (d, *J* = 6.7 Hz, 1 H, 3-H), 2.92 (A′ of A′B′, d, *J* = 19.9 Hz, 1 H, 14-H), 2.63 (B′ of A′B′, d, *J* = 19.9 Hz, 1 H, 14-H), 2.50 (m, 1 H, 6-H), 2.21 (s, 3 H, OAc), 2.17 (s, 3 H, OAc), 2.16 (s, 3 H, 18-CH_3), 1.82 (m, 1 H, 6-H), 1.65 (s, 3 H, 19-CH_3), 1.25 (s, 3 H, 16-CH_3), 1.17 (s, 3 H, 17-CH_3),

(62) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

0.90 (t, J = 7.9 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.65−0.45 (band, 6 H, Si(CH_2-CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 198.3, 170.1, 168.9, 166.8, 153.0, 140.2, 133.9, 130.0, 128.8, 128.7, 83.9, 80.5, 78.4, 76.1, 76.0, 72.8, 72.2, 59.4, 46.2, 43.4, 42.4, 37.1, 33.0, 21.7, 21.0, 18.2, 13.5, 9.5, 6.7, 5.1; FAB HRMS (NBA) *m/e* 699.3220, M + H$^+$ calcd for $C_{37}H_{50}O_{11}Si$ 699.3201.

Diol 26. A. Hydrolysis of 25 to 26. To a solution of enone **25** (124 mg, 0.034 mmol) in MeOH (29 mL) at 0 °C was added an aqueous solution of K_2CO_3 (291 mg in 7.3 mL H_2O). The solution was stirred at 0 °C for 4 h. The reaction was quenched with aqueous NH_4Cl (30 mL), and the resulting mixture was extracted with $CHCl_3$ (2 × 50 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 25 → 50% EtOAc in petroleum ether) to give triol **26** (96 mg, 91%) containing a small amount of the 10-acetylated product (^{1}H NMR).

B. Hydrolysis of 31 to 26. To a solution of enone **31** (1.44 g, 2.19 mmol) in MeOH (300 mL) at 0 °C was slowly added an aqueous solution of K_2CO_3 (3.0 g in 32 mL of H_2O). The solution was stirred at 0 °C for 2.5 h. The reaction was quenched with aqueous NH_4Cl (150 mL), and the resulting mixture was extracted with CH_2Cl_2 (2 × 200 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica, 35 → 50% EtOAc in petroleum ether) to give enone **31** (270 mg, 19%) and triol **26** (912 mg, 93% based on 81% conversion): R_f = 0.24 (silica, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ +38 (*c* 0.15, $CHCl_3$); IR (thin film) ν_{max} 3414, 2957, 2881, 1727, 1664, 1370 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (d, J = 9.5 Hz, 1 H, 10-H), 4.89 (d, J = 9.5 Hz, 1 H, 5-H), 4.63 (A of AB, d, J = 9.5 Hz, 1 H, 20-H), 4.56 (B of AB, d, J = 9.5 Hz, 1 H, 20-H), 4.32 (dd, J = 11.0, 7.0 Hz, 1 H, 7-H), 4.28 (d, J = 2.5 Hz, 1 H, 10-OH), 3.89 (dd, J = 6.5, 4.0 Hz, 1 H, 2-H), 3.57 (d, J = 6.5 Hz, 1 H, 3-H), 2.78 (A′ of A′B′, d, J = 19.5 Hz, 1 H, 14-H), 2.58 (d, 4.0 Hz, 1 H, 2-OH), 2.52 (B′ of A′B′, d, J = 19.5 Hz, 1 H, 14-H), 2.46 (m, 1 H, 6-H), 2.03 (s, 3 H, OAc), 1.88 (m, 1 H, 6-H), 1.68 (s, 3 H, 18-CH_3), 1.21 (s, 3 H, 16-CH_3), 1.04 (s, 3 H, 17-CH_3), 0.90 (t, J = 8.0 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.60−0.40 (band, 6 H, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9, 198.5, 170.1, 156.7, 138.8, 83.8, 81.2, 77.6, 75.7, 72.8, 72.5, 58.8, 45.8, 43.1, 42.8, 37.3, 32.7, 21.6, 17.5, 13.6, 9.7, 6.7, 5.1; FAB HRMS (NBA/NaI) *m/e* 575.2648, M + Na$^+$ calcd for $C_{28}H_{44}O_9Si$ 575.2652.

Carbonate 29. Method A. To a solution of diol **26** (96.0 mg, 0.187 mmol) in pyridine (10 mL) at 0 °C was added phosgene (0.97 mL of a 1.93 M solution in toluene, 1.87 mmol). The solution was stirred at 0 °C for 0.5 h and poured onto ice (10 mL). After dilution with Et_2O (25 mL), the organic layer was separated, washed with aqueous $CuSO_4$ (2 × 15 mL) and aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated to give carbonate **29** (86 mg, 85%) as an amorphous solid.

Method B. A solution of diol **26** (60.0 mg, 0.109 mmol) in THF (2 mL) was treated with carbonyldiimidazole (110.0 mg, 0.678 mmol) and stirred at 40 °C for 0.5 h. The reaction mixture was concentrated and redissolved in THF (5 mL). TLC analysis confirmed total consumption of starting material. Then 1 N aqueous HCl (5 mL) was added, and the resulting solution was allowed to stir for 15 min at 25 °C. Et_2O (25 mL) was added, and the organic layer was separated, washed with aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to give carbonate **29** (58 mg, 93%) as a white foam: R_f = 0.50 (silica, 35% EtOAc in hexanes); $[\alpha]^{22}_D$ +48 (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 3438, 2957, 2882, 1820, 1731, 1685, 1370, 1236 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (d, J = 2.5 Hz, 1 H, 10-H), 4.89 (d, J = 9.0 Hz, 1 H, 5-H), 4.60 (A of AB, d, J = 9.0 Hz, 1 H, 20-H), 4.45 (B of AB, d, J = 9.0 Hz, 1 H, 20-H), 4.43 (d, J = 6.0 Hz, 1 H, 2-H), 4.33 (dd, J = 10.0, 7.5 Hz, 1 H, 7-H), 4.28 (d, J = 2.5 Hz, 1 H, 10-OH), 3.54 (d, J = 6.0 Hz, 1 H, 3-H), 2.88 (A′ of A′B′, d, J = 20.0 Hz, 1 H, 14-H), 2.75 (B′ of A′B′, d, J = 20.0 Hz, 1 H, 14-H), 2.50 (m, 1 H, 6-H), 2.08 (s, 3 H, OAc), 2.06 (s, 3 H, 18-CH_3), 1.88 (m, 1 H, 6-H), 1.77 (s, 3 H, 19-CH_3), 1.31 (s, 3 H, 16-CH_3), 1.15 (s, 3 H, 17-CH_3), 0.88 (t, J = 8.5 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.55−0.45 (band, 6 H, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 195.5, 170.5, 154.0, 152.0, 141.2, 88.4, 83.9, 79.8, 79.0, 76.7, 75.7, 71.9, 60.3, 43.0, 41.6, 39.8, 37.7, 31.6, 21.5, 17.8, 14.4, 9.7, 6.6, 5.0; FAB HRMS (NBA) *m/e* 579.2652, M + H$^+$ calcd for $C_{29}H_{42}O_{10}$-Si 579.2626.

Acetate 30. To a solution of carbonate **29** (86.0 mg, 0.159 mmol) in CH_2Cl_2 (2 mL) were added 4-(dimethylamino)pyridine (DMAP, 177.0 mg, 1.45 mmol) and acetic anhydride (0.069 mL, 0.723 mmol). The solution was stirred at 25 °C for 0.5 h, diluted with Et_2O (100 mL), washed with 10% aqueous HCl (5 mL), 10% aqueous NaOH (5 mL) and brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 10 → 50% EtOAc in petroleum ether) to give carbonate **30** (94 mg, 95%) as an amorphous solid: R_f = 0.50 (silica, 35% EtOAc in hexanes); $[\alpha]^{22}_D$ +14 (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 2926, 1823, 1754, 1731, 1689 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (s, 1 H, 10-H), 4.89 (d, J = 9.0 Hz, 1 H, 5-H), 4.60 (A of AB, d, J = 9.0 Hz, 1 H, 20-H), 4.48 (d, J = 5.5 Hz, 1 H, 2-H), 4.45 (B of AB, d, J = 9.0 Hz, 1 H, 20-H), 4.42 (dd, J = 9.5, 7.0 Hz, 1 H, 7-H), 3.49 (d, J = 5.5 Hz, 1 H, 3-H), 2.90 (A′ of A′B′, d, J = 20.0 Hz, 1 H, 14-H), 2.78 (B′ of A′B′, d, J = 20.0 Hz, 1 H, 14-H), 2.55 (m, 1 H, 6-H), 2.19 (s, 3 H, OAc), 2.16 (s, 3 H, OAc), 2.07 (s, 3 H, 18-CH_3), 1.87 (m, 1 H, 6-H), 1.71 (s, 3 H, 19-CH_3), 1.28 (s, 3 H, 16-CH_3), 1.26 (s, 3 H, 17-CH_3), 0.89 (t, J = 8.0 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.60−0.50 (band, 6 H, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 195.7, 170.5, 168.7, 152.0, 150.4, 142.5, 88.2, 83.9, 79.8, 79.2, 76.6, 75.7, 71.5, 61.0, 43.1, 39.8, 37.7, 31.6, 21.5, 20.7, 18.4, 14.4, 9.7, 6.7, 5.1; FAB HRMS (NBA) *m/e* 621.2745, M + H$^+$ calcd for $C_{31}H_{44}O_{11}Si$ 621.2731.

Enone 31. A. Oxidation of 16 to 31. To a solution of 7-TES-deacetylbaccatin III (**16**, 1.5 g, 2.28 mmol) and 4-methylmorpholine *N*-oxide (NMO, 240 mg, 2.05 mmol) in CH_2Cl_2 (5 mL) was added 4-Å molecular sieves (200 mg), and the suspension was stirred at 25 °C for 10 min. A catalytic amount of tetrapropylammonium perruthenate (TPAP, 40 mg, 0.11 mmol) was added by portions, and the reaction mixture was stirred at 25 °C for 0.5 h. Small amounts of 4-methylmorpholine *N*-oxide and TPAP were added alternatively at 0.5 h intervals until the starting material was consumed to the extent of *ca.* 95% by TLC. The reaction mixture was filtered through silica gel, eluted with CH_2Cl_2 (100 mL), and concentrated to give enone **31** (1.44 g, 96%) as a white solid.

B. Conversion of Carbonate 29 to 31. A solution of carbonate **29** (1.5 mg, 0.0026 mmol) in THF (0.3 mL) at −78 °C was treated with PhLi (0.013 mL, 0.026 mmol) and stirred at −78 °C for 0.5 h. The reaction was quenched with aqueous NH_4Cl (10 mL). After dilution with Et_2O (20 mL), the organic layer was separated, washed with brine (10 mL), dried (Na_2SO_4), and purified by flash chromatography (silica, 25 → 35% EtOAc in petroleum ether) to give hydroxy benzoate **31** (1.4 mg, 85%) as a film: R_f = 0.5 (silica, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ +11 (*c* 0.56, $CHCl_3$); IR (thin film) ν_{max} 3446, 2957, 2882, 1726, 1672, 1456, 1367, 1243, 1106 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.0, 1.0 Hz, 2 H, Bz), 7.61 (t, J = 7.5 Hz, 1 H, Bz), 7.45 (t, J = 7.5 Hz, 2 H, Bz), 5.63 (d, J = 7.5 Hz, 1 H, 2-H), 5.30 (d, J = 2.0 Hz, 1 H, 10-H), 4.90 (d, J = 8.0 Hz, 1 H, 5-H), 4.36 (dd, J = 10.5, 7.0 Hz, 1 H, 7-H), 4.31 (A of AB, d, J = 8.5 Hz, 1 H, 20-H), 4.30 (d, J = 2.0 Hz, 1 H, 10-OH), 4.11 (B of AB, d, J = 8.5 Hz, 1 H, 20-H), 3.93 (d, J = 7.5 Hz, 1 H, 3-H), 2.92 (A′ of A′B′, d, J = 19.5 Hz, 1 H, 14-H), 2.62 (B′ of A′B′, d, J = 19.5 Hz, 1 H, 14-H), 2.46 (m, 1 H, 6-H), 2.17 (s, 3 H, OAc), 2.08 (s, 3 H, 18-CH_3), 1.87 (m, 1 H, 6-H), 1.77 (s, 1 H, 1-OH), 1.70 (s, 3 H, 19-CH_3), 1.21 (s, 3 H, 16-CH_3), 1.14 (s, 3 H, 17-CH_3), 0.90 (t, J = 8.0 Hz, 9 H, Si(CH_2CH_3)$_3$), 0.60−0.42 (band, 6 H, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 198.1, 170.2, 166.8, 156.6, 139.1, 134.0, 130.0, 128.8, 128.8, 84.0, 80.4, 78.5, 76.2, 75.7, 72.9, 72.8, 58.8, 45.9, 43.4, 42.5, 37.2, 33.0, 21.7, 17.5, 13.6, 9.6, 6.7, 5.1; FAB HRMS (NBA/NaI) *m/e* 657.3070, M + Na$^+$ calcd for $C_{35}H_{48}O_{10}Si$ 657.3095.

Thiocarbamate 34. A solution of 7-TES-baccatin III (**17**, 48 mg, 0.069 mmol) in THF (1 mL) was treated with 4-(dimethylamino)-pyridine (DMAP, 251 mg, 2.05 mmol) and (thiocarbonyl)diimidazole (244 mg, 1.37 mmol) and stirred at 75 °C in a sealed flask for 18 h. The reaction mixture was diluted with EtOAc (15 mL), washed with 10% aqueous HCl (5 mL) and aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 20 → 50% EtOAc in petroleum ether) to give thiocarbamate **34** (48 mg, 86%) as a white solid: R_f = 0.27 (silica, 25% EtOAc in benzene); $[\alpha]^{22}_D$ −59 (*c* 0.17, $CHCl_3$); IR (thin film) ν_{max} 3478, 2954, 1726, 1465, 1388, 1284, 1238, 1104 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1 H, imid.), 8.01 (d, J = 7.5 Hz, 2 H, Bz), 7.79 (s, 1 H, imid.), 7.56

(t, J = 7.5 Hz, 1 H, Bz), 7.42 (t, J = 7.5 Hz, 2 H, Bz), 7.10 (s, 1 H, imid.), 6.53 (t, J = 9.0 Hz, 1 H, 13-H), 6.46 (s, 1 H, 10-H), 5.66 (d, J = 7.0 Hz, 1 H, 2-H), 4.89 (d, J = 8.5 Hz, 1 H, 5-H), 4.46 (dd, J = 10.5, 7.0 Hz, 1 H, 7-H), 4.25 (A of AB, d, J = 8.5 Hz, 1 H, 20-H), 4.13 (B of AB, d, J = 8.5 Hz, 1 H, 20-H), 3.85 (d, J = 7.0 Hz, 1 H, 3-H), 2.72 (dd, J = 15.0, 9.0 Hz, 1 H, 14-H), 2.53 (m, 1 H, 6-H), 2.21 (s, 3 H, OAc), 2.17 (s, 3 H, OAc), 2.12 (dd, J = 15.0, 7.5 Hz, 1 H, 14-H), 1.91 (s, 3 H, 18-CH_3), 1.88 (m, 1 H, 6-H), 1.65 (s, 3 H, 19-CH_3), 1.25 (s, 3 H, 16-CH_3), 1.17 (s, 3 H, 17-CH_3), 0.91 (t, J = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.62−0.51 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 183.5, 170.0, 169.3, 166.9, 138.7, 137.7, 134.8, 133.8, 131.3, 130.0, 128.9, 128.6, 118.3, 84.1, 81.3, 80.1, 78.9, 76.6, 75.0, 74.3, 72.5, 58.9, 46.8, 43.3, 37.4, 35.0, 29.7, 26.9, 21.9, 20.9, 20.3, 15.4, 9.9, 6.7, 5.2; FAB HRMS (NBA/NaI) *m/e* 833.3110, M + Na^+ calcd for $C_{41}H_{54}O_{11}N_2SSi$ 833.3115.

Benzoate 35. A. Deoxygenation of 34 to 35. To a solution of thiocarbamate **34** (960 mg, 1.18 mmol) in degased toluene (250 mL) stirred at 85 °C were added tributyltin hydride (3.2 mL, 11.8 mmol) and azobis(isobutyronitrile) (AIBN, 16.4 mg in 1 mL of toluene, 0.1 mmol). The reaction mixture was stirred at 85 °C for 2 h, concentrated, and purified by flash chromatography (silica, 15 → 25% EtOAc in petroleum ether) to give a mixture of alcohol **35** and isomer **36** (620 mg, 76%) as one single fraction containing 77% of **35** (59% yield) and 23% of **36** (17% yield). Analytical samples of both isomers were obtained by preparative TLC (silica, 30% EtOAc in benzene).

Isomer 35: R_f = 0.47 (silica, 25% EtOAc in benzene); $[\alpha]^{22}_D$ −50.6 (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 3517, 2922, 1728, 1456, 1371, 1242, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 2 H, Bz), 7.58 (t, J = 7.5 Hz, 1 H, Bz), 7.45 (t, J = 7.5 Hz, 2 H, Bz), 6.45 (s, 1 H, 10-H), 5.59 (d, J = 7.0 Hz, 1 H, 2-H), 4.95 (d, J = 9.0 Hz, 1 H, 5-H), 4.45 (dd, J = 10.5, 7.0 Hz, 1 H, 7-H), 4.30 (A of AB, d, J = 8.5 Hz, 1 H, 20-H), 4.14 (B of AB, d, J = 8.5 Hz, 1 H, 20-H), 3.75 (d, J = 7.0 Hz, 1 H, 3-H), 2.65 (m, 1 H, 13-H), 2.53 (m, 1 H, 13-H), 2.30 (s, 3 H, OAc), 2.30−2.17 (band, 2 H, 6-CH_2), 2.16 (s, 3 H, OAc), 2.07 (s, 3 H, 18-CH_3), 1.93−1.81 (band, 2 H, 14-CH_2), 1.64 (s, 3 H, 19-CH_3), 1.18 (s, 3 H, 16-CH_3), 1.04 (s, 3 H, 17-CH_3), 0.89 (t, J = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.65−0.49 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 169.8, 169.5, 167.0, 141.6, 133.6, 132.3, 130.0, 129.3, 128.6, 84.0, 81.4, 80.6, 76.5, 75.9, 73.8, 72.4, 58.8, 46.8, 42.2, 37.4, 30.0, 26.7, 25.2, 22.1, 21.1, 20.5, 19.0, 9.6, 6.7, 5.3; FAB HRMS (NBA/CsI) *m/e* 817.2380, M + Cs^+ calcd for $C_{37}H_{52}O_{10}Si$ 817.2384.

Isomer 36: R_f = 0.48 (silica, 25% EtOAc in benzene); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.0 Hz, 2 H, Bz), 7.58 (t, J = 7.5 Hz, 1 H, Bz), 7.47 (t, J = 7.5 Hz, 2 H, Bz), 5.96 (s, 1 H, 10-H), 5.48 (dd, J = 5.0, 1.5 Hz, 1 H, 2-H), 5.45 (m, 1 H, 13-H), 4.98 (dd, J = 8.3, 1.9 Hz, 1 H, 5-H), 4.39 (A of AB, d, J = 8.5 Hz, 1 H, 20-H), 4.35 (dd, J = 10.4, 6.5 Hz, 1 H, 7-H), 4.25 (B of AB, d, J = 8.5 Hz, 1 H, 20-H), 4.00 (d, J = 5.0 Hz, 1 H, 3-H), 2.72 (m, 1 H, 14-H), 2.48 (m, 1 H, 6-H), 2.29 (s, 3 H, OAc), 2.16 (s, 3 H, OAc), 2.05−1.93 (band, 2 H, 6-H and 14-H), 1.89 (s, 3 H, 18-CH_3), 1.60 (s, 3 H, 19-CH_3), 1.23 (s, 3 H, 16-CH_3), 1.07 (s, 3 H, 17-CH_3), 0.88 (t, J = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.65−0.49 (band, 6 H, $Si(CH_2CH_3)_3$).

B. Conversion of Carbonate 38 to 35. A solution of carbonate **38** (1 mg, 0.0016 mmol) in THF (1 mL) at −78 °C was treated with PhLi (0.016 mL, 2 M in cyclohexane, 0.008 mmol) and stirred at −78 °C for 15 min. The reaction was quenched with aqueous NH_4Cl (2 mL). After dilution with Et_2O (10 mL), the organic layer was separated, dried ($MgSO_4$), concentrated, and purified by preparative TLC (silica, 25% Et_2O in benzene) to give benzoate **35** (0.9 mg, 80%) as a colorless film.

Diol 37. To a mixture of benzoates **35** and **36** (71.8 mg, 0.105 mmol, *ca.* 77:23) in MeOH (13.5 mL) and THF (3.6 mL) at 0 °C was added an aqueous solution of K_2CO_3 (270 mg in 3.5 mL of H_2O). The solution was stirred at 0 °C for 6 h and at −20 °C for 10 h. The reaction was quenched with aqueous NH_4Cl (20 mL), and the resulting mixture was extracted with $CHCl_3$ (2 × 100 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 20 → 40% EtOAc in petroleum ether) to give the benzoate mixture **35/36** (27 mg, 38%) and diol **37** (27 mg, 94% based on 62% conversion): R_f = 0.18 (silica, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ −43.6 (*c* 0.28, $CHCl_3$); IR (thin film) ν_{max} 3479, 2923, 1721, 1461, 1372, 1237 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1 H, 10-H), 4.95 (dd, J = 9.5, 1.5 Hz, 1 H, 5-H), 4.64 (A of AB, d, J = 9.0 Hz, 1 H, 20-H), 4.55 (B of AB, d, J = 9.0 Hz, 1 H, 20-H), 4.40 (dd, J = 10.5, 7.0 Hz, 1 H, 7-H), 3.83 (dd, J = 6.5, 4.5 Hz, 1 H, 2-H), 3.38 (d, J = 6.5 Hz, 1 H, 3-H), 2.69−2.58 (band, 1 H, 13-H), 2.54 (d, 4.5 Hz, 1 H, 2-OH), 2.51 (m, 1 H, 6-H), 2.16 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 2.13−2.01 (band, 1 H, 13-H), 2.01 (s, 3 H, 18-CH_3), 1.92−1.83 (band, 2 H, 14-CH_2), 1.78 (m, 1 H, 6-H), 1.62 (s, 3 H, 19-CH_3), 1.07 (s, 3 H, 16-CH_3), 1.05 (s, 3 H, 17-CH_3), 0.88 (t, J = 7.5 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.61−0.48 (band, 6 H, $Si(CH_2CH_3)_3$); FAB HRMS (NBA/NaI) *m/e* 603.2970, M + Na^+ calcd for $C_{30}H_{48}O_9Si$ 603.2965.

Carbonate 38. A. Conversion of Diol 37 to Carbonate 38. To a solution of diol **37** (16 mg, 0.028 mmol) in pyridine (2 mL) at 25 °C was added phosgene (0.143 mL of a 1.93 M solution in toluene, 0.28 mmol). The solution was stirred at 25 °C for 15 min. After dilution with Et_2O (20 mL), the organic layer was separated, washed with aqueous $CuSO_4$ (3 × 10 mL) and aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 10 → 35% EtOAc in petroleum ether) to give carbonate **38** (14.4 mg, 86%) as a white foam.

B. Silylation of 39 to 38. A solution of alcohol **39** (1.0 mg, 0.002 mmol) in pyridine (0.5 mL) was treated with chlorotriethylsilane (TESCl, 0.017 mL, 0.1 mmol) and stirred at 25 °C for 24 h. After dilution with Et_2O (10 mL), the organic layer was separated, washed with aqueous $CuSO_4$ (3 × 5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 10 → 35% EtOAc in petroleum ether) to give carbonate **38** (1.0 mg, 85%) as a colorless film: R_f = 0.82 (silica, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ −49.4 (*c* 0.93, $CHCl_3$); IR (thin film) ν_{max} 2924, 1814, 1728, 1461, 1372, 1238 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (s, 1 H, 10-H), 4.95 (d, J = 9.0 Hz, 1 H, 5-H), 4.60 (A of AB, d, J = 9.0 Hz, 1 H, 20-H), 4.47 (B of AB, d, J = 9.0 Hz, 1 H, 20-H), 4.43 (dd, J = 10.0, 7.5 Hz, 1 H, 7-H), 4.39 (d, J = 5.5 Hz, 1 H, 2-H), 3.36 (d, J = 5.5 Hz, 1 H, 3-H), 2.71 (m, 1 H, 13-H), 2.56 (m, 1 H, 13-H), 2.17 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 2.12 (m, 1 H), 2.07 (s, 3 H, 18-CH_3), 1.97 (m, 1 H), 1.88 (m, 2 H), 1.78 (s, 3 H, 19-CH_3), 1.23 (s, 3 H, 16-CH_3), 1.17 (s, 3 H, 17-CH_3), 0.88 (t, J = 7.5 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.60−0.50 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 170.3, 169.2, 153.1, 144.0, 130.7, 92.8, 84.0, 80.3, 80.0, 76.4, 76.1, 60.3, 43.5, 38.0, 29.7, 29.4, 25.5, 23.1, 21.9, 21.1, 19.1, 9.8, 6.7, 5.2; FAB HRMS (NBA/CsI) *m/e* 739.1929, M + Cs^+ calcd for $C_{31}H_{46}O_{10}Si$ 739.1915.

Alcohol 39. A solution of silyl ether **38** (3.0 mg, 0.0049 mmol) in THF (1.5 mL) was treated with HF·pyridine (0.5 mL) and stirred for 2 h at 25 °C. The reaction mixture was diluted with EtOAc (10 mL), and the reaction was quenched with aqueous $NaHCO_3$ (10 mL). The organic layer was separated, washed with 10% aqueous NaOH (10 mL) and brine (10 mL), dried ($MgSO_4$), and purified by preparative TLC (silica, 30% EtOAc in petroleum ether) to give alcohol **39** (2.1 mg, 88%) as a colorless film: R_f = 0.22 (silica, 50% EtOAc in petroleum ether); $[\alpha]^{22}_D$ −23 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2923, 2854, 1809, 1723, 1460, 1374, 1238, 1018 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (s, 1 H, 10-H), 4.94 (d, J = 8.0 Hz, 1 H, 5-H), 4.56 (A of AB, d, J = 9.0 Hz, 1 H, 20-H), 4.41 (B of AB, dd, J = 9.0, 0.5 Hz, 1 H, 20-H), 4.38 (m, 1 H, 7-H), 4.31 (d, J = 5.5 Hz, 1 H, 2-H), 3.33 (d, J = 5.5 Hz, 1 H, 3-H), 2.73 (m, 1 H, 13-H), 2.57 (m, 1 H, 6-H), 2.28 (d, J = 4.0 Hz, 1 H, OH), 2.15 (s, 3 H, OAc), 2.13 (s, 3 H, OAc), 2.12−2.02 (band, 2 H, 14-CH_2), 1.94 (d, J = 1.0 Hz, 3 H, 18-CH_3), 1.95−1.80 (band, 2 H, 13-H and 6-H), 1.65 (s, 3 H, 19-CH_3), 1.18 (s, 3 H, 16-CH_3), 1.08 (s, 3 H, 17-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 170.9, 170.2, 153.0, 146.4, 92.8, 84.2, 80.4, 76.7, 75.9, 71.5, 60.3, 43.0, 36.4, 31.0, 29.7, 29.6, 25.5, 23.2, 21.9, 21.6, 20.9, 19.0, 9.2.

2′,7-diTES-Taxol (42). To a solution of 7-TES-baccatin III (**17**, 20.0 mg, 0.0285 mmol) and β-lactam **40** (38 mg, 0.0998 mmol) in THF (1.5 mL) at 0 °C was added $NaN(SiMe_3)_2$ (0.086 mL of a 1.0 M solution in THF, 0.086 mmol) dropwise. The reaction mixture was stirred at 0 °C for 0.5 h, and the reaction was quenched with aqueous NH_4Cl (2 mL). After dilution with Et_2O (15 mL), the organic layer was separated, washed with brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica, 10 → 50% EtOAc in petroleum ether) to give starting material **17** (2.2 mg, 11%) and 2′,7-diTES-Taxol (**42**) (23.7 mg, 86% based on 89% conversion) as a white solid: R_f = 0.59 (silica, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ −48 (*c* 0.4,

$CHCl_3$); IR (thin film) ν_{max} 3440, 2958, 1719, 1664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 7.0 Hz, 2 H, Bz), 7.72 (d, J = 7.5 Hz, 2 H, Bz), 7.60−7.25 (band, 11 H, Ar), 7.11 (d, J = 9.0 Hz, 1 H, NH), 6.43 (s, 1 H, 10-H), 6.22 (b t, J = 8.5 Hz, 1 H, 13-H), 5.69 (m, 2 H, 3′-H and 2-H), 4.93 (b d, J = 8.0 Hz, 1 H, 5-H), 4.69 (d, J = 2.0 Hz, 1 H, 2′-H), 4.45 (dd, J = 11.0, 7.0 Hz, 1 H, 7-H), 4.30 (A of AB, d, J = 8.5 Hz, 1 H, 20-H), 4.19 (B of AB, d, J = 8.5 Hz, 1 H, 20-H), 3.82 (d, J = 7.0 Hz, 1 H, 3-H), 2.53 (s, 3 H, OAc), 2.38 (dd, J = 9.5, 15.0 Hz, 1 H, 14-H), 2.18 (s, 3 H, OAc), 2.12 (dd, J = 15.0, 8.0 Hz, 1 H, 14-H), 2.00 (s, 3 H, 18-CH_3), 1.89 (m, 2 H, 6-CH_2), 1.68 (s, 3 H, 19-CH_3), 1.20 (s, 3 H, 16-CH_3), 1.16 (s, 3 H, 17-CH_3), 0.89 (t, J = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.80 (t, J = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.62−0.51 (band, 6 H, $Si(CH_2CH_3)_3$), 0.51−0.35 (band, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 170.1, 169.3, 167.2, 167.0, 140.1, 138.3, 134.2, 133.7, 133.6, 131.8, 130.2, 130.1, 129.2, 128.7, 128.3, 127.9, 127.0, 126.4, 84.2, 81.2, 78.7, 76.6, 75.0, 74.9, 74.8, 72.2, 71.5, 58.4, 55.7, 46.6, 43.3, 37.2, 35.5, 26.5, 23.1, 21.5, 20.9, 14.1, 10.1, 6.7, 6.5, 5.3, 4.3; FAB HRMS (NBA/CsI) *m/e* 1214.4089, M + Cs^+ calcd for $C_{59}H_{79}O_{14}NSi_2$ 1214.4093.

Taxol (1). A solution of silyl ether **42** (22 mg, 0.020 mmol) in THF (1 mL) was treated with HF·pyridine (0.2 mL) and stirred for 1.25 h at 25 °C. The reaction mixture was diluted with Et_2O (15 mL), and the reaction was quenched with aqueous $NaHCO_3$ (5 mL). The organic layer was separated, washed with aqueous $CuSO_4$ (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4), and purified by flash chromatography (silica, 50 → 75% EtOAc in petroleum ether) to give Taxol (**1**, 13.9 mg, 80%) as a white solid: R_f = 0.125 (silica, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ −49 (*c* 0.45, MeOH); IR (thin film) ν_{max} 3432, 2937, 1720, 1652, 1520, 1241 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, J = 8.5, 1.2 Hz, 2 H, Bz), 7.74 (dd, J = 8.2, 1.2 Hz, 2 H, Bz), 7.62, (t, J = 7.5 Hz, 1 H, Bz), 7.52−7.32 (band, 7 H, Ar), 7.02 (d, J = 9.0 Hz, 1 H, NH), 6.27 (s, 1 H, 10-H), 6.23 (b t, J = 9.0 Hz, 1 H, 13-H), 5.79 (dd, J = 9.0, 2.5 Hz, 1 H, 3′-H), 5.67 (d, J = 7.0 Hz, 1 H, 2-H), 4.95 (b d, J = 8.0 Hz, 1 H, 5-H), 4.79 (dd, J = 2.5, 5.5 Hz, 1 H, 2′-H), 4.40 (m, 1 H, 7-H), 4.31 (A of AB, d, J = 8.5 Hz, 1 H, 20-H), 4.19 (B of AB, d, J = 8.5 Hz, 1 H, 20-H), 3.79 (d, J = 7.0 Hz, 1 H, 3-H), 3.61 (d, J = 5.5 Hz, 1 H, 2′-OH), 2.55 (m, 1 H, 6-H), 2.49 (d, J = 4.0 Hz, 1 H, 7-OH), 2.39 (s, 3 H, OAc), 2.40−2.25 (band, 2 H, 14-CH_2), 2.24 (s, 3 H, OAc), 1.88 (m, 1 H, 6-H), 1.82 (s, 1 H, 1-OH), 1.79 (s, 3 H, 18-CH_3), 1.69 (s, 3 H, 19-CH_3), 1.24 (s, 3 H, 16-CH_3), 1.14 (s, 3 H, 17-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 172.7, 171.3, 170.4, 167.0, 167.0, 142.0, 137.9, 133.7, 133.6, 133.1, 132.0, 130.2, 129.1, 129.0, 128.7, 128.7, 128.4, 127.1, 127.0, 84.4, 81.1, 79.0, 76.5, 75.5, 74.9, 73.2, 72.3, 72.2, 58.6, 55.0, 45.6, 43.1, 35.6, 35.6, 26.8, 22.6, 21.8, 20.9, 14.9, 9.5; FAB HRMS (NBA) *m/e* 854.3360, M + H^+ calcd for $C_{47}H_{51}O_{14}N$ 854.3388.

Acknowledgment. We thank Dr. E. Bombardelli for a generous gift of 10-deacetylbaccatin III and Drs. Dee H. Huang and Gary Siuzdak for NMR and mass spectroscopic assistance, respectively. This work was financially supported by NIH, The Scripps Research Institute, fellowships from Mitsubishi Kasei Corporation (H.U.), Rhône-Poulenc Rorer (P.G.N.), The Office of Naval Research (R.K.G.), The Agricultural University of Athens (E.A.C.), R.W. Johnson−ACS Division of Organic Chemistry (E.J.S.), and grants from Merck Sharp & Dohme, Pfizer, Inc., Schering Plough and the ALSAM Foundation.

Supplementary Material Available: Experiment techniques and data for compounds **15**, **16**, **18**, and **28** (3 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.

JA9421922