Total Synthesis of Baccatin III and Taxol

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Abstract: An intramolecular Heck reaction (**90** → **91**) serves as the key step in the total synthesis of the titled compounds. The synthetic route is based on utilizing the Wieland−Miescher ketone (**5**) as a matrix to provide the C and D rings of the targets and to provide functionality implements for joining this sector to an A ring precursor (**6**). Catalytically induced enantiotopic control and early emplacement of the oxetane are other features of the route.

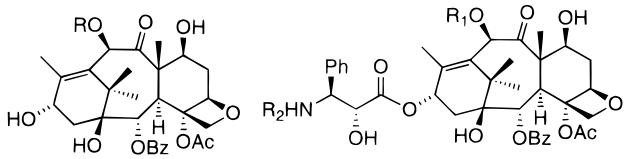
Background

In 1964, Wall and co-workers discovered that extracts from the bark of *Taxus brevifolia* exhibited significant cytotoxicity against KB cells. From these extracts was isolated a particularly active principle which was termed taxol. It was deduced, again by Wall and co-workers, that taxol corresponds to structure **3**[2] (see Figure 1). Taxol (**3**) fared well in early preclinical cytotoxicity challenges against a variety of cell lines, and in time, emerged as a candidate compound for clinical evaluation.

Another step in the ascension of taxol (**3**) arose from a disclosure of Horwitz and colleagues wherein the drug was described to be a promoter of microtubule assembly.[3] The identification of such a mechanism of action for taxol (and putative analogs) at the cellular level would facilitate biochemical and pharmacological investigation to go along with clinically oriented investigations.

Relentlessly, taxol (**3**) and its analog taxotere (**4**)[4] advanced from the status of esoteric research curiosities to compounds of serious clinical value. At the present time, taxol (**3**) has been approved for use against metastatic ovarian and breast cancers and is undergoing evaluation against a variety of other indications. The status of taxotere as an active drug is not as yet as advanced as is that of taxol.[5]

Early on, it appeared that clinical applications of taxol would be hindered by a lack of availability of the drug. The phytochemical route to taxol itself is, even at this writing, complicated. Thus, in most taxol-containing plants, the fully functional drug tends to be localized in nonrenewable domains. On the other hand, baccatin III (**1**) and 10-deacetylbaccatin III (**2**), themselves bereft of useful biological function, constitute rather more accessible raw materials. They are isolable in quantity from renewable regions of a variety of plants. Intense efforts to achieve the semisynthesis of taxol (**3**) from **1** or **2** have been successful in ameliorating the drug availability problem. Particularly critical in this regard were major semisynthesis contributions from Holton, Ojima, and Greene.[6]



1 R=Ac
2 R=H

3 taxol R_1=Ac, R_2=Bz
4 taxotere R_1=H, R_2=*t*-BuOOC

Figure 1. Structures of baccatin III (**1**), 10-deacetylbaccatin III (**2**), taxol (**3**), and taxotere (**4**).

Interest in the total synthesis of taxol (**3**) (via a total synthesis of baccatin III (**1**)) was triggered by several factors. The novel confluence of functionality of the tetracyclic ring system of **1** constitutes a challenge which must be accommodated in any successful effort. It seemed likely that solutions of this total synthesis problem would bring with them collateral advances in the theory and practice of organic chemistry. Needless to say, the favorable clinical findings pertinent to taxol (since given the trademark name of Paclitaxel) added to the general interest in the total synthesis goal. During the era where the availability of taxol was feared to be a seriously limiting factor in its oncological applications, total synthesis was seen by a hearty few as a possible source of the drug.

Consideration of the chemical complexity of baccatin III (**1**), which in suitably protected form (at C_7) would be the likely synthetic intermediate *en route* to taxol (**3**), should have

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

(3) Horwitz, S. B.; Fant, J.; Schiff, P. B. *Nature* **1979**, *277*, 665.

(4) Mangatal, L.; Adeline, M. T.; Guenard, D.; Gueritte-Voegelein, F.; Potier, P. *Tetrahedron* **1989**, *45*, 4177.

(5) For reviews, see: (a) Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M. *Taxane Anticancer Agents*; American Cancer Society: San Diego, 1995. (b) Kingston, D. G. I.; Molinero, A. A.; Rimoldo, J. M. *Progress in the Chemistry of Organic Natural Products 61*; Springer-Verlag: New York, 1993.

(6) (a) Denis, J. N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. (b) Holton, R. A. Eur. Pat. Appl. EP400,971, 1990; *Chem. Abstr.* **1990**, *114*, 164568q. (c) Holton, R. A. Workshop on Taxol and Taxus, 1991. (d) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681. (e) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985. (f) Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. M.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149.

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engendered considerable skepticism and even disbelief that total synthesis would supplant natural sources as a route to the drug. More plausible, though as yet unrealized in practice, is the prospect that mastery of the synthesis of baccatin III (**1**) will bring with it new nuclei which, upon suitable conjugation with biologically critical side chains, might provide medically promising variants of taxol.

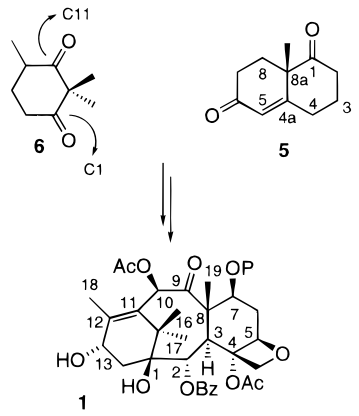
Indeed much interesting chemistry has been developed following synthetic explorations pertinent to taxol.[7] Many fascinating constructions and proposed constructions have been adumbrated and disclosed. However, upon critical examination, very few have carried with them realistic prospects for maturing into comprehensive total syntheses—practical or otherwise. The baccatin III (**1**) total synthesis problem has served as a stark but useful reminder of the distinction between "regional contributions" *as opposed to programs which take account of the full scope of a complex problem in synthesis.*

The first total molecular solutions to the taxol problem, again via 7-protected baccatin III, were provided in virtually concurrent disclosures by the research groups of Nicolaou[8] and Holton.[9] Given the difficulty of the challenge, and the multiple opportunities for failure, these two successes were clearly important events in the field. In this paper, we document the total synthesis of baccatin III and thence taxol which were achieved in our laboratory.[10]

Synthetic Planning

Our planning and thinking about a total synthesis of taxol (**3**) (which in reality meant a total synthesis of baccatin III (**1**) or a 7-protected derivative thereof) was guided from the beginning by a central perception from which we never deviated. It seemed that a suitable confluence of the Wieland−Miescher ketone[11ab] (**5**) with the known and easily prepared (though not commercially available) trimethylcyclohexane-1,3-dione (**6**)[11c] might eventually lead to baccatin III (Scheme 1). This prospectus had several alluring features. The sum of the two eminently accessible components contain more than an ample number of carbons (11 + 9 = 20) to reach the core ABC sector (19 carbons) of **1**. Of greater significance than this type of carbon count was the recognition that the functionalities for development of the components and suitable melding were, in

Scheme 1



principle, in place. Thus, in **5**, the future angular (C_{19}) methyl group and the oxygenated C_7 of baccatin III (**1**) are readily discerned as is the 6-membered C ring. A wealth of precedent from terpenoid chemistry could be drawn upon to allow for fashioning the necessary stereochemistry at C_3 and C_7 (baccatin III numbering) from carbons 4a and 1 of **5**. Furthermore, if one imagines an eminently plausible deconjugation of the conjugated enone double bond, originally present in compound **5**, functionality emerges at C_4 of baccatin III (**1**) (corresponding to carbon 4 of the Wieland−Miescher ketone). Such a ketone at C_4 might be further exploitable to introduce a required oxygen at C_3 (Wieland−Miescher ketone numbering) corresponding to C_5 of baccatin III (**1**).

Left unspecified for the moment is the timing for introduction of oxygenation at C_9 of the baccatin (corresponding to C_8 of the Wieland−Miescher ketone). One could easily imagine using the matrix of the bicyclic system of compound **5** to achieve orderly functionalization at C_8. However, there was concern, as the synthesis began to unfold, that early inclusion of an oxygen-based functional group at this center could lead to intermediates whose additional complexity could prove to be unmanageable.

We now consider the A ring substructure **6**. The 1,3-diketone system corresponds, overall, to functionality sites at C_1 and C_{11} of baccatin III (**1**) and contains the required *C*-methyl pattern (see Scheme 1). Two possibilities were entertained for bringing together fragments derived from **5** and **6** in a useful way. For this purpose we particularly concentrate on C_9 and C_{10} of baccatin III (**1**). Clearly, C_9 is to be derived from building block **5**. No possibility for bonding **6** to a fragment derived from Wieland−Miescher ketone, in which C_8 of **5** were dissipated, was ever given serious credence. Such an excision would place C_{8a} (cf. **5**) at great risk from a stereochemical standpoint and would open up major hazards inherent in reconstruction. In short, *C_9 of baccatin III (**1**) must be derived from C_8 of compound **5**.*

Two formulations for deriving C_{10} of the baccatin goal presented themselves (Scheme 2). In one plan, an incision into the matrix derived from **5** would be made between C_7 and C_8 as well as between C_6 and C_5 (see cleavage mode A). In this view, a one-carbon fragment, destined to become C_{10} of baccatin III (**1**), would be appended to **6** (at its carbon slated to emerge at C_{11}) and a bond established between C_{10} and C_9 (baccatin numbering). Alternatively, both C_{10} and C_9 would be derived from **5**. The fragment to be presented for coupling with **6** could have arisen from excision of C_6 of the original Wieland−Miescher ketone construct, with emergence of suitably differentiated functionality fragments presented at its erstwhile C_7 and C_5 (see cleavage mode B). We note that compelling

(7) For reviews, see: (a) Swindell, C. S. *Studies in Natural Products Chemistry, Vol. 12*; Elsevier Science Publishers: New York, 1993; pp 179−231. (b) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.

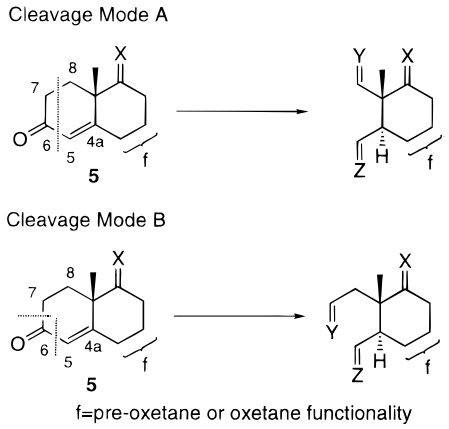
(8) (a) Nicolaou, K. C.; Zang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630. (b) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Coulandouros, E. A.; Sorensen, E. J. *J. Am. Chem Soc.* **1995**, *117*, 624. (c) Nicolaou, K. C.; Liu, J. J.; Yang, H.; 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. (d) 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*, 645. (e) 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*, 653.

(9) (a) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, 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. S.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (b) Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, 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. S.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599.

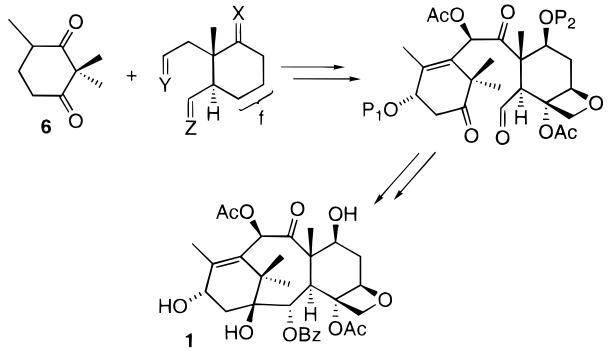
(10) For a preliminary account of this work, see: Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B. and Danishefsky, S. J. *Angew. Chem.* **1995**, *34*, 1723.

(11) (a) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215. (b) Ramachandrin, S.; Newman, M. S. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 486. (c) Hargreaves, J. H.; Hickmott, P. W.; Hopkins, B. J. *J. Chem. Soc. C* **1968**, 2599.

Scheme 2



Scheme 3

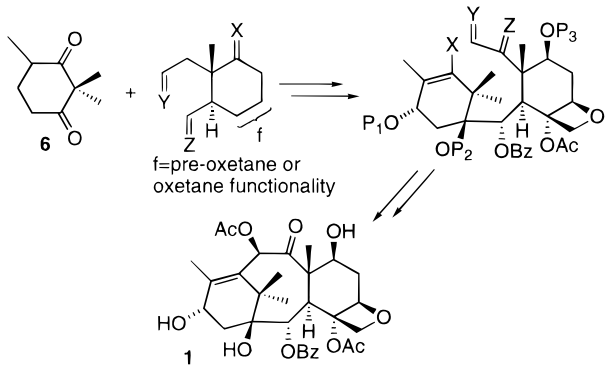


arguments (similar to those advanced above as to C_8 of **5**) dictated that C_5 could not be sacrificed to the degradation. Any scheme to excise this carbon from a construct derived via **5** would again undermine the otherwise securable stereochemistry at C_{4a} (slated to become C_3 of baccatin III (**1**)). We were understandably apprehensive about confronting the serious questions which would be raised by attempts to reattach C_{4a} of a degraded version of **5** to an A ring derived intermediate.

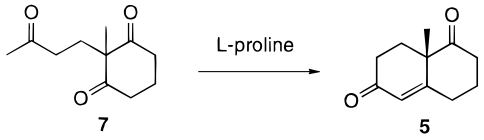
We favored schemes anticipating formation of the $C_{10}-C_{11}$ baccatin bond on grounds of synthetic freshness. Thus, a C_9-C_{10} closure had already been investigated in Kende's groundbreaking assembly of the skeleton.[12] Furthermore, as described by the Rochester workers, such a coupling carried with it its own risks and serious complications. Left unspecified at this planning stage, is the matter of the sequencing of the C_1-C_2 and $C_{10}-C_{11}$ attachments. One could imagine establishing the $C_{10}-C_{11}$ bond in the intermolecular step, reserving formation of the C_1-C_2 bond for cyclization (Scheme 3). Alternatively, the reverse order could be considered, wherein the C_1-C_2 bond would be formed first through intermolecular means, delaying $C_{10}-C_{11}$ bond construction for the cyclization (Scheme 4).

In practice, both sequences were explored, and we shall return to this matter as the synthesis unfolds. At this stage, however, it is well to emphasize that the concept of the Wieland–Miescher ketone matrix gained particular favor from the fact that the enantiomerically pure compound could be obtained in quantity by L-proline-induced aldolization of the prochiral trione **7** (Scheme 5).[13] *Thus all stereochemistry of baccatin III (**1**) would flow from a single stereogenic center (C_{8a} of the Wieland–Miescher ketone, corresponding to C_8 of the baccatin), which was itself induced by catalytic means.*

Scheme 4



Scheme 5



The exploratory studies were conducted on racemic material. Actually, the synthesis of the appropriate C_{8a} *S*-enantiomer is no more demanding than is that of the racemate. However, the racemate is commercially available, and we drew on this convenience during the reconnaissance phases of, what was likely to be, an arduous journey.[14] After validation in the racemic series, the chemistry was translated to the single enantiomer regime arising from compound **5**, $C_{8a} = S$.

We conclude the section on analysis by consideration of the timing of oxetane installation. The oxetane is, by all indications, rather important for biological activity.[15] Maximization of the prospects that the total synthesis exercise might produce significantly truncated, but still active, versions of taxol (**3**) constituted a strong argument for early emplacement of the oxetane. Moreover, such a strategy would avoid the need for elaborate protecting devices to contain the "access handles" which would be needed for a late stage fashioning of the oxetane.

We were mindful that the presence of the oxetane ring from nearly the outset might restrict the scope of feasible operations for the orchestration of the synthesis. However, we hoped that successful management of the problems engendered by the resident oxetane might, in the long run, reduce the number of steps. Furthermore, we would learn much about the "chemical personality" of the oxetane. This knowledge could be helpful in developing an analog program. Though at several stages of the expedition we were destined to face serious consequences from this high-risk course, it would in time be shown to be sound (*vide infra*).

Results and Discussion

Compound **5** was reduced with sodium borohydride according to known protocols,[16] affording **8** and thence the deconjugated ketal **9** (Scheme 6). The secondary alcohol of **9**, targeted to emerge at C_7 of the baccatin, was protected as its *tert*-butyl dimethylsilyl ether.

Treatment of **10** with diborane was followed by oxidation with hydrogen peroxide. Oxidation of the alcohol, thus ob-

(12) Kende, A. S.; Johnson, S.; Sanfillipo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513.

(13) Harada, N.; Sugioka, T.; Hisashi, U; Kuriki, T. *Synthesis* **1990**, 53 and references therein.

(14) The *R* version of **5** is equally accessible and could be used to synthesize *ent*-baccatin III. We have, in fact, prepared late stage *ent* intermediates by this method.

(15) *The Chemistry and Pharmacology of Taxol*; Farina, V., Ed.; Elsevier Press: New York, 1995.

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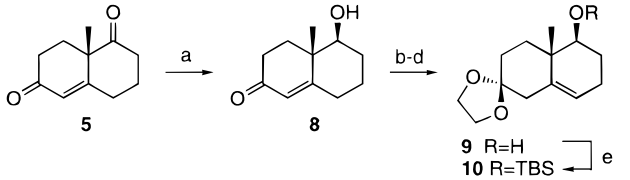
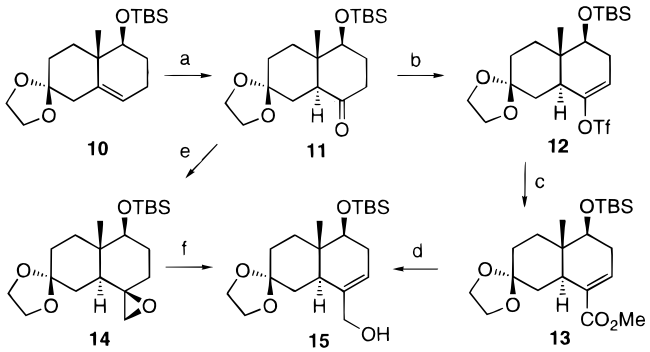
Scheme 6[a]



[a] Reagents: (a) $NaBH_4$, EtOH, 0 °C, 97%; (b) Ac_2O, DMAP, pyr, CH_2Cl_2, 0 °C, 99%; (c) $(HOCH_2)_2$, PhH, naphthalenesulfonic acid, reflux, 70%; (d) NaOMe, MeOH, THF, 98%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 97%.

Scheme 7[a]



[a] Reagents: (a) (i) BH_3·THF, THF, 0 °C → room temperature; (ii) H_2O_2, NaOH, H_2O; (iii) PDC, CH_2Cl_2, 0 °C → room temperature; (iv) NaOMe, MeOH, 62%; (b) (i) KHMDS, THF, −78 °C; (ii) $PhNTf_2$, 81%; (c) $Pd(OAc)_2$, PPh_3, CO, Hunig's base, MeOH, DMF, 73%; (d) DIBAL, hexanes, −78 °C, 99%; (e) $Me_3S^+I^-$, KHMDS, THF, 0 °C, 99%; (f) $Al(OiPr)_3$, PhMe, reflux, 99%.

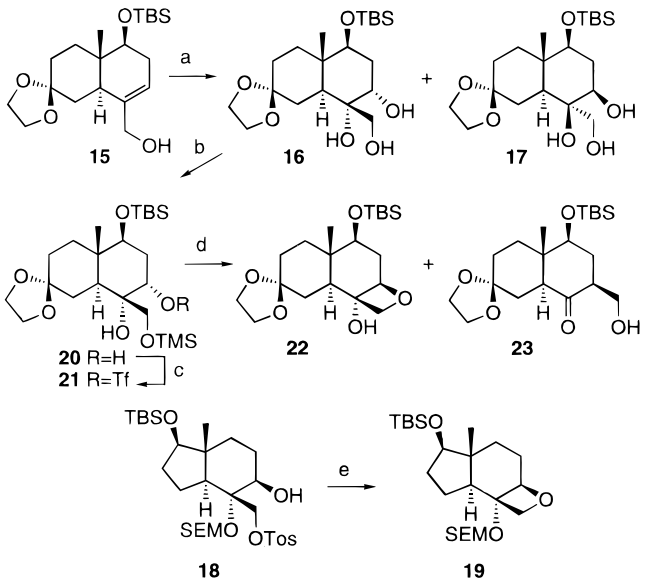
tained, with PDC followed by equilibration of the resultant crude ketone mixture[16] afforded homogeneous, trans-fused **11** (Scheme 7). Having secured the *R* configuration at C_3 (baccatin numbering), we directed our attention to the fashioning of the oxetane linkage.

We set as our next interim goal compound the allylic alcohol **15**. It was hoped that a triol derived from **15** might be transformed into the desired oxetane. In practice, two protocols were pursued for addition of the methylene group destined to become C_{20} of the oxetane. In one, the ketone **11** was converted to its vinyl triflate **12**.[17] The latter, upon palladium-mediated carbonylation−methoxylation gave rise to α,β unsaturated ester **13** which, upon reduction, led to the desired allylic alcohol **15**.

However, as the synthesis progressed and large quantities of intermediates had to be generated, this protocol was less than optimal. Rather, we took recourse to Corey's sulfonium ylide methodology.[18] Conversion of ketone **11** to spiroepoxide **14** occurred in high yield under the conditions shown. Lewis acid-induced epoxide opening following precedents gave rise to the desired allylic alcohol **15**.[19]

Many possibilities were explored to convert allylic alcohol **15** to the next goal system, oxetane **22**.[17] Treatment of the allylic alcohol **15** with osmium tetroxide gave rise to triol **16** (Scheme 8). In light of the lineup of resident β-face functionality, we were surprised that this reaction was not stereospecific. Approximately 15% of **17** wherein osmylation had occurred from the more hindered β face was also obtained. Fortunately, even on large scale, the separation of the two diols was a straightforward matter and we proceeded to advance triol **16** toward the desired oxetane. It would have been possible, in

Scheme 8[a]



[a] Reagents: (a) OsO_4, NMO, acetone, H_2O, 66%; (b) TMSCl, pyr, CH_2Cl_2, −78 °C → room temperature; (c) Tf_2O, −78 °C → room temperature; (d) $(HOCH_2)_2$, 40 °C, 69%; (e) NaH, THF, 45 °C, 74%.

principle, to follow the lead of Berkowitz,[20] toward this objective. Indeed, such a transformation was accomplished in our laboratory on the closely related hydrindenone-derived system **18** *en route* to **19**.[21]

However, in the case at hand, a new approach was feasible. The primary alcohol of **16** was readily differentiated by silylation with TMS chloride (see compound **20**). The secondary alcohol was then activated by triflation (see structure **21**). Remarkably, treatment of **21** with ethylene glycol at reflux gave rise to the desired oxetane **22**. We presume that this transformation entails a hypervalent silicon ether species on C_{20}, triggering displacement of the triflate. Another product, **23**, arising from a pinacol-like rearrangement was also detected in this reaction.[17]

We note that the formation of the oxetane by inversion of C_5 bearing a leaving group has subsequently been employed, though with different experimental protocols, in both the Nicolaou[8] and Holton[9] syntheses. During the preparation of our initial disclosure of this strategy,[17] there appeared a similar outcome in a semisynthetic setting.[22] However, the Potier chemistry was conducted on a substrate which lacked functionality at C_7. The demonstration shown here for building the oxetane onto a ring system bearing four differentiated alcohol centers had significant implications for total synthesis and for organizing an analog program.

Considerable thought and experimentation was devoted to selecting the proper blocking group for the tertiary hydroxyl center of compound **22**. Much would be expected from this blocking group, not the least demanding property being its susceptibility to removal at a late stage of the synthesis. It was also necessary to differentiate, in a secure way, the C_4 site from the other alcohol centers at C_1, C_7, and C_{10} of the emerging baccatin III. On the basis of these considerations, and after surveying several other possibilities (*vide infra*), we installed a benzyl protecting group on the tertiary alcohol. This transformation was accomplished in high yield on compound **22** giving

(17) Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274. This exploratory effort was conducted in the racemic series.

(18) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

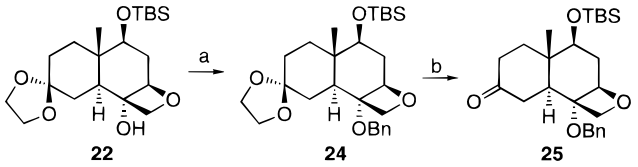
(19) Waddell, T. G.; Ross, P. A. *J. Org. Chem.* **1987**, *52*, 4802.

(20) Berkowitz, W. F.; Amarasekara, A. S.; Perumattam, J. J. *J. Org. Chem.* **1987**, *52*, 3745.

(21) Isaacs, R. C. A.; Di Grandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938.

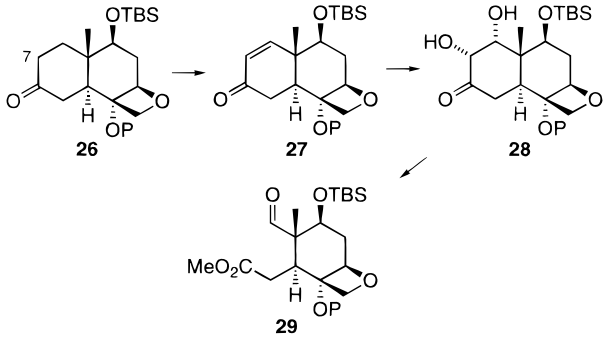
(22) Ettouate, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823.

Scheme 9[a]

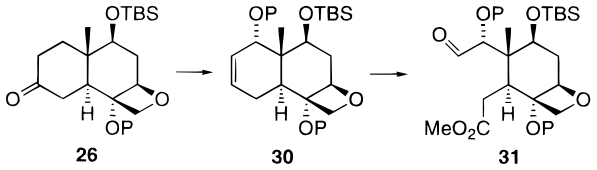


[a] Reagents: (a) BnBr, NaH, TBAI, THF, 0 °C → room temperature, 98%; (b) TsOH, acetone, H_2O, 70 °C, 84%.

Scheme 10



Scheme 11



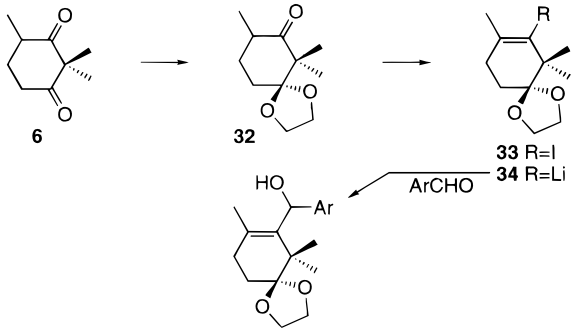
rise to benzyl ether **24** (Scheme 9). It was further possible to cleave the ketal linkage of compound **24** without damaging the oxetane moiety and without cleaving the silyl ether protecting group (see compound **25**).

With ketone **25** in hand, a variety of efficient degradation sequences were developed.[23] Some of these transformations were conducted before the benzyl blocking group was settled upon (see general system **26**, Scheme 10). A key feature which opened up a range of degradative options was the highly selective enolization of the C_6 ketone in the direction of C_7 (see Scheme 1 for Wieland−Miescher ketone numbering). That being the case, it was possible by well-precedented chemisty to prepare enone type **27**, as well as aldehyde−ester **29** (derived from the enone dihydroxylation product **28**).

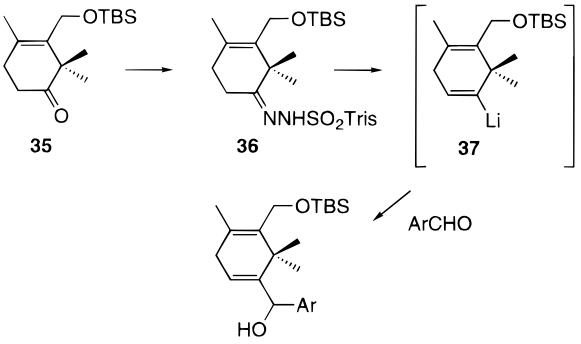
Another type of degradation product available from enone type **27** was the α-oxygenated aldehydo ester **31** (Scheme 11). This compound was derived by Schreiber type directed ozonolysis[24] of allylic alcohol derivatives (**30**). The latter arose from **27** by a Wharton type transposition.[25]

The use of compound **6** as a nucleophilic coupling partner with fragments obtained from system type **26** was facilitated by the selective chemistry which this β-diketone undergoes. For instance, monoketalization of **6** gave rise to **32** which could be converted to vinyl iodide **33** (Scheme 12). The latter could be lithiated to give rise to a C_{11}-based nucleophile **34**, which was coupled to aromatic aldehydes as previously documented.[26] We shall return to lithio system **34** in discussing attempts to reduce Scheme 3 to practice.

Scheme 12



Scheme 13



Prototype C_1 nucleophiles were also developed early in our investigations. Some were fashioned in systems in which the future C_{10} was already preinstalled on the A ring (see discussion above appropriate to Scheme 1). For instance, we demonstrated the feasibility of a Shapiro reaction on trisylhydrazone **36** derived from ketone **35** (Scheme 13). The lithio derivative **37** was coupled to a variety of aromatic aldehydes and to the highly functionalized aldehyde **47** (*vide infra*) derived from another fragmentation strategy discussed below. In this way, we gained confidence that compound **6** could be converted to effective nucleophiles corresponding to either C_1 or C_{11} of baccatin III (**1**). It was our hope to exploit these capabilities for bond formation with fragmentation products derived from a suitable version of **26**.

After many of the options were explored, the one shown in Scheme 14 was adopted owing to its amenability to large-scale work. Taking advantage of selective enolization of the keto group in systems of the type **26** toward C_7 (Wieland−Miescher ketone numbering) specific ketone **25** was converted to silyl enol ether **38**. The latter was hydroxylated via a modified Rubottom type protocol,[27a] with 3,3-dimethyldioxirane, followed by treatment with camphorsulfonic acid (see compound **39**). Ring fragmentation was accomplished with lead tetraacetate, **40**. The carboxyl carbon emerged as a methyl ester (see compound **40**) since the fragmentation was performed in methanol. The aldehyde function in **40** was converted to the dimethyl acetal (see compound **41**). Lithium aluminum hydride reduction of the ester gave rise to carbinol **42**, which was converted in a Grieco protocol to the *o*-nitrophenyl selenide **43**.[27b] Oxidation with hydrogen peroxide then provided alkene **44**. Ozonolysis of **44** gave aldehyde **45** which was destined to serve as a key intermediate *en route* to baccatin III.

The previously mentioned aldehyde **47** was prepared from **46** which was in turn prepared by a sequence identical to that described for **44**, starting with compound **26a** (the 4-OTBS

(23) Di Grandi, M. J.; Coburn, C. A.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 7728.

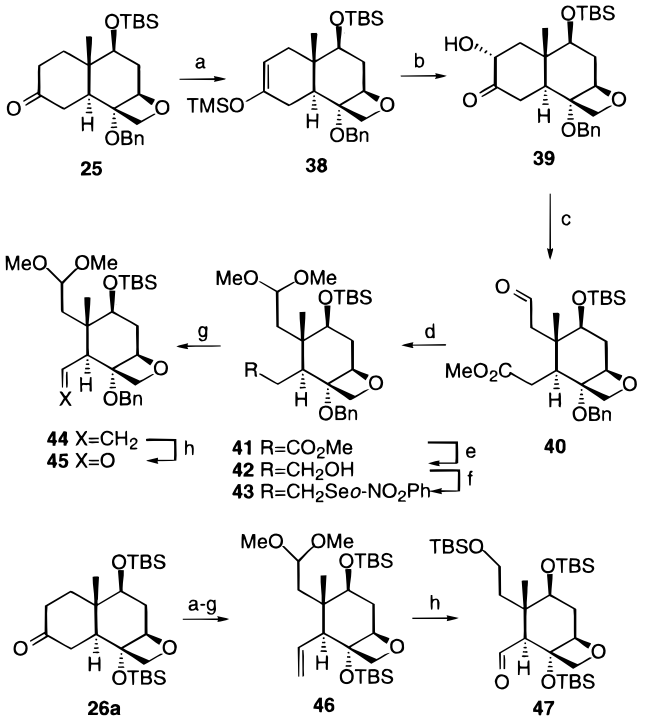
(24) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

(25) (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Maas, D. D.; Blagg, M.; Wiemer, D. F. *J. Org. Chem.* **1984**, *49*, 853.

(26) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989.

(27) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1972**, 3375. (b) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

Scheme 14[a]



[a] Reagents: (a) TMSOTf, Et_3N, CH_2Cl_2, −78 °C; (b) 3,3-dimethyldioxirane, CH_2Cl_2, 0 °C; CSA, acetone, room temperature, 89%; (c) $Pb(OAc)_4$, MeOH, PhH, 0 °C, 97%; (d) MeOH, CPTS, 70 °C, 97%; (e) $LiAlH_4$, THF, 0 °C, 100%; (f) *o*-$NO_2C_6H_4SeCN$, PBu_3, THF, room temperature, 88%; (g) 30% H_2O_2, THF, room temperature, 90%; (h) O_3, CH_2Cl_2, −78 °C; PPh_3, 79%.

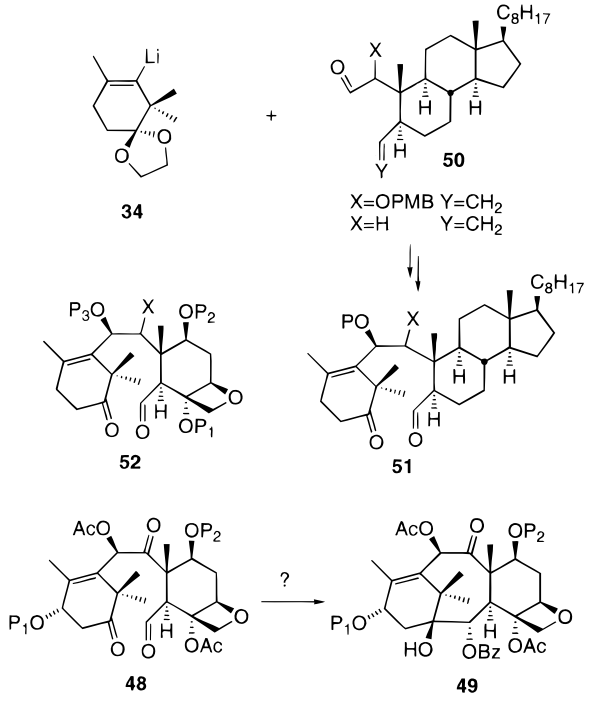
version of **26**). Cleavage of the dimethyl acetal of **46** followed by reduction with lithium aluminum hydride, protection of the resultant carbinol as its OTBS ether, and ozonolysis of the vinyl group afforded aldehyde **47**.

Before discussing our successful route to baccatin III (**1**) via initial C_1-C_2 bond formation (Scheme 4), we summarize our efforts in the direction of first establishing a C_9-C_{10} bond and postponing the C_1-C_2 merger for the cyclization step (Scheme 15). Actually we had preferred this plan. Reductive cyclization of a keto aldehyde precursor (cf. **48**) was of particular interest because it offered the prospect of delivering the C_1-C_2 functionality, configured in its required sense (see **49**).[28] We achieved the coupling of lithium reagent **34** with several relevant aldehydes. For the most part, these studies were carried out with cholestanone-derived aldehydes of the type **50**. The ready accessibility of such steroid-based substrates greatly facilitated the reconnaissance phase of our investigations. The translatability of steroid models to actual pre-taxol constructs was excellent save for those initiatives in the latter series wherein the oxetane ring proved to be unstable.

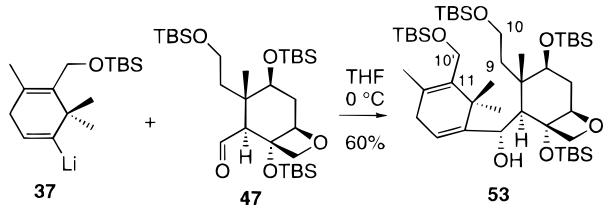
While coupling of **34** and aldehydes of the type **50** could be achieved, we have not at this writing succeeded in traversing all of the steps required to reach a keto aldehyde corresponding to **51** in the steroid series, or **52** in the oxetane containing series. The problems were encountered when trying to constrain (through an acetal linkage) or to otherwise protect the oxygens at C_9 and C_{10} (future baccatin numbering). Even protection of the secondary alcohol in seco system **52** (X = H) was problematic. Furthermore, the revealing of the C_1-C_2 keto

(28) For two examples describing the reduction of this scheme to practice, albeit in much simpler (ring C aromatic) settings, see: (a) Swindell, C. S.; Chander, M. C.; Heerding, P. G.; Rahman, L. T.; Raman, V.; Venkataraman, H. *Tetrahedron Lett.* **1993**, *34*, 7005. Swindell; (b) C. S.; Fan, W. and Klimko, P. G. *Tetrahedron Lett.* **1994**, *35*, 4959.

Scheme 15



Scheme 16



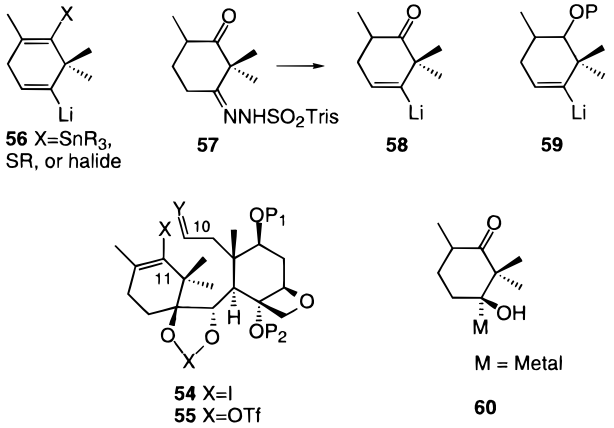
aldehyde ensemble (cf. **51** or **52**) from its precursor guarding group added further difficulties to an already complicated program. While various potential solutions to this problem remain to be explored, our preferences came to be focused on a plan which called for establishing the C_1-C_2 bond first.

Our first demonstration that it would be possible to establish the C_1-C_2 bond by the coupling strategy which we envisioned, arose from the reaction of vinyllithium agent **37** (described above) with aldehyde **47** (Scheme 16). A 60% yield of **53** was obtained as a single stereoisomer. While this was a key advance, its context did not fit the formulation implicit in Scheme 4. In particular, the presence of a one-carbon unit at C_{11} (which we number as $C_{10'}$) deviated from the plan calling for a $C_{10}-C_{11}$ closure.

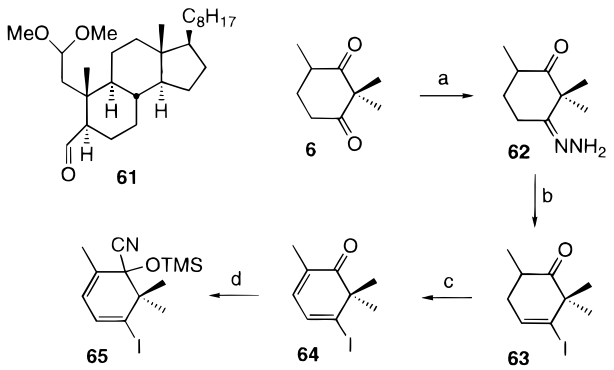
Actually, we would have been willing to depart from our plan. However, serious difficulties soon surfaced. Attempts to protect the secondary alcohol (C_2 of seco baccatin system **53**) in this congested environment were unsuccessful. Failure to protect this alcohol undermined efforts to develop the functional groups along the "northern rim". Again, while other possibilities remained to be investigated, the results of these expeditions were sufficiently discouraging to oblige a return to the basic Scheme 4 prospectus.

For this program to be implemented, a methodological advance had to be achieved. The problem involved the status of C_{11} as we exploited the C_1 vinyl nucleophile. In the case of **37**, this issue had been obviated by employment of a carbon−carbon bond ($C_{11}-C_{10'}$). This bond served to stabilize C_{11} during lithiation. In the conduct of the actual synthesis, however, we could not employ such "protection".

Scheme 17



Scheme 18[a]



[a] Reagents: (a) H_2NNH_2, Et_3N, EtOH, 72%; (b) I_2, DBN, THF, 52%; (c) I_2, DBN, THF, 89%; (d) TMSCN, cat. KCN, 18-crown-6, CH_2Cl_2, 89%.

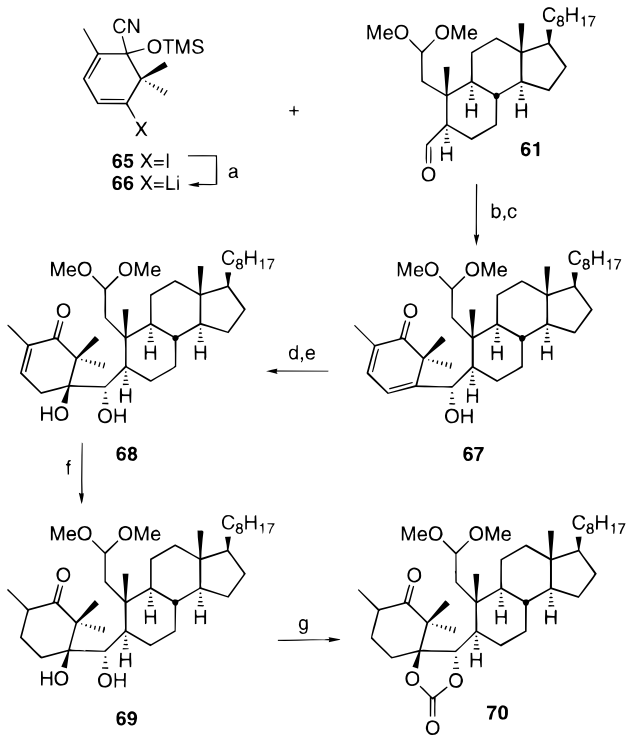
Two options for the status of C_{11} at the stage of cyclization to C_{10} were considered (Scheme 17). In one case, this carbon would have emerged as the $C_{11}-C_{12}$ vinyl iodide of **54**. Alternatively, it might be presented as a vinyl triflate as shown in structure **55**. Recourse to a carbon appendage at C_{11} would complicate reaching either **54** or **55**.

Much effort was expended generating 1,4-cyclohexadienyllithium reagents of the type **56**. These efforts were unsuccessful. Since we could not store the implement eventually needed at C_{11} of the hypothetical vinyllithium reagent **56**, it would be necessary to create this functionality after coupling of C_1 and C_2. To eventually reach **54** or **55**, a C_{11} ketone seemed to be required. Thus, the exact status of the "pro-ketonic" C_{11} during the vinyllithium formation had to be determined. The possibility of generating an agent of the type **58** with the C_{11} ketone already in place from a precursor of the type **57** was shown to be feasible in one instance,[26] but was subsequently abandoned for lack of generality.

We also did not pursue solutions where C_{11} was carried as a protected alcohol at the stage when the vinlylmetal nucleophile (cf. **59**) was generated. The disentanglement of the fate of such a C_{11} alcohol from the other resident hydroxyls (cf. C_1, C_2, C_4, and C_7) during the manipulations prior to cyclization would be very complicated.

The dilemma which we now faced could be formulated by the need to generate a synthetic equivalent of hypothetical construct **60**. A solution was discovered (Scheme 18).[29] It was decided that the aldehyde acetal **61**, which was derived by the degradation of cholestanone, would serve as a model for aldehyde **45** (which was destined to be advanced to baccatin III (**1**)). The sequence started with dione **6**, which was converted to its monohydrazone **62**. The latter, on treatment with iodine in a Barton reaction,[30] gave rise to *iododienone* **64**. This substance presumably arose from iodine induced dehydrogenation of the expected monoene iodide intermediate **63**. Compound **64** could be converted to its cyanohydrin **65** in racemic form. The complications associated with the coupling of racemic intermediates with optically pure agents would not be of consequence since the sp^3 hybridization, introduced for purposes of metalation, would be discharged during workup.

Scheme 19[a]



[a] Reagents: (a) tBuLi, THF −78 °C; (b) add **61**, THF, −78 °C, 90%; (c) TBAF, THF, 0 °C, 100%; (d) $VO(acac)_2$, tBuOOH, CH_2Cl_2, 0 °C, 91%; (e) H_2, Pd/C, EtOH, 0 °C, 90%; (f) e, then HOAc 0 °C to room temperature, 56% from epoxide; (g) Cl_2CO, pyr, CH_2Cl_2, 0 °C, 100%.

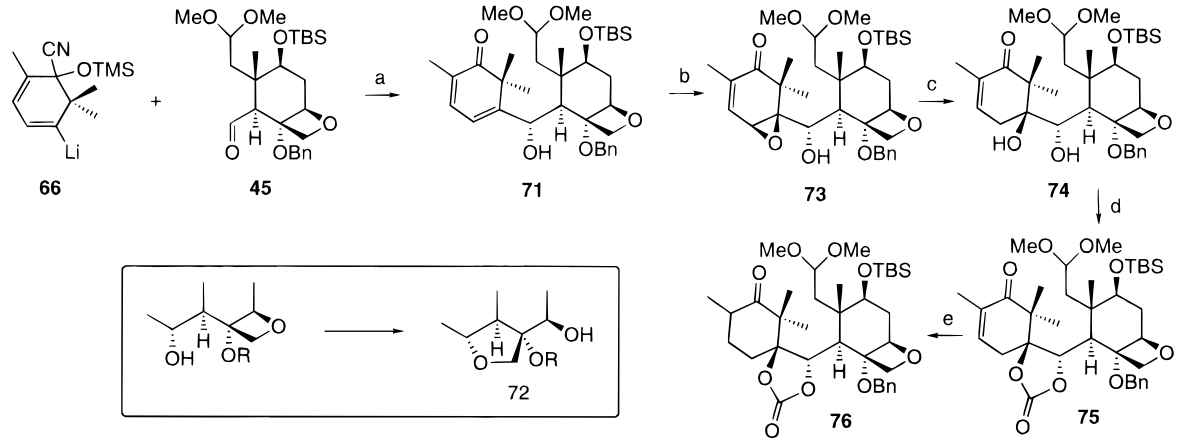
A key finding was that compound **65** could, in fact, be lithiated to give rise to **66** (Scheme 19). The latter reacted with aldehyde **61** to give, after decyanation, a single stereoisomer formulated as **67**. While the configuration at the secondary hydroxyl group in this substance was not proven at this stage, it was established through crystallographic analysis of subsequent reaction products (*vide infra)*. It was then found that directed epoxidation of the $C_{14}-C_1$ olefin produced a single epoxide. Furthermore, this epoxide could be cleaved by palladium-induced hydrogenolysis to generate diol **68** or further reduced to the saturated diol **69** by the addition of acetic acid. Compound **69** could be converted to cyclic carbonate **70** under the conditions shown. It was in this way that the problem, captured in the hypothetical expression **60**, was solved.

We shall return to ketone **70** and to its utility in various cyclization possibilities shortly. However, first we describe the application of these findings to the oxetane-bearing **45** (Scheme 20). Compound **45** and lithium reagent **66**, again, gave rise to a single carbinol **71** after deprotection of the C_{11} ketone. At

(29) Masters, J. J.; Jung, D. K.; Danishefsky, S. J.; Snyder, L. B.; Park, T. K.; Isaacs, R. C. A.; Alaimo, C. A.; Young, W. B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 452.

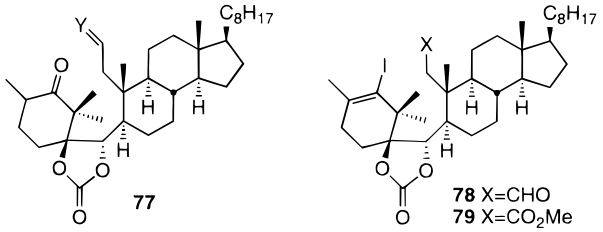
(30) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147−162.

Scheme 20[a]



[a] Reagents: (a) (i) THF, −78 °C, 93%; (ii) TBAF, THF, −78 °C, 80%; (b) mCPBA, CH_2Cl_2, room temperature, 80%; (c) H_2, Pd/C, −5 °C, EtOH, 65%; (d) CDI, NaH, DMF, 81%; (e) L-Selectride, THF, −78 °C, 93%.

Scheme 21



this juncture, it was necessary to develop mild protocols to preserve the oxetane ring during the course of the transformations to be described. In various constructs and at various stages, the hydoxyl group at C_2 tended to displace the carbon−oxygen link at C_{20} with formation of products of the type **72**.

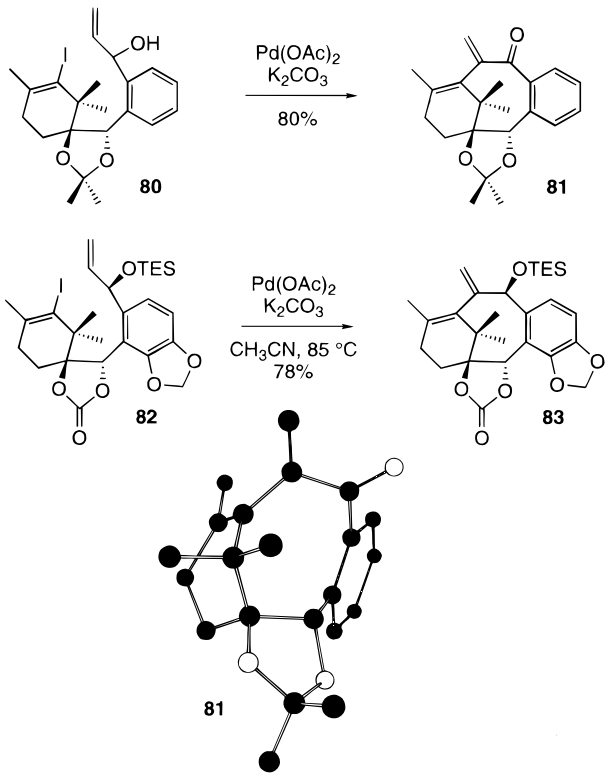
Directed epoxidation of **71** produced **73** which underwent hydrogenation to produce diol **74**, wherein the C_1 and C_2 hydroxyl groups could be protected as a cyclic carbonate (see compound **75**). With the cyclic carbonate in place, the ketone **76** could be obtained by conjugate reduction of **75**.

The steroid derived ketone **70** was used to explore ring closures which we hoped to employ in closing the C_{10}−C_{11} bond *en route* to baccatin III (**1**). Many permutations were investigated. One setback was our inability to convert ketone type **77** (derived from **70**) to the corresponding vinyl iodide (Scheme 21). Eventually, we were able to reach a vinyl iodide via a circuitous route (*vide infra*). Unfortunately, we were unable to effect Barbier[31] or Nozaki−Kishi[32] type ring closures of **78** or **79** in the model steroid-derived series.

We then turned to the possibility of an intramolecular Heck type olefination reaction[33,34] to construct the $C_{10} \rightarrow C_{11}$ baccatin bond. The feasibility of such a palladium-catalyzed internal Heck reaction was first demonstrated in our laboratory with aromatic C ring substrates (see transformations **80** → **81** and **82** → **83**, Scheme 22).[35]

It was well appreciated that the successful Heck reaction of substrates **80** and **82** could not be taken as secure precedents for producing C-saturated derivatives. For instance, in the case

Scheme 22



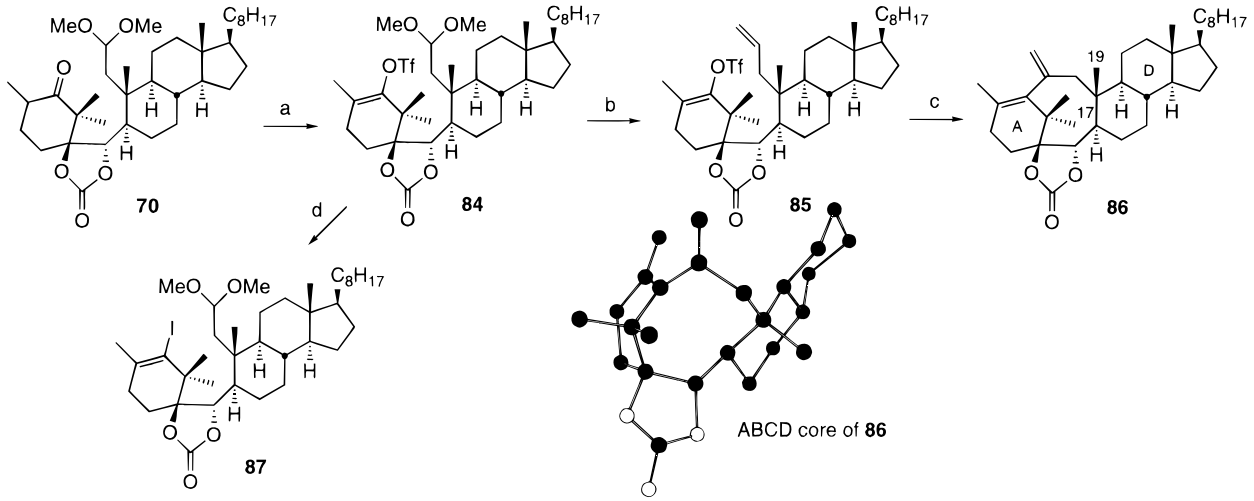
of the steroid−baccatin III hybrid, cyclization would involve creation of a potentially serious C_{17}−C_{19} methyl−methyl abutment. Of course, just such a condition would have to be met for such a reaction to be of value in the baccatin III (**1**) directed enterprise.

To initiate the plan for the Heck reaction we needed to extend the linker arm providing C_9 and C_{10} of the baccatin target (Scheme 23). This was accomplished as follows. The ketone **70** underwent conversion to vinyl triflate **84** under carefully specified conditions. The dimethyl acetal was cleaved, and the resultant aldehyde underwent Wittig olefination to produce **85**. The key advance in the program was realized when **85** underwent intramolecular Heck closure. In this case, however, addition of stochiometric tetrakis(triphenylphosphine)palladium over several hours was required and a 50% yield of **86** was realized.[29]

It seemed that the oxidative addition step to the hindered C_{11} vinyl triflate bond was not the limiting feature of the reaction. Indeed, after several hours it was possible to isolate a palladium-

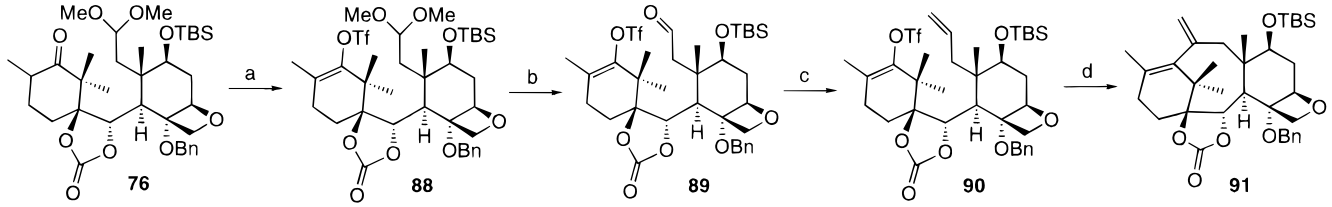
(31) For a review, see: Blomberg and Hartog. *Synthesis* **1977**, 18−30.
(32) Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999−6003.
(33) Heck, R. F. *Palladium Reagents in Organic Syntheses;* Academic Press: New York, 1985; p 179.
(34) For a review, see: Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.
(35) (a) Masters, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 7253. (b) Young, W. B.; Masters, J. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5228.

Scheme 23[a]



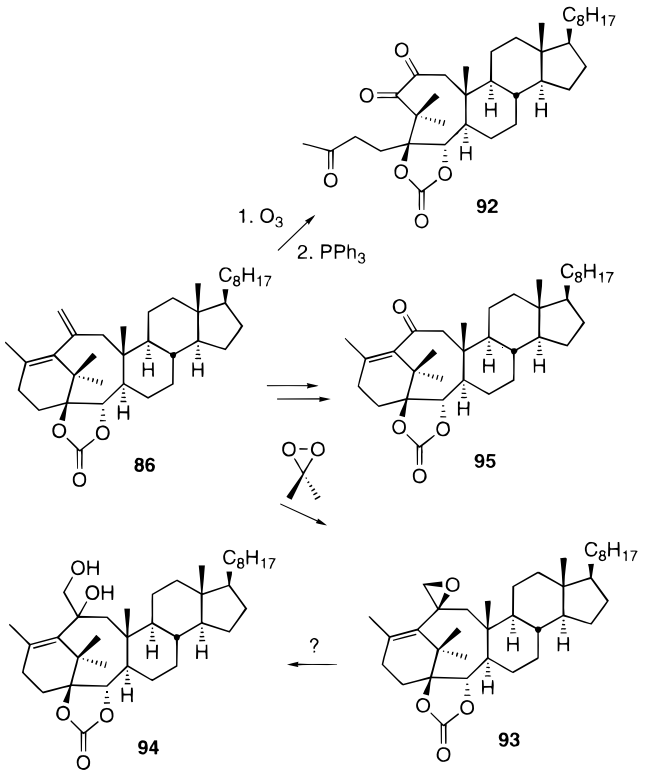
[a] Reagents: (a) KHMDS, $PhNTf_2$, THF, −78 °C, 90%; (b) pTsOH, acetone, H_2O, 75 °C, 80%; Ph_3PCH_3Br, KOtBu, THF, 0 °C, 95%; (c) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, 85 °C, 50%; (d) $Pd(PPh_3)_4$ (1.1 equiv), K_2CO_3, CH_3CN, 85 °C, 2 h; I_2, Et_2O.

Scheme 24



[a] Reagents: (a) $PhNTf_2$, KHMDS, THF, −78 °C, 98%; (b) PPTS, acetone, H_2O, 96%; (c) $Ph_3P{=}CH_2$, THF, −78 °C → 0 °C, 77%; (d) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, 85 °C, 49%.

Scheme 25



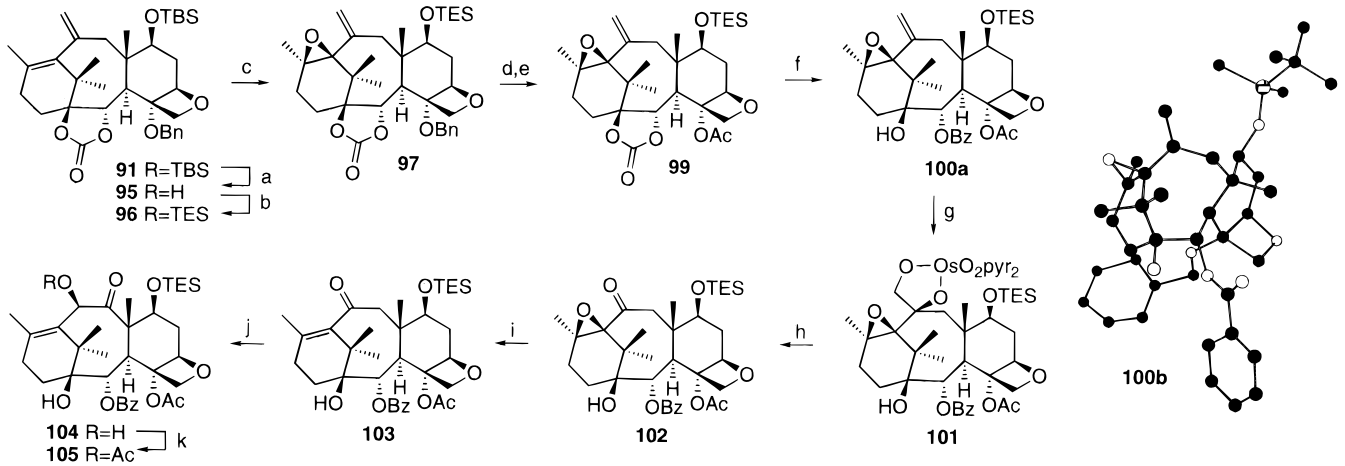
containing product whose structure could not be specified in detail. Treatment of this entity with iodine led to compound **87**.[36] (The latter was used to produce the potential cyclization substrates **78** and **79**, discussed above.) The main difficulty in the Heck reaction seemed to arise from the olefin insertion−elimination phases. The prolonged reaction time may reflect the strain of the bridgehead olefin and the close methyl−methyl contact in the cyclized baccatin−steroid diene **86**. A further complication arising from precipitation of palladium black during the reaction brought with it the requirement of stoichiometric amounts of the palladium mediator.

The important point, however, was that a pathway had been discovered which was potentially relevant to synthesizing baccatin III (**1**). Of course, it was not clear that corresponding steps could be reduced to practice in the more functionalized oxetane-containing series (Scheme 24). The previously discussed ketone **76** was converted to vinyl triflate **88**. Hydrolysis of the acetal afforded **89**. The latter, upon Wittig olefination, provided substrate **90**. *The intramolecular Heck reaction proceeded in a fashion similar to our findings in the cholestanone-derived series (cf.* ***85*** *→* ***86****) and the tetracyclic* ***91*** *was in hand*!

It had been hoped that the now extraneous carbon ($C_{10'}$) of the exocyclic methylene group attached to C_{10} would be easily excised by oxidative cleavage (cf. **95**). Unfortunately, the concluding phase of the synthesis proved to be very difficult. Harbingers of difficulties were already present from our model studies. Several attempts to achieve selective cleavage of the $C_{10}-C_{10'}$ double bond in Heck products **81**, **83**, and **86** were unsuccessful. The matter was probed in detail in the case of **86** (Scheme 25). Both ozone and osmium tetroxide attacked the tetrasubstituted double bond first. In the case of ozonolysis (cf. **86**) this was followed by cleavage of the exocyclic olefin to produce compound **92**. It seemed that oxidants were directed to the tetrasubstituted double bond first. The only oxidizing agent which selectively attacked the exocyclic double bond was dimethyldioxirane. This reaction gave rise to compound **93**.

(36) Masters, J. J. Unpublished results.

Scheme 26[a]



[a] Reagents: (a) TBAF, THF, room temperature, 92%; (b) TESOTf, Et_3N, CH_2Cl_2, −78 °C, 92%; (c) MCPBA, $NaHCO_3$, CH_2Cl_2, room temperature, 45%; (d) H_2, Pd/C, EtOH, room temperature, 82%; (e) Ac_2O, DMAP, pyr, room temperature, 66%; (f) PhLi, THF, −78 °C, 93%; (g) OsO_4, pyr, 105 °C; (h) $Pb(OAc)_4$, PhH, MeOH, 0 °C, 61%; (i) SmI_2, Ac_2O, THF, −78 °C, 92%; (j) KOtBu, $(PhSeO)_2O$, THF, −78 °C; KOtBu, THF, −78 °C, 81%; (k) Ac_2O, DMAP, pyr, 76%.

Unfortunately, attempts to transform the epoxide of compound **93** to a system where $C_{10'}$ could be excised were unsuccessful. For instance, compound **93** was resistant to conversion to a system of the type **94**.

It is our sense that the unusual chemistry encountered during explorations directed at oxidation of the exocyclic methyl group of compound **86** can be accommodated in a common rationale. Thus sp^3 hybridization at C_{10} would cause a significant abutment of its α group (if this group is not a proton) with the vinylic C_{18} methyl group (baccatin numbering). The acute bond angles of the epoxide, of course, lessen this impact. In these terms, there would be significant resistance to the attack of any agents at the exocyclic double bond which involve transition states leading to higher membered rings with sp^3-hybridized bonds (cf. ozonolysis, osmium tetroxide, ruthenium tetroxide).

After significant improvisation, it eventually proved to be possible to cleave the $C_{10'}$ methylene group in the steroidal hybrid, resulting in conversion of **86** to enone **95**. An account of these experiments was recently provided elsewhere.[37] Here, we return to compound **91** and describe its conversion to baccatin III (**1**) (Scheme 26).

The first step in this concluding phase involved changing the stabilizing arrangement at C_7. The robust TBS group had successfully protected that future alcohol function from various chemical incursions. However, in model probes to be described shortly, it was discovered that the removal of the TBS group would be problematic in substrates which carry significant functionality beyond that present in **91**. Hence, the TBS group was removed at virtually the last feasible stage, and the alcohol at C_7 was reprotected with a more labile TES group (see conversion of **91** → **96**).

In this substrate, epoxidation of the tetrasubstituted double bond to produce compound **97** could be accomplished, albeit in only 45% yield. The complication here was the tendency for additional oxidation at the exocyclic methylene to provide an unwanted bis-epoxide. The next step involved adjustment of the status of the masked alcohol at C_4. Throughout the journey from compound **24**, we had benefited from the stability of the benzyl protecting group. However, it was determined that the benzyl group was now going to be vulnerable to some of the required oxidizing agents. Model probes also suggested that it may be difficult to conduct debenzylation in the later stages of the synthesis.

The issue of when the benzyl group would be discharged caused much concern. Eventually, the courage was mustered to attempt its removal at the stage of **97** by hydrogenolysis. Remarkably, the exocyclic methylene ($C_{10'}$) group, true to its "tradition" of stability toward many chemical reactions, survived this hydrogenolysis unscathed! The resultant C_4 alcohol was converted to its acetate, **99**.

In the next phase of the synthesis, the cyclic carbonate was cleaved with phenyllithium to give the C_2 benzoate (see compound **100a**)[38] as precedented in the experiments of both Nicolaou[8,39] and Holton[9] on closely related substrates. It was at this stage that the exocyclic methylene group was to be cleaved. The campaign started with the formation of putative osmate ester **101** obtained by treatment with osmium tetroxide under forcing conditions. This substance was treated with lead tetraacetate, whereby ketone **102** was obtained in a 61% yield. The now extraneous epoxide oxygen was removed through the action of samarium iodide in the presence of acetic anhydride (see compound **103**).[40] We were now obliged to face the possible consequences of having kept C_9 underfunctionalized throughout the course of the synthesis. Fortunately, we could draw upon the powerful chemistry of the Holton group to rectify the problem.[9] Thus, treatment of **103** with potassium *tert*-butoxide and phenylseleninic anhydride led, after acetylation, to the acetoxy ketone **105**.

In our original conceptions about synthesizing taxol (**3**), we had envisioned a late stage oxidation of C_{13}. Indeed, in 1992 we reported the earliest experiments on the matter which indicated that such an oxidation could work.[41] However, a closer and still more reassuring analogy was reported by Nicolaou and co-workers.[8] The La Jolla team had shown that

(37) Young, W. B.; Link, J. T.; Masters, J. J.; Snyder, L. B.; Danishefsky, S. J. *Tetrahedron Lett.* **1995**, *36*, 4963.

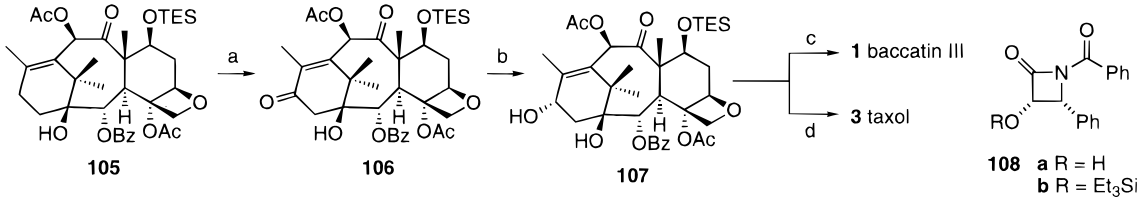
(38) The stereochemistry of the epoxidation reaction was established through a crystal structure on compound **100b**. The latter is the C_7-TBS, C_4-Bn version of compound **100a** formed through analogous chemistry via **91**.

(39) Nicolaou, K. C.; Renaud, J.; Nantermet, P. G.; Couladouros, E. A.; Guy, R. K.; Wrasidlo, W. *J. Am. Chem. Soc.* **1995**, *117*, 2409. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1994**, 295.

(40) For a review on the uses of samarium diiodide, see: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(41) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043.

Scheme 27[a]



[a] Reagents: (a) PCC, NaOAc, PhH, reflux, 64%; (b) $NaBH_4$, MeOH, 79%; (c) HF·pyr, THF, 85%; (d) refs 8, 9, and 42.

the oxidation could be performed on *the very substrate in question*. Indeed, in formal terms, our expedition could have been terminated by the synthesis of **105** since this compound was described as an intermediate in the Nicolaou total synthesis.[8] It was, however, our intention to complete a fully self-contained independent synthesis of baccatin III (**1**) itself. For that purpose, an allylic oxidation with PCC was carried out on our fully synthetic material to give **106** (Scheme 27). This product, in turn, was reduced with sodium borohydride to provide 7-OTES baccatin III (**107**). Compound **107**, as well, had been an intermediate in the Nicolaou total synthesis.[8] For our purposes, however, we removed the triethylsilyl group with HF·pyr. *In so doing we completed our relay-free total synthesis of baccatin III (1).* The material, thus obtained, was identical with a natural sample in all respects, including optical rotation.

As indicated earlier, baccatin III (**1**) has been converted to taxol (**3**) by numerous groups. Indeed, this transformation is currently practiced on a commercial scale. Thus, there would seem to be little need to execute such a conversion as part of our own program. However, for sentimental reasons, we carried out the formalities involved. For that purpose, we substantially followed the regimen of Ojima and co-workers[42] to reach β-lactam **108a**. This was converted to **108b** which served to acylate 7-TES-baccatin III (**107** obtained from natural 10-deacetylbaccatin III (**2**)). By following these previously described protocols[8,9,42] we completed a total synthesis of taxol (**3**), identical with the natural product in all respects, including optical rotation.

Conclusions

The total synthesis of baccatin III (**1**) has been achieved. From baccatin III (**1**), following known protocols, taxol (**3**) itself was obtained. The most rewarding aspect of the synthesis was the ability to start with Wieland−Miescher ketone, itself available through catalytic asymmetric induction, and to install all of the stereochemistry required to reach baccatin III in a sequential fashion. Our synthesis, though arduous, involves no relays, no resolutions, and no recourse to awkwardly available antipodes of the "chiral pool".

In these studies we have discovered a variety of efficient degradative schemes by which differentiated appendages mounted to optically pure CD fragments could be retrieved. An original protocol for delivering a synthetic equivalent of **60** was developed and found to be compatible with an oxetane-containing CD fragment. From here, after coupling vinyllithium reagent **66** to CD construct **45**, and appropriate functional group manipulations, the vinyl triflate **90** was prepared. The defining bond construction in the synthesis was the Heck reaction to produce **91**. The ability to carry out this reaction in such a complicated setting could not have been anticipated in advance. The capacity to carry the oxetane from the earliest stages of the synthesis to and through this step also has taught us much about the stability, as well as the vulnerability, of this fascinating structural element. Unfortunately, the procedure for cleaving the extraneous $C_{10'}$ *exo*-methylene group proved to be unexpectedly complicated. The setbacks sustained on this front eroded the efficiency of the total synthesis.

Nonetheless, much has been learned about the chemical nature of baccatin-like structures and about bicyclic and tricyclic analogues *en route* to the baccatin skeleton. We are currently developing an oxetane-containing analog synthesis program which draws heavily from the chemistry used in the total synthesis. Results of this effort will be disclosed shortly.

Experimental Section

General Procedures. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-400. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR. Optical rotations were measured on a JASCO DIP-370 polarimeter. Mass spectra were obtained on a JOEL JMS-DX-303 HF mass spectrometer. Analytical chromatography was performed on E. Merck silical gel 60 F_{254} plates (0.25 mm). Flash chromatography was performed on Mallinckrodt silica gel 60 (230−400 mesh). Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), acetonitrile, benzene (PhH), triethylamine, and pyridine were distilled from calcium hydride. *N*,*N*-Dimethylformamide (DMF) was purchased from Aldrich in sure seal containers. All other commercially obtained reagents were used as received.

Ketone 11. A solution of **10**[43] (30.9 g, 91.3 mmol) in 300 mL of THF at 0 °C was treated dropwise with BH_3 (1 M solution in THF, 93.0 mL, 93.0 mmol). After complete addition, the mixture was slowly allowed to warm to room temperature and stir for 13 h. The mixture was cooled to 0 °C and treated dropwise with H_2O (7.1 mL), followed by 3 M NaOH (50 mL) and 30% H_2O_2. After 1 h, the mixture was warmed to room temperature, stirred for 3 h, and concentrated under reduced pressure. The residue was dissolved ether (600 mL) and H_2O (300 mL). The aqueous layer was washed with ether (4 × 200 mL) and the combined extracts were washed with saturated NaCl (2 × 200 mL), dried ($MgSO_4$), and concentrated under reduced pressure. A solution of the crude carbinol in 300 mL of CH_2Cl_2 at 0 °C was treated with PDC (66.7 g, 177 mmol) and 4 Å sieves (66.5 g) in portions over a period of 1 h. The mixture was allowed to stir at 0 °C for 0.5 h and then warmed to room temperature and stirred for 10 h. The mixture was diluted with ether (500 mL), treated with Celite (50 g), and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, affording the crude ketone as a brown oil. A solution of the crude ketone in 250 mL of MeOH at room temperature was treated with NaOMe (25 wt % in MeOH, 28 mL). After 10 h, the mixture was concentrated under reduced pressure and the residue was dissolved in ether (500 mL) and H_2O (300 mL). The aqueous layer was washed with ether (2 × 150 mL), and the combined extracts were washed with H_2O (200 mL) and saturated NaCl (200 mL), dried ($MgSO_4$), filtered through Celite/$MgSO_4$, and concentrated under reduced pressure, affording 30.0 g (93%) of the trans-fused ketone **11** as an orange oil: ^1H NMR (400 MHz, $CDCl_3$) δ 3.97−3.83 (m, 4H), 3.78 (dd, J = 11.1, 5 Hz, 1H), 2.46 (dd, J = 12.3, 3.7 Hz, 1H), 2.41−2.27 (m, 2H), 2.00−1.58 (m, 7H), 1.42 (dt, J = 13.4, 4.9 Hz, 1H), 0.88 (s, 9H), 0.78 (s,

(42) Cf.: Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149. Ojima, I.; Habus, I.; Zucco, M.; Park, Y. M.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.

(43) Enantiomerically pure **10** was generated via the same procedures as described for racemic **10**; see ref 17.

3H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 109.0, 77.3, 64.3, 64.2, 52.2, 46.7, 42.4, 38.8, 35.1, 30.7, 30.5, 29.6, 25.8, 18.0, 10.5, −4.1, −4.8; IR (film) 2952, 2857, 1716, 1110, 1093, 1051, 869, 837 cm^{-1}; $[\alpha]^{20}_D$ 11.1° (c = 1.8, $CHCl_3$).

Spiroepoxide 14. A solution $Me_3S^+I^-$ (25.9 g, 127 mmol) in 275 mL of THF at 0 °C was treated with KHMDS (23.1 g, 110 mmol) in portions over a period of 0.5 h. After 1 h, a solution of **11** (30.0 g, 84.6 mmol) in 100 mL of THF was added via cannula over a period of 0.5 h. After 0.5 h, the mixture was treated with H_2O (25 mL) and concentrated under reduced pressure. The residue was dissolved in ether (500 mL) and H_2O (300 mL). The aqueous layer was washed with ether (150 mL), and the combined extracts were washed with H_2O (150 mL) and saturated NaCl (150 mL), dried ($MgSO_4$), and concentrated under reduced pressure, affording 31.1 g (99%) of **14** as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93−3.89 (dd, J = 10.8, 4.4 Hz, 1H), 3.30 (m, 4H), 2.63 (d, J = 4.4 Hz, 1H), 2.23 (d, J = 4.4 Hz, 1H), 1.99−1.92 (m, 1H), 1.87−1.76 (m, 3H), 1.64−1.58 (m, 3H), 1.48 (t, J = 13.2 Hz, 1H), 1.24−1.19 (m, 3H), 0.94 (s, 3H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.6, 78.8, 64.3, 64.1, 58.4, 47.1, 41.0, 40.1, 35.3, 32.9, 30.5, 30.4, 28.6, 25.8, 18.0, 10.7, −4.0, −4.8; IR (neat) 2950, 2856, 1471, 1252, 1106, 872, 836 cm^{-1}; $[\alpha]^{20}_D$ −0.7° (c = 2.5, $CHCl_3$).

Allylic Alcohol 15. A solution of **14** (31.1 g, 84.5 mmol) and Al(iPrO)$_3$ (50.0 g, 245 mmol) in 300 mL of toluene was heated at reflux for 38 h. The mixture was cooled to room temperature, diluted with ether (1100 mL), and treated with saturated Na^+K^+ tartrate (500 mL). The layers were separated, and the aqueous layer was treated with 1 M NaOH (500 mL) and washed with ether (3 × 300 mL). The combined organic extracts were washed with saturated NaCl (500 mL), dried ($MgSO_4$), filtered through Celite, and concentrated under reduced pressure, affording 30.9 g (99%) of **15** as a light yellow solid: mp 72−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (m, 1H), 4.03−3.92 (m, 6H), 3.53 (dd, J = 9.8, 6.5 Hz, 1H), 2.49 (br d, 1H), 2.23 (br d, 1H), 2.02 (m, 1H), 1.90 (dt, J = 12.9, 2.5 Hz, 1H), 1.83 (dq, J = 13.0, 2.5 Hz, 1H), 1.75 (dd, J = 13.7, 4.7 Hz, 1H), 1.67 (dq, J = 13.8, 2.5 Hz, 1H), 1.56 (t, J = 13.2 Hz, 1H), 1.21 (dt, J = 12.8, 4.5 Hz, 1H), 0.87 (s, 9H), 0.79 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 123.0, 109.4, 75.8, 65.0, 64.23, 64.17, 41.6, 37.4, 33.3, 33.2, 32.1, 30.8, 25.8, 18.0, 8.9, −4.1, −4.8; IR (film) 3416, 2951, 2856, 1472, 1360, 1250, 1106, 1072, 872, 836, 774 cm^{-1}; $[\alpha]^{20}_D$ 25.4° (c = 1.4, $CHCl_3$).

Triol 16.[44] A solution of **15** (30.9 g, 84.5 mmol) and NMO (19.8 g, 170 mmol) in 1300 mL of acetone and 170 mL of H_2O at room temperature was treated with OsO_4 (5 wt % in iPrOH, 42.0 mL, 4.23 mmol). After 15 h, the mixture was treated with saturated $NaHSO_3$ (400 mL) and stirred for 0.5 h. The mixture was then poured into EtOAc (400 mL) and saturated NaCl (400 mL). The aqueous layer was washed with EtOAc (3 × 300 mL), and the combined extracts were concentrated under reduced pressure. The residue was dissolved in EtOAc (750 mL) and washed with saturated NaCl (300 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc), affording 15.3 g (45%) of **16** as an off-white solid: mp 157−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98−3.90 (m, 5H), 3.77 (dd, J = 11.5, 5.5 Hz, 1H), 3.56 (m, 2H), 3.10 (s, 1H), 2.62 (d, J = 2.4 Hz, 1H), 2.31−2.29 (m, 1H), 2.06 (dd, J = 14.7, 2.7 Hz, 1H), 1.87 (m, 2H), 1.80−1.70 (m, 2H), 1.62 (m, 2H), 1.52 (t, J = 13.2 Hz, 1H), 1.29 (td, J = 12.6, 6.4 Hz, 1H), 0.87 (s, 9H), 0.82 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.3, 73.8, 73.7, 69.3, 64.2, 64.18, 62.0, 42.4, 38.8, 37.9, 34.8, 30.8, 30.1, 25.8, 18.0, 12.3, −4.1, −4.8; IR (film) 3441, 2950, 2856, 1256, 1102, 864, 835 cm^{-1}; $[\alpha]^{20}_D$ 32.3° (c = 1.1, $CHCl_3$).

Oxetane 22.[45] A solution of **16** (8.70 g, 21.6 mmol) and pyridine (19.2 mL, 238 mmol) in 540 mL of CH_2Cl_2 at −78 °C was treated with chlorotrimethylsilane (2.8 mL, 22.0 mmol). The mixture was allowed to warm to room temperature, and chlorotrimethylsilane (280 μL, 2.2 mmol) was added every hour until starting material was consumed as determined by TLC. After 3 h, the mixture was cooled to −78 °C, treated with trifluoromethanesulfonic anhydride (14.5 mL, 86.4 mmol), and then allowed to warm to room temperature. After 1.5 h, ethylene glycol (90.0 mL, 1.62 mol) was added and the mixture was heated at reflux for 14.5 h. The mixture was then cooled and poured into saturated NaCl (400 mL) and saturated $NaHCO_3$ (400 mL). The aqueous layer was washed with CH_2Cl_2 (3 × 250 mL), and the combined extracts were washed with 1:1 H_2O:saturated $CuSO_4$ (400 mL), saturated $NaHCO_3$ (250 mL), and saturated NaCl (250 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 3:2 to 1:1 hexane:EtOAc), affording 5.5 g (66%) of **22** as a white solid: mp 152−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (dd, J = 9.1, 2.2 Hz, 1H), 4.46 (d, J = 7.6 Hz, 1H), 4.26 (d, J = 7.6 Hz, 1H), 3.96−3.89 (m, 4H), 3.44 (dd, J = 10.6, 7.2 Hz, 1H), 2.40 (s, 1H), 2.27 (ddd, J = 16.3, 9.2, 7.1 Hz, 1H), 1.88 (ddd, J = 15.1, 10.7, 2.4 Hz, 1H), 1.83−1.72 (m, 2H), 1.68−1.55 (m, 5H), 1.21 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.9, 88.2, 77.1, 76.4, 73.9, 64.3, 64.2, 46.6, 37.5, 36.5, 30.9, 30.1, 25.8, 18.0, 9.5, −4.1, −4.8; IR (film) 3416, 1094, 859, 836, 774 cm^{-1}; $[\alpha]^{20}_D$ 19.0° (c = 3.65, $CHCl_3$).

Benzyloxetane 24. A solution of **22** (7.40 g, 19.2 mmol) in 100 mL of THF at 0 °C was treated with NaH (2.3 g, 96 mmol). After 0.5 h, the mixture was treated with benzyl bromide (3.0 mL, 25 mmol) and TBAI (2.13 g, 5.76 mmol) and allowed to warm to room temperature. After 4 h, the mixture was cooled to 0 °C, and saturated NH_4Cl was added until a homogeneous biphasic mixture resulted. The mixture was poured into ether (700 mL) and saturated NaCl (300 mL). The aqueous phase was washed with ether (2 × 200 mL), and the combined extracts were washed with saturated $Na_2S_2O_3$ (2 × 150 mL) and saturated NaCl (150 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 9:1 to 17:3 hexane:EtOAc), affording 8.90 g (98%) of **24** as a white solid: mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H), 4.95 (dd, J = 9.0, 1.6 Hz, 1H), 4.55 (d, J = 11.6 Hz, 1H), 4.42−4.38 (m, 3H), 3.95−3.89 (m, 4H), 3.41 (dd, J = 10.4, 7.4 Hz, 1H), 2.22−2.20 (m, 1H), 2.00−1.91 (m, 2H), 1.85−1.79 (m, 2H), 1.68−1.58 (m, 3H), 1.30−1.25 (m, 1H), 1.25 (s, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.4, 127.6, 127.3, 109.0, 82.8, 79.0, 76.7, 74.6, 65.0, 64.3, 64.2, 41.3, 38.1, 37.5, 36.9, 31.1, 29.5, 25.8, 18.0, 9.9, −4.0, −4.8; IR (film) 2951, 2856, 1471, 1360, 1256, 1095, 837 cm^{-1}; $[\alpha]^{20}_D$ 33.3° (c = 6.3, $CHCl_3$).

Ketone 25. A solution of **24** (8.90 g, 18.8 mmol) in 950 mL of 15:1 acetone:H_2O was treated with pTsOH (4.64 g, 24.4 mmol), and the mixture was heated at reflux for 2.5 h. The mixture was cooled to room temperature, treated with saturated $NaHCO_3$, and concentrated with a stream of nitrogen. The residue was dissolved in ether (800 mL) and poured into saturated $NaHCO_3$ (300 mL). The aqueous phase was washed with ether (150 mL) and CH_2Cl_2 (200 mL). The combined extracts were washed saturated $NaHCO_3$ (2 × 200 mL) and saturated NaCl (150 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 3:1:1 hexane:CH_2Cl_2:EtOAc), affording 6.80 g (84%) of **25** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.04 (dd, J = 9.2, 2.1 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.50−4.44 (m, 2H), 3.43 (dd, J = 10.6, 7.2 Hz, 1H), 2.48 (ddd, J = 15.6, 14.0, 6.5 Hz, 1H), 2.39−2.38 (m, 1H), 2.34 (s, 1H), 2.32 (s, 1H), 2.30−2.24 (m, 1H), 2.15 (ddd, J = 13.2, 6.3, 2.0 Hz, 1H), 2.03−1.94 (m, 2H), 1.42 (s, 3H), 1.36 (dt, J = 14.1, 5.0 Hz, 1H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 137.9, 128.5, 127.7, 127.2, 82.4, 79.1, 76.3, 73.2, 65.1, 45.1, 38.9, 37.9, 37.7, 37.6, 36.6, 25.8, 18.0, 10.0, −4.0, −4.9; IR (film) 2948, 1707, 1455, 1255, 1098, 940, 734 cm^{-1}; $[\alpha]^{20}_D$ 27.4° (c = 6.3, $CHCl_3$).

α-Hydroxy Ketone 39. A solution of **27** (7.20 g, 16.7 mmol) and triethylamine (23.3 mL, 167 mmol) in 450 mL of CH_2Cl_2 at −78 °C was treated with trimethylsilyl trifluoromethanesulfonate (16.7 mL, 83.5 mmol). After 4 h, the mixture was treated with saturated $NaHCO_3$ (25 mL) and allowed to warm for 10 min. The mixture was poured into hexane (900 mL) and saturated $NaHCO_3$ (250 mL). The aqueous phase was washed with hexane (200 mL), and the combined extracts were washed with saturated $NaHCO_3$ (2 × 250 mL) and saturated NaCl (150 mL), quickly dried ($MgSO_4$), and concentrated under reduced pressure. The crude enol ether was dissolved in CH_2Cl_2 (300 mL),

(44) Formation of side product **17** has been described previously; see ref 17.

(45) Formation of side product **23** has been described previously; see ref 17.

cooled to 0 °C, and rapidly treated with 3,3-dimethyldioxirane (0.1 M solution in acetone, 180 mL, 18.0 mmol). After 10 min, the mixture was concentrated under reduced pressure. The residue was dissolved in acetone (350 mL) and treated with CSA (106 mg). After 0.5 h, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (SiO_2, 6.5:2:1.5 to 6:2:2 hexane:CH_2Cl_2: EtOAc), affording 6.60 g (89%) of **39** as a white solid: mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 5.04 (dd, J = 9.0, 1.6 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.51 (m, 1H), 4.42 (d, J = 7.9 Hz, 1H), 4.33 (dd, J = 6.9, 12.4 Hz, 1H), 4.33 (dd, J = 12.4, 6.9 Hz, 1H), 3.50−3.60 (br s, 1H), 3.44 (dd, J = 10.3, 7.4 Hz, 1H), 2.58 (dd, J = 10.3, 7.0 Hz, 1H), 2.52−2.46 (m, 2H), 2.27−2.26 (m, 1H), 2.01−1.96 (m, 2H), 1.51 (s, 3H), 1.20 (t, J = 12.6 Hz, 1H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 137.7, 128.6, 127.8, 127.2, 82.3, 78.9, 76.1, 73.0, 72.5, 65.2, 48.7, 46.5, 39.4, 37.7, 34.6, 25.8, 17.9, 11.3, −4.0, −4.9; IR (film) 3446, 1719, 1471, 1251096, 838 cm^{-1}; $[\alpha]^{20}_D$ 37.2° (c = 1.95, $CHCl_3$).

Aldehyde 40. A solution of **39** (3.90 g, 8.72 mmol) in 170 mL of 1:1 C_6H_6:MeOH at 0 °C was treated with lead(IV) acetate (5.05 g, 11.4 mmol). After 10 min, the mixture was diluted with ether (600 mL), affording a yellow slurry which was then filtered through SiO_2 (300 mL) using ether as eluent. The clear filtrate was concentrated under reduced pressure. The residue was dissolved in ether (800 mL), washed with saturated $NaHCO_3$ (2 × 150 mL) and saturated NaCl (150 mL), dried ($MgSO_4$), and concentrated under reduced pressure, affording 4.4 g (97%) of **40** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.37−7.26 (m, 5H), 4.89 (dd, J = 9.2, 3.5 Hz, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 7.8 Hz, 1H), 4.53 (d, J = 7.8 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 3.99 (dd, J = 11.2, 6.1 Hz, 1H), 3.48 (s, 3H), 2.80 (dd, J = 9.9, 7.8 Hz, 1H), 2.62 (d, J = 17.1 Hz, 1H), 2.41 (dd, J = 14.8, 5.0 Hz, 1H), 2.36−2.21 (m, 3H), 1.96−1.94 (m, 1H), 1.22 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 173.1, 137.9, 128.4, 127.60, 127.55, 81.8, 80.5, 75.9, 71.8, 64.9, 51.8, 50.4, 41.9, 40.6, 36.9, 31.0, 25.8, 18.0, 14.4, −3.8, −4.7.

Acetal 41. A solution of crude **40** in 1100 mL of MeOH was treated with collidinium *p*-toluenesulfonate (910 mg, 3.10 mmol), and the mixture was heated at reflux. After 10 h, the mixture was concentrated under reduced pressure and the residue was dissolved in ether (600 mL). The resulting white slurry was then filtered through basic alumina (150 mL) using ether as eluent. The filtrate was concentrated under reduced pressure, affording 4.40 g (97%) of **41** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.23 (m, 5H), 4.83 (dd, J = 9.2, 3.8 Hz, 1H), 4.66−4.62 (m, 2H), 4.58 (d, J = 11.1 Hz, 1H), 4.51 (d, J = 7.7 Hz, 1H), 4.31 (d, J = 11.1 Hz, 1H), 3.78 (dd, J = 10.9, 6.0 Hz, 1H), 3.43 (s, 3H), 3.33 (s, 3H), 3.32 (s, 3H), 2.58−2.53 (m, 2H), 2.28 (ddd, J = 9.3, 5.9, 14.9 Hz, 1H), 2.20 (dd, J = 10.5, 13.8 Hz, 1H), 2.05−1.95 (m, 2H), 1.50 (dd, J = 14.8, 5.6 Hz, 1H), 1.07 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 138.2, 128.3, 127.49, 127.46, 101.6, 81.8, 81.1, 76.1, 71.2, 64.5, 52.5, 51.6, 39.9, 39.7, 38.8, 37.3, 31.1, 25.8, 18.1, 15.6, −3.7, −4.9; IR (film) 2952, 2856, 1737, 1255, 1.89, 991, 837 cm^{-1}; $[\alpha]^{20}_D$ 18.4° (c = 2.25, $CHCl_3$).

Alcohol 42. A solution of **41** (6.60 g, 12.6 mmol) in 20 mL of THF was transferred via cannula to a 0 °C solution of $LiAlH_4$ (623 mg, 16.4 mmol) in 180 mL of THF. After 1 h, the mixture was treated with EtOAc (20 mL) followed by saturated NH_4Cl (2 mL). After 0.5 h, the mixture was diluted with EtOAc (500 mL), treated with SiO_2 (100 mL), and filtered through Celite and $MgSO_4$ using EtOAc as eluent. The filtrate was concentrated under reduced pressure, affording 2.78 g (quant.) of **42** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 4.90 (dd, J = 9.6, 4.6 Hz, 1H), 4.65−4.64 (m, 2H), 4.57−4.49 (m, 3H), 3.72 (dd, J = 11.8, 5.6 Hz, 1H), 3.56 (q, J = 5.9 Hz, 2H), 3.30 (s, 3H), 3.28 (s, 3H), 2.98 (t, J = 6.4 Hz, 1H), 2.29 (ddd, J = 5.7, 9.7, 14.8 Hz, 1H), 2.19 (d, J = 9.4 Hz, 1H), 1.99−1.90 (m, 2H), 1.82−1.79 (m, 1H), 1.64 (dd, J = 14.7, 6.7 Hz, 1H), 1.47−1.46 (m, 1H), 1.05 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 128.6, 127.9, 127.6, 101.5, 82.0, 81.6, 76.2, 70.8, 64.9, 61.8, 52.5, 51.8, 40.2, 39.7, 38.1, 37.1, 29.1, 25.8, 18.1, 15.4, −3.5, −4.9; IR (film) 3460, 2953, 2856, 1463, 1362, 1254, 1156, 1086, 984, 837, 775, 734 cm^{-1}; $[\alpha]^{20}_D$ 6.2° (c = 2.7, $CHCl_3$).

***o*-Nitrophenyl Selenide 43.** A solution of crude **42** and (2-nitrophenyl)selenyl cyanide (3.15 g, 13.9 mmol) in 130 mL of THF at room temperature was treated with tributylphosphine (3.73 mL, 15.2 mmol). After 0.25 h, the mixture was concentrated under reduced aspirator pressure in a well-ventilated hood. The residue was slurried in 17:3 hexane:EtOAc and purified by flash chromatography (SiO_2, 17:3 hexane:EtOAc), affording 7.20 g (88%) of **43** as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.0 Hz, 1H), 7.39−7.24 (m, 8H), 4.90 (dd, J = 9.6, 4.4 Hz, 1H), 4.69 (d, J = 4.3 Hz, 1H), 4.66 (s, 1H), 4.57−4.50 (m, 3H), 3.72 (dd, J = 11.6, 5.7 Hz, 1H), 3.33 (s, 3 H), 3.32 (s, 3), 3.04 (dt, J = 11.6, 4.6 Hz, 1H), 2.85−2.78 (m, 1H), 2.34−2.27 (m, 2H), 2.04−1.93 (m, 2H), 1.90 (d, J = 3.5 Hz, 1H), 1.74−1.60 (m, 2H), 1.03 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 138.0, 133.7, 133.4, 129.0, 128.5, 127.7, 127.4, 126.5, 125.1, 101.5, 81.9, 76.3, 70.9, 64.6, 53.2, 51.5, 41.7, 40.4, 38.6, 37.1, 25.9, 25.6, 25.2, 18.1, 15.6, −3.4, −4.9; IR (film) 2952, 2855, 1513, 1332, 1087, 984, 837, 730 cm^{-1}; $[\alpha]^{20}_D$ 2.7° (c = 0.85, $CHCl_3$).

Olefin 44. A solution of **43** (7.20 g, 11.1 mmol) in 140 mL of THF at room temperature was treated with 11.5 mL of 30% H_2O_2. After 12 h, the mixture was poured into ether (800 mL) and 10% NaOH (200 mL). The aqueous layer was washed with ether (250 mL), and the combined extracts were washed with 10% NaOH (3 × 150 mL) and saturated NaCl (200 mL) and dried ($MgSO_4$). Concentration under reduced pressure afforded 4.72 g (90%) of **44** as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H), 6.00−5.91 (m, 1H), 5.18 (d, J = 17.2 Hz, 1H), 5.15 (dd, J = 17.3, 10.2 Hz, 1H), 4.90 (dd, J = 8.0, 3.4 Hz, 1H), 4.63 (d, J = 7.4 Hz, 1H), 4.59 (t, J = 5.3 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 7.4 Hz, 1H), 3.72 (dd, J = 9.2, 5.4 Hz, 1H), 3.26 (s, 6H), 2.77 (d, J = 9.3 Hz, 1H), 2.28 (ddd, J = 3.2, 9.4, 13.4 Hz, 1H), 2.00−1.93 (m, 1H), 1.71 (dd, J = 14.4, 4.7 Hz, 1H), 1.61 (dd, J = 14.3, 4.7 Hz, 1H), 1.12 (s, 3H), 0.90 (s, 9H), 0.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 135.0, 128.4, 127.5, 127.2, 119.5, 102.1, 82.9, 79.7, 77.2, 75.9, 71.9, 65.0, 52.5, 52.3, 48.7, 39.8, 39.2, 36.2, 25.9, 18.1, 16.9, −3.7, −4.8; IR (film) 2948, 2929, 2850, 1461, 1250, 1078, 985, 832, 774 cm^{-1}; $[\alpha]^{20}_D$ 15.9° (c = 3.1, $CHCl_3$); FAB HRMS *m/e* calcd for (M + K) $C_{27}H_{44}K_1O_5Si_1$ 515.2586, found 515.2595.

Aldehyde 45. A solution of **44** (3.40 g, 7.15 mmol) and 5.25 g of solid $NaHCO_3$ in 525 mL of CH_2Cl_2 at −78 °C was treated with ozone until a light blue solution resulted. The excess ozone was removed by passing a stream of nitrogen through the solution for 5 min, and the mixture was then treated with PPh_3 (1.87 g, 7.15 mmol) and allowed to warm to room temperature. After 0.5 h, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (SiO_2, 9:1 to 4:1 hexane:EtOAc), affording 2.7 g (79%) of **45** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (d, J = 2.6 Hz, 1H), 7.34−7.32 (m, 5H), 4.92 (dd, J = 7.6, 2.4 Hz, 1H), 4.65 (d, J = 8.0 Hz, 1H), 4.56−4.49 (m, 3H), 4.44 (d, J = 11.2 Hz, 1H), 3.72 (dd, J = 6.4, 4.8 Hz, 1H), 3.25 (s, 3H), 3.24 (s, 3H), 2.96 (d, J = 2.8 Hz, 1H), 2.25−2.18 (m, 1H), 2.00−1.94 (m, 1H), 1.77 (dd, J = 12.4, 4.8 Hz, 1H), 1.69 (dd, J = 14.4, 6.0 Hz, 1H), 1.20 (s, 3H), 0.090 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.9, 138.0, 128.4, 127.6, 127.4, 101.9, 83.1, 77.4, 77.2, 76.0, 71.7, 65.5, 56.7, 52.7, 52.4, 39.6, 39.3, 34.1, 25.8, 19.1, 18.1, −4.0, −4.9; IR (film) 2929, 2856, 1708, 1471, 1387, 1254, 1089, 837, 775, 697 cm^{-1}; $[\alpha]^{20}_D$ 9.4° ($CHCl_3$, c = 0.51); FAB HRMS *m/e* calcd for (M + K) $C_{26}H_{42}K_1O_6Si_1$ 517.2388, found 517.2379.

Monohydrazone 62. A solution of **6**[11] (34.5 g, 224 mmol) in 250 mL of EtOH was treated with triethylamine (93.3 mL, 669 mmol) and hydrazine monohydrate (21.7 mL, 447 mmol). After 1.5 h, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (SiO_2, ether), affording 27.0 g (72%) of **62** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (br s, 2H), 2.59 (ddd, J = 9.3, 6.3, 3.0 Hz, 1H), 2.49 dd, J = 11.2, 6.8 Hz, 1H), 2.42 (m, 1H), 2.05 (m, 1H), 1.62 (m, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 1.10 (d, J = 6.8 Hz, 3H); IR (film) 3385, 2973, 2933, 1708, 1635, 1459 cm^{-1}; CI (NH_3) MS *m/e* calcd for (M + H) $C_9H_{16}N_2O_1$ 169, found 169.

Vinyl Iodide 63. A solution of **62** (13.5 g, 80.4 mmol) and DBN (98 mL, 793 mmol) in 2.7 L of ether was treated dropwise with a solution of I_2 (40.8 g, 161 mmol) in 1 L of ether over 40 min. After

0.75 h, the mixture was filtered through SiO_2 using ether as eluent. Concentration of the filtrate under reduced pressure and purification of the residue by flash chromatography (SiO_2, 9:1 to 4:1 hexane:EtOAc) afforded 11.0 g (52%) of **63** as a colorless oil and 4.1 g (19%) of **64** as a yellow oil.

Iodo Dienone 64. A solution of **63** (11 g, 41.6 mmol) in 500 mL of THF at 0 °C was treated with DBN (103 mL, 825 mmol). Three portions of I_2 (53 g, 209 mmol total) were added over 30 min, and the reaction mixture was allowed to warm to room temperature. After 8 h, the mixture was poured into ether (750 mL) and H_2O (500 mL). The organic layer was washed with H_2O (2 × 500 mL), saturated $Na_2S_2O_3$ (2 × 300 mL), and saturated NaCl (400 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2, 4:1 hexane:EtOAc) afforded 9.8 g (89%) of **64** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, J = 6.7 Hz, 1H), 6.54 (dd, J = 7.9, 0.2 Hz, 1H), 1.83 (s, 3H), 1.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 138.1, 132.7, 131.9, 120.9, 53.7, 28.5, 15.3; IR (film) 2971, 1655, 1560, 1456, 1374, 1361, 1033 cm^{-1}; CI(NH_3) MS *m/e* calcd for (M + H) $C_9H_{12}O_1I_1$ 263, found 263.

Cyanohydrin 65. A solution of **64** (9.8 g, 37 mmol) in 150 mL of CH_2Cl_2 at 0 °C was treated with TMSCN (6.0 mL, 45 mmol), KCN (0.24 g, 3.7 mmol), and 18-crown-6 (1.0 g, 3.8 mmol). The reaction was allowed to warm to room temperature and stir for 8 h. After cooling to 0 °C, the reaction was quenched by the addition of saturated $NaHCO_3$ (200 mL). The mixture was poured into CH_2Cl_2 (250 mL) and washed with saturated $NaHCO_3$ (200 mL). The organic layer was concentrated under reduced pressure in a fume hood. The residue was purified by flash chromatography (SiO_2, 19:1 hexane:ether), affording 12.0 g (89%) of **65** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 6.0 Hz, 1H), 5.52 (ddd, J = 6.0, 3.3, 1.6 Hz, 1H), 1.95 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H), 0.23 (s, 9H); IR (film) 2975, 1590, 1463, 1254, 1141, 1099, 844 cm^{-1}; CI(NH_3) MS *m/e* calcd for (M + H_2O) $C_{13}H_{22}N_1O_1Si_1I_1$ 379, found 379.

Carbinol 71. A solution of diene **65** (3.93 g, 10.9 mmol) in 130 mL of THF at −78 °C was treated dropwise with tBuLi (1.7 M solution in pentane, 12.5 mL, 21.2 mmol). After 0.5 h, a solution of aldehyde **45** in 40 mL of THF was added dropwise to the mixture via cannula. An additional 20 mL of THF was used to transfer any remaining aldehyde. After 0.25 h, the mixture was treated with saturated NH_4Cl (50 mL), diluted with ether (200 mL), and allowed to warm to room temperature. The mixture was poured into ether (400 mL) and saturated NH_4Cl (150 mL). The aqueous layer was washed with ether (200 mL), and the combined extracts were washed with saturated NaCl (200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 9:1 to 4:1 hexane:EtOAc), affording 5.57 g of a mixture of diastereomers (white foam). This mixture of diastereomers (3.04 g, 4.26 mmol) in 26 mL of THF at −78 °C was then treated dropwise with tetrabutylammonium fluoride (1.0 M solution in THF, 25.6 mL, 25.6 mmol). After 0.25 h, the mixture was diluted with hexane (26 mL) and directly purified by flash chromatography (SiO_2, hexane to 9:1 to 4:1 hexane:EtOAc), affording 2.11 g (75% from **45**) of **71** as a single diastereomer (white foam): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.16 (m, 5H), 6.74 (d, J = 6.6 Hz, 1H), 6.27 (d, J = 6.6 Hz, 1H), 5.61 (d, J = 8.1 Hz, 1H), 4.98 (d, J = 6.9 Hz, 1H), 4.90 (s, 1H), 4.81 (d, J = 11.7 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 4.68 (d, J = 8.1 Hz, 1H), 4.53 (s, 1H), 4.43 (t, J = 4.9 Hz, 1H), 3.75 (t, J = 4.0 Hz, 1H), 3.26 (s, 3H), 3.18 (s, 3H), 2.38 (d, J = 2.4 Hz, 1H), 2.34−2.25 (m, 1H), 2.01 (d, J = 15.8 Hz, 1H), 1.85 (s, 3H), 1.42−1.40 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.97 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 157.9, 138.5, 137.2, 130.6, 128.3, 127.3, 127.2, 117.7, 102.4, 82.2, 81.2, 77.2, 76.0, 74.7, 69.6, 64.5, 53.1, 52.6, 51.2, 50.8, 42.9, 40.4, 34.8, 29.6, 25.9, 21.7, 20.5, 18.3, 15.6, −4.4, −4.6; IR (film) 3378, 2929, 2856, 1654, 1471, 1376, 1256, 1050, 837 cm^{-1}; $[\alpha]^{20}_D$ 29.3° (c = 0.7, $CHCl_3$); FAB HRMS *m/e* calcd for (M^+) $C_{35}H_{54}O_7Si_1$ 614.3639, found 614.3623.

Epoxide 73. A solution of **71** (1.49 g, 2.43 mmoles) and $NaHCO_3$ (2.97 g) in 69 mL of CH_2Cl_2 at room temperature was treated with mCPBA (95%, 1.04 g, 6.05 mmol). After 11 h, the mixture was treated with Me_2S (890 μL, 12.1 mmol) and diluted with H_2O (40 mL) and ether (200 mL). The mixture was poured into ether (400 mL) and saturated $NaHCO_3$ (200 mL), and the aqueous layer was washed with ether (200 mL). The combined extracts were washed with saturated $NaHCO_3$ (200 mL) and saturated NaCl (200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 4:1 to 3:1 to 2:1 petroleum ether:ether), affording 1.21 g (80%) of **73** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 6.27 (dd, J = 3.1, 1.4 Hz, 1H), 5.39 (d, J = 9.0 Hz, 1H), 4.97 (d, J = 11.4 Hz, 1H), 4.86 (app t, J = 7.4 Hz, 1H), 4.77 (d, J = 11.3 Hz, 1H), 4.68 (d, J = 9.0 Hz, 1H), 4.64 (t, J = 5.0 Hz, 1H), 4.52 (s, 1H), 3.59 (dd, J = 11.8, 4.3 Hz, 1H), 3.51 (d, J = 4.5 Hz, 1H), 3.27 (s, 6H), 2.89 (s, 1H), 2.34−2.28 (m, 1H), 2.17−2.10 (m, 2H), 1.76 (d, J = 6.4 Hz, 1H), 1.62 (s, 3H), 1.44 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 138.5, 137.5, 135.5, 128.3, 127.9, 127.6, 102.2, 82.7, 81.7, 77.5, 77.2, 72.7, 67.4, 66.7, 64.9, 53.9, 52.7, 52.3, 48.0, 47.4, 41.8, 41.2, 35.9, 25.9, 24.1, 19.9, 18.1, 17.3, 16.4, −3.6, −4.6; IR (film) 3493, 2952, 2856, 1683, 1471, 1384, 1254, 1082, 837, 775 cm^{-1}; $[\alpha]^{20}_D$ −36.0° (c = 5.8, $CHCl_3$); FAB HRMS *m/e* calcd for (M + H) $C_{35}H_{55}O_8Si_1$ 631.3666, found 631.3672.

Diol 74. A solution of **73** (936 mg, 1.49 mmol) and 10% Pd/C (1.016 g) in EtOH (87 mL) at −5 °C was placed under an atmosphere of hydrogen. After 1.25 h, the mixture was diluted with EtOAc, filtered through Celite using EtOAc as eluent, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 3:1 to 7:3 to 3:2 petroleum ether:ether), affording 610 mg (65%) of **74** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.30 (m, 5H), 6.12 (br s, 1H), 5.48 (d, J = 9.2 Hz, 1H), 5.05 (d, J = 11.4 Hz, 1H), 4.96 (d, J = 11.4 Hz, 1H), 4.85 (app t, J = 7.4 Hz, 1H), 4.59 (d, J = 9.0 Hz, 1H), 4.52 (app t, J = 5.4 Hz, 1H), 4.06 (d, J = 5.6 Hz, 1H), 3.59 (dd, J = 10.6, 4.4 Hz, 1H), 3.37 (s, 1H), 3.28 (s, 3H), 3.23 (s, 3H), 3.12 (br s, 1H), 2.58−2.44 (m, 2H), 2.38−2.32 (ddd, J = 13.2, 8.4, 4.4 Hz, 1H), 2.22−2.17 (m, 1H), 2.12 (s, 1H), 1.69 (d, J = 1.2 Hz, 3H), 1.63−1.60 (m, 1H), 1.56 (s, 1H), 1.20 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 137.3, 132.8, 128.8, 128.0, 127.8, 102.1, 83.6, 82.0, 78.6, 77.2, 71.8, 70.5, 65.7, 53.1, 52.1, 51.4, 41.4, 41.3, 36.1, 34.2, 25.9, 18.2, 16.7, 16.1, −3.5, −4.6; IR (film) 3438, 2947, 1464, 1383, 1255, 1078, 1046, 837 cm^{-1}; $[\alpha]^{20}_D$ 35.2° (c = 0.27, $CHCl_3$); FAB HRMS *m/e* calcd for (M + H) $C_{35}H_{57}O_8Si_1$ 633.3823, found 633.3835.

Carbonate 75. A solution of **74** (0.76 g, 1.20 mmol) and carbonyldiimidazole (4.88 g, 30.1 mmol) in 40 mL of DMF was treated with NaH (48.6 g, 1.92 mmol, 95%) in portions over 20 min. The reaction was quenched by addition of saturated NH_4Cl (200 mL), and the mixture was poured into ether (500 mL). The organic layer was washed with $NaHCO_3$ (300 mL), H_2O (300 mL), and saturated NaCl (300 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 4:1 hexane:EtOAc), affording 0.64 g (81%) of **75** as a white solid: mp 249−250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 6.13 (br s, 1H), 5.21 (d, J = 9.9 Hz, 1H), 4.95 (d, J = 10.3 Hz, 1H), 4.88 (d, J = 10.1 Hz, 1H), 4.87−4.78 (m, 3H), 4.49 (app t, J = 5.3 Hz, 1H), 3.60 (dd, J = 11.7, 4.4 Hz, 1H), 3.25 (s, 3H), 3.23 (s, 3H), 3.07−3.02 (m, 1H), 2.69−2.65 (m, 1H), 2.41−2.39 (m, 1H), 2.24−2.16 (m, 2H), 1.70 (s, 3H), 1.58−1.55 (m, 2H), 1.27 (s, 3H), 1.19 (s, 3H), 1.13 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 154.0, 137.8, 137.4, 129.1, 128.4, 127.8, 102.1, 91.3, 83.4, 81.8, 78.8, 77.2, 76.8, 71.8, 65.8, 53.6, 53.0, 51.5, 46.4, 41.9, 41.4, 36.7, 29.8, 25.9, 18.1, 16.0, 14.9, −3.3, −4.6; IR (film) 2952, 1794, 1677, 1364, 1047, 838 cm^{-1}; $[\alpha]^{20}_D$ 15.3° (c = 0.66, $CHCl_3$); FAB HRMS *m/e* calcd for (M + Na) $C_{36}H_{54}Na_1O_9Si_1$ 681.3434, found 681.3467.

Ketone 76. A solution of **75** (984 mg, 1.50 mmol) in 30 mL of THF at −78 °C was treated dropwise with a solution of L-Selectride (1.0 M solution in THF, 4.50 mL, 4.50 mmol). After 1.25 h, the mixture was treated with saturated NH_4Cl (5 mL), diluted with ether (300 mL), and allowed to warm to room temperature. The mixture was poured into ether (100 mL), and saturated NH_4Cl (75 mL). The aqueous phase was washed with ether (100 mL) and the combined extracts were washed with saturated NH_4Cl (75 mL) and saturated NaCl (75 mL), dried (K_2CO_3), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 7:1.5:1.5 to 5:3:2

hexane:CH_2Cl_2:ether), affording 920 mg (93%) of **76** as a white solid: mp 272−273 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5H), 5.18 (d, J = 9.8 Hz, 1H), 4.97−4.81 (m, 4H), 4.75 (s, 1H), 4.52 (t, J = 5.2 Hz, 1H), 3.58 (dd, J = 12.4, 4.8 Hz, 1H), 3.28 (s, 3H), 3.27−3.25 (m, 1H), 3.25 (s, 3H), 2.58−2.39 (m, 2H), 2.34 (s, 1H), 2.22−2.16 (m, 1H), 1.97−1.86 (m, 1H), 1.67 (d, J = 14.8, 5.2 Hz), 1.54 (d, J = 14.8, 5.6 Hz, 1H), 1.28 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H), 0.95 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 153.8, 137.4, 129.1, 128.3, 127.8, 102.3, 93.5, 83.1, 82.0, 78.9, 77.2, 72.2, 65.7, 53.9, 53.6, 53.0, 46.2, 41.9, 41.4, 39.1, 37.0, 29.0, 27.0, 25.9, 23.5, 18.2, 16.8, 14.7, 14.6, −3.3, −4.6; IR (film) 2950, 1786, 1709, 1115, 1049, 840 cm^{-1}; $[\alpha]^{20}_D$ 8.1° (c = 0.27, $CHCl_3$); FAB HRMS *m/e* calcd for (M + Na) $C_{36}H_{56}Na_1O_9Si_1$ 683.3591, found 683.3620.

Vinyl Triflate 88. A solution of **76** (920 mg, 1.39 mmol) and *N*-phenyl bis(trifluoromethanesulfonimide) (1.25 g, 3.49 mmol) in 47 mL of THF at −78 °C was rapidly treated with KHMDS (0.5 M solution in toluene, 3.34 mL, 1.67 mmol). After 10 min, the mixture was treated with saturated NH_4Cl (5 mL), diluted with ether (300 mL), and allowed to warm to room temperature. The mixture was poured into ether (100 mL) and saturated NH_4Cl (75 mL). The aqueous phase was washed with ether (100 mL), and the combined extracts were washed with saturated NH_4Cl (75 mL) and saturated NaCl (75 mL), dried (K_2CO_3), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 9:1 to 17:3 petroleum ether:ether), affording 1.08 g (98%) of **88** as a white foam contaminated with <5% of *N*-phenyl trifluoromethanesulfonimide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.31 (m, 5H), 5.22 (d, J = 12.4 Hz, 1H), 4.94−4.84 (m, 4H), 4.75 (s, 1H), 4.49 (app t, J = 6.0 Hz, 1H), 3.61 (dd, J = 11.6, 4.4 Hz, 1H), 3.22 (s, 3H), 3.21 (s, 3H), 2.45−2.33 (m, 3H), 2.25−2.18 (m, 1H), 1.75 (dd, J = 16.8, 5.6 Hz, 1H), 1.64 (s, 3H), 1.66−1.47 (m, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.13 (s, 3H), 0.09 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 144.4, 137.3, 129.4, 128.4, 127.8, 126.5, 101.8, 90.3, 82.9, 82.2, 78.7, 77.2, 71.5, 65.7, 53.2, 52.8, 45.8, 45.0, 41.5, 41.4, 36.8, 30.9, 27.4, 25.9, 23.8, 23.1, 18.1, 17.4, 17.3, 15.4, −3.3, −4.6; IR (film) 2947, 1797, 1400, 1211, 1137, 1077, 991, 853 cm^{-1}; $[\alpha]^{20}_D$ −19.5° (c = 0.59, $CHCl_3$); FAB HRMS *m/e* calcd for (M + Na) $C_{37}H_{55}Na_1O_{11}S_1Si_1$ 815.3084, found 815.3125.

Aldehyde 89. A solution of **88** (1.39 mmol) and PPTS (1.75 g, 6.97 mmol) in 60 mL of 9:1 acetone:H_2O was heated at 75 °C for 9 h. The mixture was cooled to room temperature, treated with saturated $NaHCO_3$ (10 mL), and concentrated with a stream of nitrogen. The residue was diluted with ether (200 mL) and poured into saturated $NaHCO_3$ (50 mL). The aqueous phase was washed with ether (2 × 50 mL), and the combined extracts were washed with saturated $NaHCO_3$ (2 × 50 mL) and saturated NaCl (75 mL), dried (K_2CO_3), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 9:1 to 3:1 petroleum ether:ether), affording 998 mg (96%) of **89** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.5 (s, 1H), 7.50−7.29 (m, 5H), 5.15 (d, J = 10.2 Hz, 1H), 4.95−4.89 (m, 3H), 4.82 (d, J = 9.8 Hz, 1H), 4.62 (s, 1H), 3.96 (dd, J = 12.6, 4.9 Hz, 1H), 2.87 (d, J = 18.0 Hz, 1H), 2.69 (s, 1H), 2.52−2.44 (m, 1H), 2.35 (dd, J = 13.6, 6.0 Hz, 1H), 2.24−2.14 (m, 2H), 1.80 (dd, J = 18.0, 6.4 Hz, 1H), 1.64 (s, 3H), 1.60−1.41 (m, 2H), 1.32 (s, 3H), 1.13 (s, 6H), 0.88 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 153.8, 143.9, 136.9, 129.4, 128.4, 127.9, 127.0, 90.2, 82.6, 81.8, 77.9, 77.3, 77.2, 70.2, 65.7, 50.2, 44.9, 44.7, 43.1, 37.0, 27.2, 25.8, 23.3, 23.0, 18.0, 17.6, 17.3, 15.3, −3.7, −4.8; IR (film) 2938, 1796, 1722, 1403, 1211, 1137, 1083, 995, 881, 852 cm^{-1}; $[\alpha]^{20}_D$ −19.4° (c = 0.64, $CHCl_3$); FAB HRMS *m/e* calcd for (M + H) $C_{35}F_3H_{50}O_{10}S_1Si_1$ 747.2847, found 747.2857.

Cyclization Precursor 90. A solution of **89** (998 mg, 1.34 mmol) in 45 mL of THF at −78 °C was treated dropwise with a solution of $Ph_3P{\cdot}CH_2$ (0.10 M solution in THF, 13.5 mL, 1.35 mmol). After complete addition, the mixture was stirred at −78 °C for 10 min and at 0 °C for 15 min. The mixture was then treated with saturated NH_4Cl (5 mL), diluted with ether (150 mL), and allowed to warm to room temperature. The mixture was poured into ether (150 mL) and saturated NH_4Cl (75 mL). The aqueous phase was washed with ether (100 mL), and the combined extracts were washed with saturated NH_4Cl (75 mL) and saturated NaCl (75 mL), dried (K_2CO_3), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 9:1 to 17:3 petroleum ether:ether), affording 771 mg (77%) of **90** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.30 (m, 5H), 5.66−5.56 (m, 1H), 5.22−5.20 (d, J = 9.9 Hz, 1H), 5.10−5.00 (m, 2H), 4.96−4.80 (m, 4H), 4.70 (s, 1H), 3.64 (dd, J = 11.6, 4.4 Hz, 1H), 2.50−2.37 (m, 3H), 2.24−2.15 (m, 1H), 2.08 (s, 1H), 1.87 (dd, J = 16.0, 7.2 Hz, 1H), 1.80−1.72 (m, 1H), 1.64 (s, 3H), 1.59−1.41 (m, 1H), 1.24 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 144.2, 137.2, 131.9, 129.5, 128.4, 127.9, 126.6, 120.2, 119.4, 90.0, 83.0, 82.2, 78.1, 77.2, 69.4, 65.8, 44.9, 44.6, 42.2, 41.1, 36.6, 27.2, 25.8, 23.4, 23.3, 18.1, 17.4, 17.3, 15.9, −3.4, −4.7; IR (film) 2940, 1797 cm^{-1}; $[\alpha]^{20}_D$ −22.7° (c = 1.1, $CHCl_3$); FAB HRMS *m/e* calcd for (M + H) $C_{36}F_3H_{52}O_9S_1Si_1$ 672.2584, found 672.2583.

Diene 91. A solution of **90** (234 mg, 0.314 mmol), K_2CO_3 (130 mg, 0.942 mmol), and 4 Å sieves in 16 mL of CH_3CN at 90 °C was treated with $Pd(PPh_3)_4$ (400 mg, 0.345 mmol) in portions over a period of 16.5 h so as to maintain an amber-colored solution. The resulting black slurry was allowed to cool to room temperature, diluted with ether (40 mL), and filtered through Celite using ether as eluent. The orange filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (SiO_2, 17:3 to 4:1 petroleum ether:ether), affording 85.4 mg (46%) of **91** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.23 (m, 5H), 5.19 (s, 1H), 5.04−4.96 (m, 2H), 4.84 (s, 2H), 4.73−4.61 (m, 3H), 3.57 (dd, J = 7.2, 9.7 Hz, 1H), 2.81 (d, J = 16.7 Hz, 1H), 2.62−2.33 (m, 3H), 2.22 (d, J = 4.7 Hz, 1H), 2.14 (d, J = 16.4 Hz, 1H), 1.97−1.90 (m, 1H), 1.82−1.74 (m, 1H), 1.69 (s, 3H), 1.69−1.57 (m, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 1.17 (s, 3H), 0.94 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 143.2, 139.4, 138.1, 134.8, 128.4, 127.6, 127.5, 117.8, 93.7, 82.4, 80.3, 79.7, 74.5, 72.0, 64.8, 44.9, 44.7, 44.5, 40.0, 38.0, 29.4, 26.0, 25.5, 23.2, 22.6, 22.4, 20.6, 18.1, 16.4, −3.0, −4.5; IR (film) 2954, 2738, 1803, 1472, 1455, 1207, 1008 cm^{-1}; $[\alpha]^{20}_D$ 6.6° (c = 1, $CHCl_3$); FAB HRMS *m/e* calcd for (M + H) $C_{35}H_{51}O_6Si_1$ 595.3463, found 595.3455.

Alcohol 95. A solution of **91** (255.6 mg, 0.430 mmol) in 8.5 mL of THF at room temperature was treated with tetrabutylammonium fluoride (1.0 M solution in THF, 1.29 mL, 1.29 mmol). After 6 h, the mixture was diluted with EtOAc (3 mL) and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and 4:1 hexane:EtOAc and purified by flash chromatography (SiO_2, 7:3 to 3:2 hexane:EtOAc), affording 189.1 mg (92%) of **95** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (m, 5H), 5.23 (s, 1H), 5.09 (dd, J = 7.1, 2.2 Hz, 1H), 4.98 (d, J = 9.6 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1 H), 4.80 (d, J = 11.4 Hz, 1 H), 4.71 (d, J = 4.9 Hz, 1H), 4.68 (s, 1H), 4.58 (d, J = 9.6 Hz, 1H), 3.58−3.52 (m, 1H), 2.66 (d, J = 16.3 Hz, 1H), 2.58−2.43 (m, 2H), 2.37−2.32 (m, 1H), 2.22−2.16 (m, 2H), 2.02−1.92 (m, 2H), 1.81−1.73 (m, 1H), 1.68 (s, 3H), 1.65−1.58 (m, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 142.6, 138.8, 137.9, 135.6, 128.5, 127.7, 127.5, 118.4, 93.8, 82.9, 80.1, 79.6, 77.2, 74.4, 72.1, 64.9, 45.9, 45.0, 43.9, 40.2, 36.2, 29.5, 25.7, 23.2, 22.8, 21.0, 16.4; IR (film) 3472, 2926, 1799, 1455, 1021, 1009 cm^{-1}; $[\alpha]^{20}_D$ 51.4° (c = 1, $CHCl_3$); FAB HRMS *m/e* calcd for (M + K) $C_{29}H_{36}K_1O_6$ 519.2149, found 519.2166.

Diene 96. A solution of **95** (189.1 mg, 0.394 mmol) and triethylamine (0.270 mL, 1.97 mmol) in 16.0 mL of CH_2Cl_2 at −78 °C was treated with triethylsilyl trifluoromethanesulfonate (0.098 mL, 0.433 mmol). After 0.5 h, the mixture was treated with saturated $NaHCO_3$ (4 mL) and diluted with ether (30 mL), and the mixture was poured into ether (20 mL) and saturated $NaHCO_3$ (20 mL). The aqueous layer was washed with ether (20 mL), and the combined extracts were washed with saturated $NaHCO_3$ (40 mL) and saturated NaCl (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 9:1 to 4:1 hexane:EtOAc), affording 216.2 mg (92%) of **96** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 5.16 (s, 1H), 4.99 (dd, J = 9.2, 2.7 Hz, 1H), 4.93 (d, J = 9.6 Hz, 1H), 4.82 (s, 2H), 4.69 (d, J = 4.9 Hz, 1H), 4.64−4.60 (m, 2H), 3.56 (dd, J = 10.2, 7.0 Hz, 1H), 2.77 (d, J = 16.6 Hz, 1H), 2.52−2.34 (m, 3H), 2.18 (d, J = 4.9 Hz, 1H), 2.12 (d, J = 16.5 Hz, 1H), 1.93−1.90 (m, 1H), 1.84−1.72 (m, 1H), 1.67 (s, 3H), 1.67−1.59 (m, 1H), 1.28 (s, 6H), 1.15 (s, 3H), 0.98−0.93 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

154.1, 143.2, 139.4, 138.1, 134.9, 128.4, 127.6, 127.5, 127.4, 117.7, 93.7, 82.4, 80.3, 79.8, 74.6, 72.1, 64.8, 44.8, 44.4, 40.0, 37.8, 29.4, 25.5, 23.2, 22.4, 20.7, 16.2, 7.0, 5.5; IR (film) 2954, 2876, 1805, 1455, 1008 cm^{-1}; FAB HRMS *m/e* calcd for (M + H) $C_{35}H_{51}O_6Si_1$ 595.3455, found 595.3473.

Epoxide 97. A solution of **96** (171.5 mg, 0.289 mmol) and $NaHCO_3$ (343 mg) in 9.7 mL of CH_2Cl_2 at room temperature was treated with mCPBA (95%, 89.7 mg, 0.520 mmol). After 10.25 h, the mixture was treated with Me_2S (30 μL) and H_2O (10 mL). The mixture was then diluted with ether (50 mL) and poured into saturated $NaHCO_3$ (30 mL). The aqueous layer was washed with ether (20 mL), and the combined extracts were washed with saturated $NaHCO_3$ (2 × 40 mL) and saturated NaCl (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 17:3 to 4:1 to 3:1 petroleum ether:ether), affording 79.6 mg (45%) of **97** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 5.13 (m, 2H), 5.01 (m, 2H), 4.90−4.81 (m, 3H), 4.68 (d, J = 9.7 Hz, 1H), 3.67 (dd, J = 10.0, 7.6 Hz, 1H), 3.04 (d, J = 16.9 Hz, 1H), 2.59−2.50 (m, 1H), 2.44−2.40 (m, 1H), 2.28 (d, J = 16.8 Hz, 1H), 2.15 (d, J = 4.4 Hz, 1H), 1.98−1.92 (m, 2H), 1.60−1.54 (m, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 1.16 (s, 3H), 0.92 (s, 3H), 0.98−0.92 (m, 9H), 0.56 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 140.0, 137.5, 128.5, 127.9, 127.8, 119.5, 91.5, 82.4, 80.0, 79.3, 77.2, 74.1, 70.5, 69.4, 65.0, 62.6, 43.9, 43.5, 43.4, 40.2, 37.6, 25.1, 24.5, 23.0, 22.9, 20.5, 15.8, 7.0, 5.6; IR (film) 2955, 1807, 1456, 1076, 1010, 733 cm^{-1}; FAB HRMS *m/e* calcd for (M + H) $C_{35}H_{51}O_7Si_1$ 611.3404, found 611.3416.

Alcohol 98. A solution of **97** (79.6 mg, 0.130 mmol) and $Pd(OAc)_2$ (24.9 mg, 0.111 mmol) in 4.7 mL of EtOH was placed under an atmosphere of hydrogen. After 10.0 h, the mixture was diluted with EtOAc (25 mL), filtered through Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 7:3 hexane:EtOAc), affording 55.6 mg (82%) of **98** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 5.05 (s, 1H), 4.86 (d, J = 4.7 Hz, 1H), 4.78−4.69 (m, 2H), 4.34 (d, J = 9.0 Hz, 1H), 3.69 (dd, J = 9.7, 7.7 Hz, 1H), 3.02 (d, J = 16.9 Hz, 1H), 2.84−2.77 (m, 1H), 2.70 (s, 1H), 2.44−2.38 (m, 1H), 2.38 (d, J = 16.7 Hz, 1 H), 2.29−2.14 (m, 2H), 2.10 (d, J = 4.7 Hz, 1H), 2.02−1.87 (m, 2H), 1.69−1.58 (m, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 0.93 (t, J = 7.9 Hz, 9H), 0.54 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 140.0, 119.5, 91.6, 88.3, 81.0, 80.1, 77.2, 74.3, 70.5, 69.4, 62.6, 43.8, 43.5, 43.0, 40.2, 37.6, 25.4, 24.6, 23.4, 23.0, 20.5, 15.7, 7.0, 5.6; IR (film) 3507, 2955, 2876, 1792, 1458, 1235, 1011 cm^{-1}; $[\alpha]^{20}_D$ −24.5° (c = 1.0, $CHCl_3$); FAB HRMS *m/e* calcd for (M + K) $C_{28}H_{44}K_1O_7Si_1$ 559.2493, found 559.2502.

Acetate 99. A solution of **98** (55.6 mg, 0.107 mmol) and DMAP (14.4 mg, 0.118 mmol) in 0.43 mL of pyridine at room temperature was treated with acetic anhydride (100 μL, 1.07 mmol). After 16 h, the mixture was treated with saturated $NaHCO_3$ (5 mL) and then diluted with EtOAc (15 mL). The aqueous layer was washed with EtOAc (10 mL), and the combined extracts were washed with saturated $NaHCO_3$ (2 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 4:1 hexane:EtOAc), affording 40.1 mg (66%) of **99** as a white foam and 4.9 mg (9%) of recovered **98**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 5.01 (s, 1H), 4.98 (d, J = 8.8 Hz, 1H), 4.88 (d, J = 5.2 Hz, 1H), 4.63 (d, J = 8.8 Hz, 1H), 4.55 (d, J = 8.8 Hz, 1H), 3.90 (t, J = 8.0 Hz, 1H), 3.10 (d, J = 17.1 Hz, 1H), 2.60−2.52 (m, 1H), 2.46 (d, J = 5.2 Hz, 1H), 2.30 (d, J = 18.5 Hz, 1H), 2.30−2.08 (m, 2H), 2.14 (s, 3H), 1.87−1.60 (m, 4H), 1.42 (s, 3H), 1.39 (s, 3H), 1.25 (s, 3H), 1.04 (s, 3H), 0.94 (t, J = 8.0 Hz, 9H), 0.57 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 153.3, 139.8, 119.2, 108.7, 90.9, 84.1, 80.7, 79.6, 77.2, 76.3, 70.9, 69.0, 62.2, 44.9, 43.7, 41.0, 40.2, 38.0, 29.7, 25.0, 24.7, 23.8, 21.8, 21.3, 20.4, 16.3, 7.0, 5.6; IR (film) 2950, 1800, 1730, 1243, 1013, 969 cm^{-1}; $[\alpha]^{20}_D$ −17.3° (c = 0.95, $CHCl_3$); FAB HRMS *m/e* calcd for (M + K) $C_{30}H_{46}K_1O_8Si_1$ 601.2599, found 601.2623.

Benzoate 100a. A solution of **99** (40.1 mg, 0.071 mmol) in 6 mL of THF at −78 °C was treated with PhLi (0.5 M solution in 4:1 THF:Et_2O, 0.57 mL, 0.285 mmol). After 2 min, the mixture was treated with saturated NH_4Cl (10 mL) and then diluted with ether (15 mL). The aqueous layer was washed with ether (20 mL), and the combined extracts were washed with saturated NH_4Cl (10 mL) and saturated NaCl (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 4:1 to 3:1 to 7:3 petroleum ether:ether), affording 42.4 mg (93%) of **100a** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (app d, J = 7.9 Hz, 2H), 7.59−7.56 (m, 1H), 7.50−7.43 (m, 2H), 5.88 (d, J = 5.4 Hz, 1H), 5.15 (s, 1H), 5.05−5.02 (m, 2H), 4.34 (d, J = 8.2 Hz, 1H), 4.23 (d, J = 8.3 Hz, 1H), 3.91 (t, J = 8.4 Hz, 1H), 2.99 (d, J = 16.4 Hz, 1H), 2.59−2.51 (m, 3H), 2.27 (s, 3H), 2.25−2.08 (m, 2H), 1.84 (dd, J = 9.2, 14.9 Hz, 1H), 1.73−1.69 (m, 1H), 1.58 (s, 1H), 1.53 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 0.99 (s, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.60−0.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 140.7, 133.5, 130.0, 129.4, 128.6, 117.8, 108.8, 84.1, 82.3, 78.4, 77.2, 73.2, 71.5, 69.8, 62.7, 44.2, 44.1, 43.4, 42.3, 37.6, 26.0, 25.7, 25.6, 22.0, 21.4, 21.3, 16.1, 7.0, 5.7; IR (film) 3521, 2954, 2876, 1733, 1277, 1247, 1098 cm^{-1}; $[\alpha]^{20}_D$ 15.1° (c = 1.0, $CHCl_3$); FAB HRMS *m/e* calcd for (M^+) $C_{36}H_{52}O_8Si_1$ 640.3431, found 640.3410.

Ketone 102. A solution of **100** (42.4 mg, 0.066 mmol) in 2.4 mL of pyridine was treated with OsO_4 (319.7 mg, 1.258 mmol) and heated to 105 °C. After 24 h, the mixture was cooled, diluted with EtOAc (10 mL), and treated with saturated $NaHSO_3$ (10 mL). The aqueous layer was washed with EtOAc (4 × 10 mL), and the combined extracts were washed with saturated $NaHSO_3$ (2 × 10 mL), H_2O (10 mL), and saturated NaCl (10 mL), dried (Na_2SO_4), filtered through SiO_2 (1 mL), and concentrated under reduced pressure. The residue was dissolved in 1:1 C_6H_6:MeOH (8 mL), cooled to 0 °C, and treated with lead(IV) acetate (47.4 mg, 0.265 mmol). After 5 min, the mixture was diluted with ether (20 mL) and the resulting yellow slurry was filtered through SiO_2 (2 mL) using ether as eluent. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (SiO_2, 4:1 to 7:3 hexane:EtOAc), affording 26.1 mg (61%) of **102** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.09 (app d, 2H), 7.62−7.59 (app t, 1H), 7.50−7.46 (app t, 2H), 6.07 (d, J = 5.5 Hz, 1H), 5.00 (d, J = 8.6 Hz, 1H), 4.38 (d, J = 8.5 Hz, 1H), 4.26 (d, J = 8.4 Hz, 1H), 3.76 (t, J = 8.4 Hz, 1H), 3.35 (d, J = 15.5 Hz, 1H), 2.85 (d, J = 15.4 Hz, 1H), 2.70 (d, J = 5.4 Hz, 1H), 2.51−2.49 (m, 1H), 2.30 (s, 3H), 2.30−2.18 (m, 2H), 1.84−1.70 (m, 2H), 1.50 (s, 3H), 1.45 (s, 3H), 1.32 (s, 3H), 1.04 (s, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.63−0.57 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 169.8, 166.9, 133.8, 130.1, 129.1, 128.7, 84.0, 82.0, 77.9, 77.2, 76.5, 73.1, 72.1, 65.8, 62.3, 50.9, 44.8, 44.4, 40.1, 37.7, 26.3, 25.8, 25.6, 23.0, 22.0, 21.2, 16.0, 15.3, 14.2, 6.9, 5.8, 5.3; IR (film) 3515, 2955, 2876, 1731, 1695, 1272, 1247, 1098, 712 cm^{-1}; FAB HRMS *m/e* calcd for (M + H) $C_{35}H_{51}O_9Si_1$ 643.3303, found 643.3301.

Enone 103. A solution of **102** (26.1 mg, 0.041 mmol) and acetic anhydride (38 μL, 0.41 mmol) in 2.0 mL of THF at −78 °C was treated with SmI_2 (0.1 M solution in THF, 165 μL, 0.0165 mmol) until a green solution persisted. After 10 min, the mixture was treated with saturated NH_4Cl (5 mL), allowed to warm, and diluted with EtOAc (10 mL) and H_2O (2 mL). The mixture was poured into EtOAc (10 mL) and saturated NH_4Cl (5 mL), and the layers were separated. The aqueous layer was washed with EtOAc (10 mL), and the combined extracts were washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2 [2 mL], 7:3 hexane:EtOAc), affording 23.4 mg (92%) of **103** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.09 (app d, 2H), 7.61−7.57 (app t, 1H), 7.50−7.45 (app t, 2H), 5.87 (d, J = 5.8 Hz, 1H), 4.89 (d, J = 8.3 Hz, 1H), 4.34 (d, J = 8.3 Hz, 1H), 4.16 (d, J = 8.3 Hz, 1H), 3.72 (t, J = 9.1 Hz, 1H), 3.14 (d, J = 15.6 Hz, 1H), 3.08 (d, J = 5.8 Hz, 1H), 2.65−2.58 (m, 2H), 2.57 (d, J = 15.6 Hz, 1H), 2.28 (s, 3H), 2.28−2.24 (m, 1H), 1.97−1.86 (m, 1H), 1.82−1.74 (m, 1H), 1.75 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.13 (s, 3H), 0.97 (q, J = 8.0 Hz, 9H), 0.62 (t, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 170.0, 167.0, 144.6, 138.2, 133.6, 130.1, 129.3, 128.6, 84.5, 82.4, 80.2, 77.2, 76.5, 73.4, 72.7, 50.4, 44.6, 44.2, 39.6, 38.0, 30.2, 26.7, 26.0, 22.8, 22.3, 20.0, 16.1, 7.0, 5.3; IR (film) 3502, 2956, 1731, 1677, 1456, 1273, 1244, 1098, 730, 711 cm^{-1}; FAB HRMS *m/e* calcd for (M + H) $C_{35}H_{51}O_8Si_1$ 627.3353, found 627.3376.

α-Hydroxy Ketone 104. A solution of **103** (23.4 mg, 0.037 mmol) in 2.5 mL of THF at −78 °C was treated with tBuOK (0.24 M solution

in THF, 0.62 mL, 0.149 mmol), and the mixture was placed in a −20 °C bath. After 0.75 h, the mixture was briefly warmed to 0 °C and then transferred via cannula to a 0 °C solution of $(PhSeO)_2O$ (107.5 mg, 0.298 mmol) in 2.5 mL of THF. After 0.75 h, the mixture was diluted with EtOAc (20 mL) and poured into saturated $NaHCO_3$ (20 mL). The organic layer was washed with saturated $Na_2S_2O_3$ (15 mL) and saturated $NaHCO_3$ (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in 2.5 mL of THF, cooled to −78 °C, and treated with tBuOK (0.24 M solution in THF, 0.92 mL, 0.149 mmol). After 0.5 h, the mixture was treated AcOH (0.8 M solution in THF, 0.47 mL, 0.373 mmol) and allowed to stir for 10 min at −78 °C and then allowed to warm for 10 min. The mixture was diluted with EtOAc (40 mL) and poured into saturated $NaHCO_3$ (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography (SiO_2 [2 mL], 9:1 to 4:1 to 7:3 hexane:EtOAc), affording 19.3 mg (81%) of **104** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (app d, 2H), 7.58 (app t, 1H), 7.43 (app t, 2H), 5.56 (d, J = 6.64 Hz, 1H), 5.18 (d, J = 2.5 Hz, 1H), 4.95 (d, J = 8.2 Hz, 1H), 4.37 (dd, J = 6.8, 8.0 Hz, 1H), 4.30 (d, J = 8.4 Hz, 1H), 4.20 (d, J = 2.3 Hz, 1H), 4.15 (d, J = 8.5 Hz, 1H), 3.83 (d, J = 6.6 Hz, 1H), 2.70−2.65 (m, 1H), 2.49−2.45 (m, 1H), 2.30 (s, 3H), 2.28−2.20 (m, 1H), 1.96 (s, 3H), 1.92−1.77 (m, 2H), 1.70 (s, 3H), 1.53 (s, 1H), 1.50 (s, 1H), 1.30−1.23 (m, 1H), 1.09 (s, 3H), 1.08 (s, 3H), 0.91(t, J = 7.9 Hz), 0.60−0.48 (m, 6H); IR (film) 3455, 2956, 1727, 1452, 1370, 1271, 1248, 1107, 984, 821, 718 cm^{-1}; FAB HRMS *m/e* calcd for (M + H) $C_{35}H_{51}O_9Si_1$ 643.3303, found 643.3316.

13-Deoxy-7-*O*-TES-baccatin III (105).[46] A solution of **104** (19.3 mg, 0.03 mmol) and DMAP (1.8 mg, 0.015 mmol) in 0.2 mL of pyridine at room temperature was treated with acetic anhydride (28.3 mL, 0.3 mmol). After 16 h, the mixture was diluted with EtOAc (20 mL) and poured into saturated $NaHCO_3$ (15 mL). The organic layer was washed with saturated NaCl (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2 [2 mL], 4:1 hexane:EtOAc), affording 15.9 mg (76%) of **105** as a white solid.

13-Oxo-7-*O*-TES-baccatin III (106).[46] A solution of **105** (15.9 mg, 0.0232 mmol) in 3.5 mL of PhH was treated with NaOAc (57.1 mg, 0.696 mmol), celite (150 mg), and PCC (150 mg, 0.696 mmol). The resulting mixture was heated to reflux for 1 h. After cooling to room temperature and diluting with 4 mL of 9:1 PhH:ether, the crude reaction mixture was flushed through a plug of silica gel. Flash chromatography (SiO_2 [2 mL], 9:1 PhH:ether) afforded 10.3 mg (64%) of **106** as a white solid.

7-*O*-TES-baccatin III (107).[46] A solution of **106** (10.3 g, 0.0147 mmol) in 2.0 mL of MeOH was treated with $NaBH_4$ (10.3 mg, 0.272 mmol) every 30 min for 2 h. The reaction was quenched with NH_4Cl (4 mL) and stirred vigorously for 15 min. The mixture was diluted with EtOAc (20 mL), washed with saturated NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2 [2 mL], 7:3 hex:EtOAc) to provide 8.1 mg (79%) of **107** along with 1.1 mg (11%) of recovered **106**.

Baccatin III (1). A solution of **107** (8.1 mg, 0.012 mmol) in 0.8 mL of THF was treated with 0.1 mL of HF·pyr in a Teflon flask. After 2 h, the reaction was diluted with ether (20 mL) and extracted with saturated $NaHCO_3$ (2 × 10 mL), saturated $CuSO_4$ (10 mL), and saturated NaCl (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2 [2 mL], 7:3 hex:EtOAc) to afford 5.7 mg (85%) of **1** as a white solid. This material was identical to an authentic sample of baccatin III by TLC, ^{1}H NMR, ^{13}C NMR, IR, and optical rotation.

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(46) Compound reported by Nicolaou; see: Nicolaou, K. C.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 653−659.