The Chemistry of Taxanes: Skeletal Rearrangements of Baccatin Derivatives via Radical Intermediates

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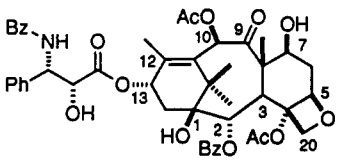
In the course of a synthetic program aimed at systematic defunctionalization of the taxol core for structure activity studies, a number of radical-based deoxygenation reactions were carried out on baccatin III derivatives. In this connection, we have discovered that formation of radicals at positions C-1, C-2, and C-7 in the taxane core of baccatin III results in a number of skeletal rearrangement cascades. Furthermore, the exact composition of the product mixture depends on the specific tin (or silicon) hydride used for the reduction. In the case of C-2- and C-7-derived radicals, direct quenching with tin hydrides without rearrangement was possible under some conditions. However, we were unable to find conditions to quench the C-1 radical, since rearrangement pathways always predominate in this case.

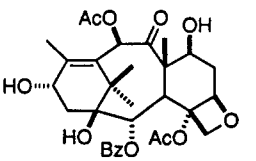
Introduction

The important antitumor diterpenoid Taxol,[2] which recently received FDA approval for the treatment of refractory ovarian cancer, has been the target of intensive synthetic[3] and structure–activity relationship (SAR) studies.[4] In order to assess the contribution of each functional group to binding at the tubulin active site, we have initiated a synthetic program aimed at the systematic deoxygenation at the various position of the taxol core (*i.e.*, C-1, C-2, C-7, and C-10). We[5,6] and others[7] have recently shown that the oxygenated functions at C-7 and C-10 contribute very little to receptor binding. On the other hand, the benzoate at C-2 of the taxol core is crucial for its biological activity.[8] In this connection, we have synthesized 7,10-dideoxytaxol by double Barton deoxygenation.[6,9]

In connection with our work on the southern portion of the core, we have attempted similar deoxygenations at C-1 and C-2. In addition to answering some key SAR questions, we have also uncovered several interesting radical rearrangement cascades. In this paper, we wish to report a full account of these reactions, initiated by radical formation at positions C-7, C-2, and C-1, respectively.



Taxol



Baccatin III

Results and Discussion

Deoxygenation at C-7/C-10. Recently, we have reported in preliminary form[6] the synthesis of 7,10-dideoxybaccatin derivative **7** along with a rearrangement product, isomer **8** (Scheme 1). Our synthesis began with 10-desacetylbaccatin (**1**), a naturally occurring taxane.[2b] This was selectively silylated at C-7 and then converted to the C-10 thionocarbonate **3**. Tributyltin hydride-mediated reduction gave **4**, which was then similarly deoxygenated at C-7 *via* xanthate **6**. The only two major products were 7,10-dideoxybaccatin **7** and isomer **8**. These were separated by semipreparative HPLC. The ratio of **7**/**8** in this case was *ca.* 2:1 and did not appreciably vary when the reaction was carried out in the temperature range 80–115 °C. In order to prevent the rearrangement and prepare **7** in higher yields for analog synthesis, we examined several deoxygenation conditions.

We felt that a higher ratio of **7**/**8** should be obtained using Ph_3SnH instead of Bu_3SnH. There are precedents in the literature supporting this hypothesis. In general, when radical rearrangements are possible, these are usually minimized by using Ph_3SnH, which is a better hydride donor than Bu_3SnH.[10] On the other hand, a lower ratio of **7**/**8** should be observed when tris(trimethylsilyl)silane was used as the reducing agent because of the higher

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(2) Taxol is a registered trademark of the Bristol-Myers Squibb company. For a recent review on the medicinal chemistry of Taxol, see: Kingston, D. G. I. *Phar. Ther.* **1991**, *52*, 1.

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(4) (a) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114. (b) Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.* **1991**, *34*, 1176. (c) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823. (d) Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1751. (e) Klein, L. L. *Tetrahedron Lett.* **1993**, *34*, 2047. (f) Chaudhary, A. G.; Kingston, D. G. I. *Tetrahedron Lett.* **1993**, *34*, 4921. (g) Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160. (h) Guéritte-Voegelein, F.; Guénard, D.; Lavelle, F.; Le Goff, M-T.; Mangatal, L.; Potier, P. *J. Med. Chem.* **1991**, *34*, 992. (i) Chen, S. H.; Huang, S.; Wei, J. M.; Farina, V. *J. Org. Chem.* **1993**, *58*, 4520. (j) Chen, S. H.; Huang, S.; Wei, J. M.; Farina, V. *Tetrahedron* **1993**, *49*, 2805.

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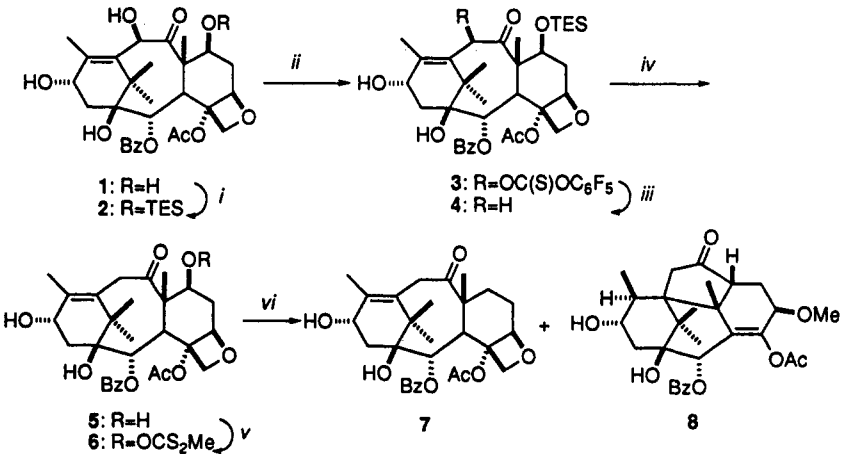
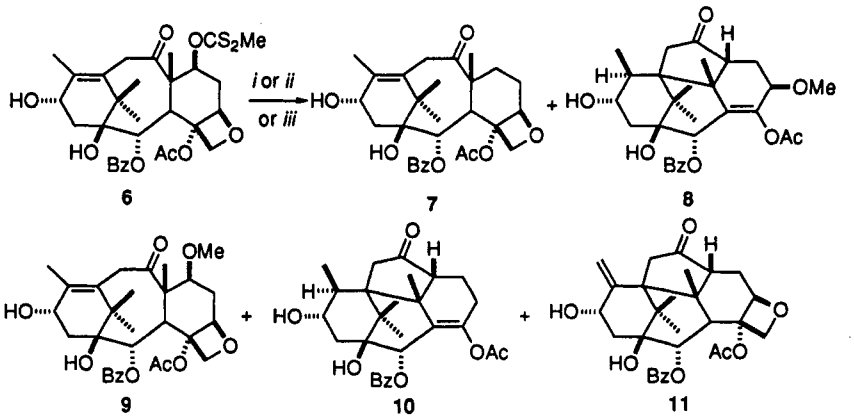
Scheme 1[a]



[a] Conditions: (i) TESCl/imidazole/DMF/0 °C (84%); (ii) BuLi/THF/−40 °C, then $F_5C_6OC(S)Cl$ (74%); (iii) Bu_3SnH/AIBN/PhMe/90 °C (99%); (iv) TBAF/THF/0 °C, (77%); (v) NaH/THF/CS_2, then MeI, rt (77%); (vi) Bu_3SnH/AIBN/PhMe/80 °C, 7 (52%); 8 (25%).

Scheme 2[a]



[a] Conditions: (i) Bu_3SnH/AIBN/PhMe/80 °C; (ii) Ph_3SnH/AIBN/PhMe/80 °C; (iii) $(TMS)_3SiH$/AIBN/PhMe/90 °C; for product distribution, see Table 1.

bonding energy of its hydrogen–silicon bond (5 kcal/mol higher than that of Bu_3SnH).[11]

Much to our surprise, when Ph_3SnH was used as the reducing agent, in addition to 7 and its isomer 8 (ratio, ca. 3:1), methyl ether 9 was also isolated in 30% yield; on the other hand, when $(TMS)_3SiH$ was employed as the reducing agent, in addition to compound 8, two new products, i.e., tetracyclic C-4 enol acetate 10 and C-12 exomethylene derivative 11, were also isolated (Scheme 2).

The structures of compounds 8, 10, and 11 were established on the basis of extensive NMR analysis.[12] The product distributions obtained with each reducing agent are listed in Table 1. In all three cases, the initial substrate concentration was 0.05 M, and the solvent used was carefully degassed with dry nitrogen prior to use. The formation of rearranged products 8, 10, and 11 can be readily rationalized by invoking a cascade of radical rearrangements (Scheme 3).

Table 1. Product Distribution (Isolated Yields, %) in the Radical Deoxygenation of 6 with Various Hydrides (Scheme 3)

reducing agent	7	8	9	10	11
Bu_3SnH	52	25			
Ph_3SnH	30	10	30		
$(TMS)_3SiH$[a]		19		19	2

[a] Only 46% conversion was observed under these conditions.

The initially formed radical 12, a β-keto radical,[13] can isomerize *via* alkoxy radical 13 to the isomeric 14. This places the radical-bearing C-8 at a close distance to the C-11/C-12 double bond, and a 5-exo cyclization[14] to 15 occurs. Surprisingly, this radical is not at all quenched by hydride, perhaps due to the hindered nature of the radical-bearing carbon. The major pathway for radical 15 is the remote intramolecular hydrogen abstraction from C-3, as in our recently published photochemical rearrangement,[15] to yield 16. Dreiding models of 15 confirm that H-3 is

(11) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

(12) Connectivity was established by standard H–H and C–H correlation. The stereochemistry at C7, C-8, and C-12 was demonstrated by NOE experiments. Especially diagnostic is the singlet in the ^1H NMR spectrum for H-2 (indicating H-3 is missing), the olefinic nature of C-4 and C-3 for compound 8 (δ 143.0 and 126.2, respectively), and the C–H three-bond couplings between H-19 and C-11 and between H-12 and C-8. Proton–proton coupling constants of 8 and NOE data are shown in the supplementary material.

(13) (a) Beckwith, A. L. J.; Duggan, P. J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1777 and references cited therein. (b) Dowd, P.; Choi, S. C. *Tetrahedron* **1992**, *48*, 4773. (c) Bowman, W. R.; Westlake, P. J. *Tetrahedron* **1992**, *48*, 4027. (d) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1990**, *55*, 5442. (e) Baldwin, J. E.; Adlington, R. M.; Kang, T. W.; Lee, E.; Schofield, C. J. *J. Chem. Soc., Chem. Commun.* **1987**, 104.

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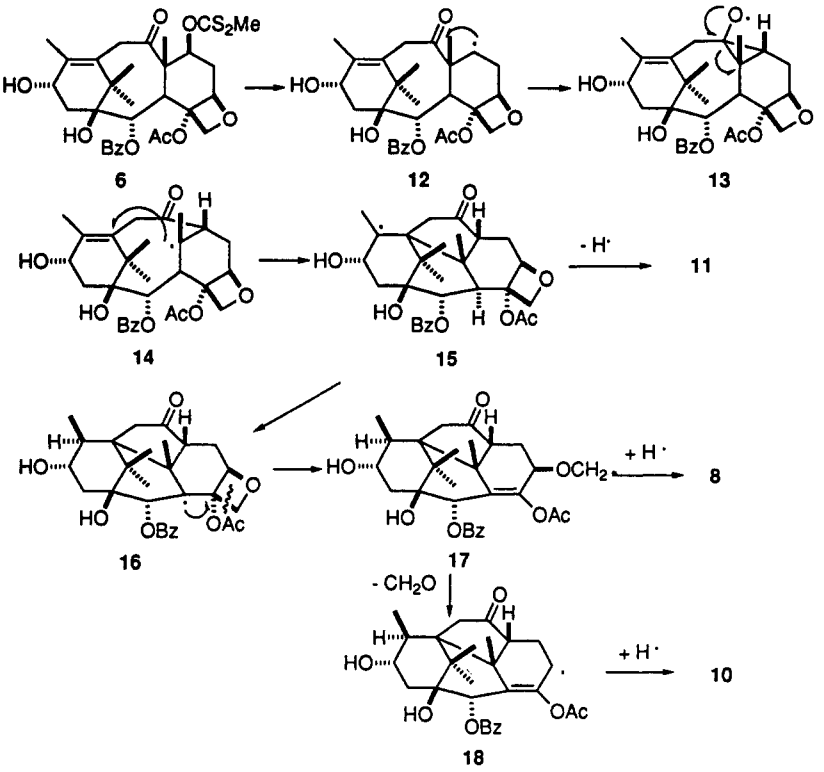
Scheme 3



extremely close to C-12, and the pathway of hydrogen transfer can almost achieve linearity, as required for a facile translocation.[16]

Radical **15** also suffers a disproportionation to give the minor product **11** when $(TMS)_3SiH$ was employed as hydrogen donor. This is a very unusual product in a hydride reduction. Disproportionation, *i.e.*, reaction with a second radical to yield two neutral molecules, is common especially in the thermolysis or photolysis of peroxo compounds.[17] Here the formation of **11** may be aided, once again, by the hindrance to hydrogen delivery at C-12 and by the ease with which the system can present a coplanar hydrogen (at the methyl group) to the radical center, as is needed for hydrogen abstraction by (presumably) the $(TMS)_3Si$ radical.[18]

Radical **16**, produced by intramolecular hydrogen transfer, is evidently also sterically hindered and undergoes an unusual oxetane fragmentation reaction, analogous to the one recently "clocked" by Nonhebel and Walton.[19] These authors measured a rate of opening of $8.9 \times 10^2\ s^{-1}$, a rate much slower than that of the oxiranylmethyl radical and even slower than that of the cyclobutylmethyl radical.[20] This suggests that it is the hindered nature of the radical-bearing carbon in **16** that prevents trapping by hydride and accounts for the formation of **8**, although there may be structural factors that promote the oxetane fragmentation in this particular system. The resulting α-alkoxy radical, **17**, is then trapped by tributyltin or triphenyltin hydride to give **8**. When the reducing agent employed was tributyltin deuteride, the product was specifically labeled only at the C-5 methoxy group. However, in the case of $(TMS)_3SiH$ reduction, in addition to **8**, alkoxymethyl radical fragmentation,[21] with loss of formaldehyde, led to allylic radical **18**, presumably due to slow trapping of **17** by the rather unreactive silane reagent. After this cascade of six sequential intramolecular reactions, radical **18** was finally quenched by silane to give compound **10**.

The proposed mechanism for the C-7 methyl ether formation is shown in Scheme 4. According to the mechanism proposed by Barton for the deoxygenation reaction,[22] addition of the triphenyltin radical onto xanthate **6** led to the unstable intermediate **19**. Usually, this radical undergoes a β-scission to afford C-7 radical **12**, as shown in Scheme 3. However, the highly reactive hydrogen donor triphenyltin hydride was able to trap **19** to form **20**. This suffered elimination of triphenyltin thiomethoxide to give C-7 thionoformate **21**. Further reduction by excess triphenyltin hydride gave thioacetal **23**, which was finally converted to the methyl ether **9** via another carbon–sulfur bond cleavage reaction. This uncommon reaction pathway, involving intermediates such as thionoformate **21** and monothioacetal **23**, was in part reported by Barton[23] and more recently by Pradham[24] and Bowman.[25] The cleavage of the carbon–sulfur bond in thiols by alkyltin hydride is also precedented.[26]

Interestingly, when the 7-xanthate derivative of baccatin was employed in the reaction with tributyltin hydride, only clean deoxygenation at C-7 was observed. No

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(18) Agosta, W. C.; Wolff, S. *J. Am. Chem. Soc.* **1976**, *98*, 4316; **1977**, *99*, 3355.
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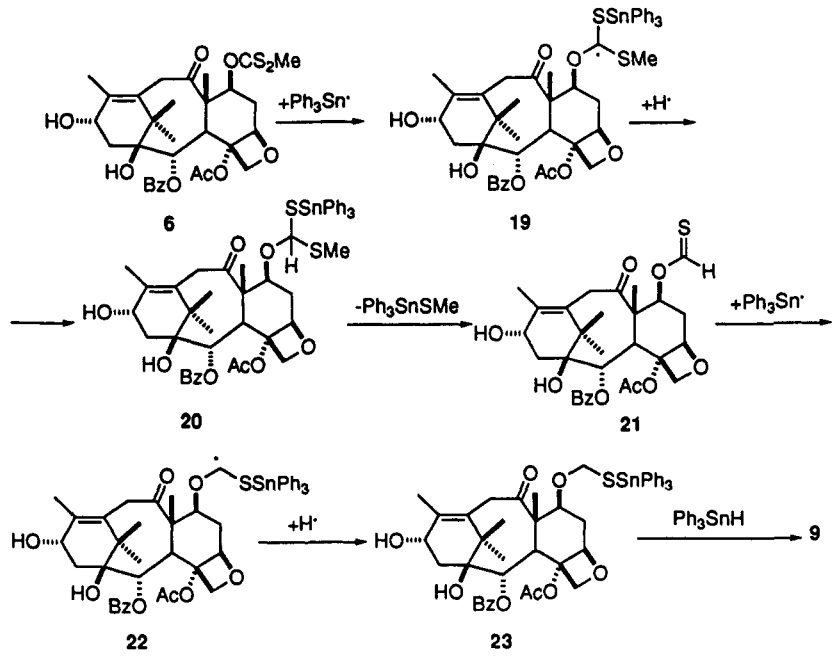
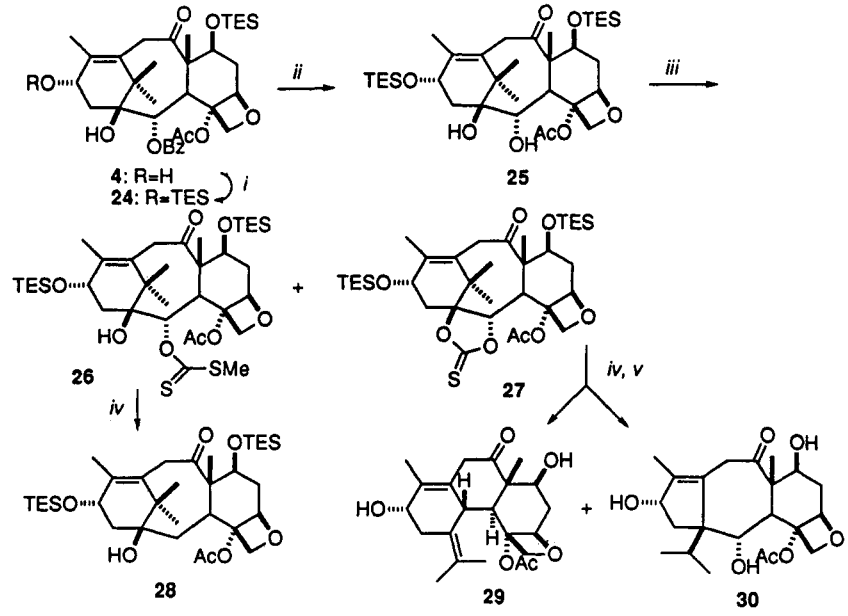
Scheme 4



Scheme 5[a]



[a] Conditions: (i) TESCl/imidazole/DMF, rt (74%); (ii) Red-Al/THF/0 °C (78%); (iii) NaH/THF/CS_2, rt, then MeI, **26** (41%) and **27** (53%); (iv) Bu_3SnH/AIBN/Toluene/100 °C, from **26** to **28** (77%); (v) TFA/THF/H_2O, two steps from **27** to **29** (42%) and **30** (8%).

rearranged products analogous to **8** or **10** were detected.[6] We also note that when 7,10-dideoxybaccatin was made directly by high-temperature deoxygenation of baccatin C-7 methyl xanthate, presumably *via* 7-deoxy-10-acetylbaccatin, no such skeletal rearrangement was observed.[9] From Dreiding models, it appears that the C-10 acetate group might increase steric interactions in the transition state leading to the ring closure reaction that affords the tetracyclic product. Although the exact nature of this effect in not certain, this intriguing phenomenon is once again an illustration of the subtleties one encounters in taxane chemistry.

Deoxygenation at C-1/C-2. Recently, we have published a synthesis of 2-deoxytaxol, in which we used a C-2 xanthate of baccatin as the precusor.[8] In the same study, we reported the preparation of a C-1,2 cyclic thiocarbonate (**34**), an inevitable side product in the preparation of the C-2 xanthate.[8] During our efforts toward the synthesis of C-2,C-10-dideoxytaxol,[27] a similar cyclic thiocarbonate **27** (Scheme 5) was also obtained, along with the desired 2-xanthate **26**, when **25** was treated with base and carbon disulfide, followed by methyl iodide. We immediately recognized that **27** was an interesting substrate on which to study the possibility of deoxygenating the C-1 position of taxol, with the ultimate aim of preparing C-1 deoxytaxol.

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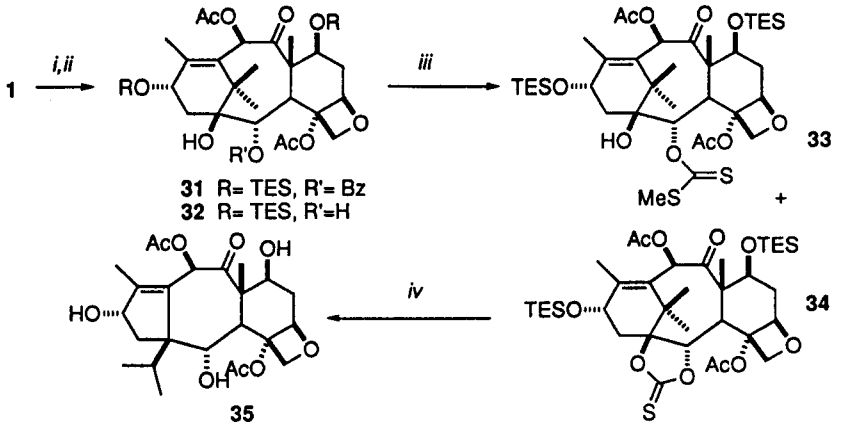
(27) Chen, S. H. Unpublished results.

Scheme 6[a]



[a] Conditions: (i) TESCl/imidazole/rt (90%); (ii) Red-Al/THF/0 °C (87%); (iii) NaH/THF/CS_2 (5:1), then MeI, rt (61% of **33**; 21% of **34**); (iv) Bu_3SnH/AIBN/toluene/90 °C; then TFA/THF/H_2O (21%).

Several years ago, Barton[28] reported that tributyltin hydride-mediated deoxygenation of certain nonsymmetrical diol thiocarbonates proceeded regioselectively to introduce hydride at the more substituted carbon, because production of the more stable radical is preferred. On the other hand, recent examples of altered selectivity have been reported, showing competitive formation of both secondary and tertiary radical from the same cyclic thiocarbonate.[29] More recently, Ziegler demonstrated the subtle role of bond angle strain energy in directing selective formation of primary radicals (over secondary) in a number of cyclic 1,3-diol thiocarbonates.[30] Given these interesting precedents, we carried out deoxygenation studies on substrates **26**, **27**, and **34**.

The synthesis of **26** and **27** (Scheme 5) began with 10-deoxybaccatin derivative **4**. Standard silylation followed by Red-Al mediated regioselective C-2 deacylation[31] afforded **25** in good overall yield. Treatment of **25** with sodium hydride in the presence of carbon disulfide and methyl iodide thus afforded a mixture of **26** and **27**, which were separated by flash chromatography. The analogous 1,2-thiocarbonate **34** was prepared in similar fashion,[8] as illustrated in Scheme 6.

The deoxygenation of xanthate **26** with 2 equiv of tributyltin hydride in toluene proceeded very smoothly to give the desired 2,10-dideoxybaccatin derivative **28**, in analogy with the behavior of congener **33**.[8]

However, treatment of cyclic thiocarbonate **27** with tributyltin hydride and AIBN in toluene failed to give the expected 2,10-dideoxybaccatin **28**, the product from the C-2/O bond cleavage reaction. Instead, after treatment of the crude product with trifluoroacetic acid in aqueous tetrahydrofuran, two new products, **29** (major) and **30** (minor), were isolated (Scheme 5). Inspection of the ^{1}H-NMR spectrum clearly revealed that both compounds had been produced by skeletal rearrangement. Their structure was secured by extensive NMR analysis and confirmed by X-ray crystallography. Similarly, treatment of 1,2-thiocarbonate derivative **34** with tributyltin hydride under identical conditions yielded a complex mixture of products, from which only **35** could be isolated in low yield after standard desilylation (Scheme 6).

A mechanistic rationale for the observed products is presented in Scheme 7. The initial adduct resulting from addition of the tributyltin radical to **27** apparently led to both of the two conceivable cleavage products, *i.e.*, radicals **36** and **37**. One may speculate that intermediate radical **36** is hindered by the presence of its neighboring bulky tributyltin thiocarbonate residue at C-1, and consequently, it is not rapidly trapped by tin hydride to give the corresponding C-2 deoxy analog, which was the observed pathway in the clean deoxygenation of **26**. Therefore, intramolecular processes, as already seen for the C-7 radical, take over: **36**, a 4-pentenyl-type radical, undergoes a thermodynamically unfavorable and quite unusual 4-exo cyclization to the cyclobutylcarbinyl radical **38**. The rate for this process has been estimated at *ca.* 1.0 s^{-1} at 60 °C,[32] although it is likely that the steric constraints imposed by the bridged nature of the system have an appreciable effect on this value (*i.e.*, entropic factors may favor the cyclization, although inspection of Dreiding models suggests that **38** is extremely strained). In any case, it is very surprising that this rearrangement can compete with intermolecular trapping of **36** by tin hydride. Increasing the concentration of tin hydride in the reaction failed to prevent formation of this product.

As the cyclobutylcarbinyl radical is highly unstable,[32] rapid opening with concomitant β-elimination evidently ensues, as **38** is not trapped by hydride but selectively affords tricyclic diene **40** and, after desilylation, **29**.

Radical formation at C-1 is apparently also taking place: radical **37** undergoes a cyclopropylcarbinyl rearrangement[32] to yield, following hydrolytic deprotection, A ring-contraction product **30**. This type of skeleton has also been obtained by acid-promoted rearrangement.[4a,h,33]

Trapping of the postulated C-1 radical by running the reaction in neat tributyltin hydride failed to produce any 1-deoxygenated product, and in fact, **29** and **30** were the only isolable products.

The ratio of **29**:**30** (*ca.* 5:1) clearly indicates that the initial C–O bond cleavage at C-2 is preferred, which is

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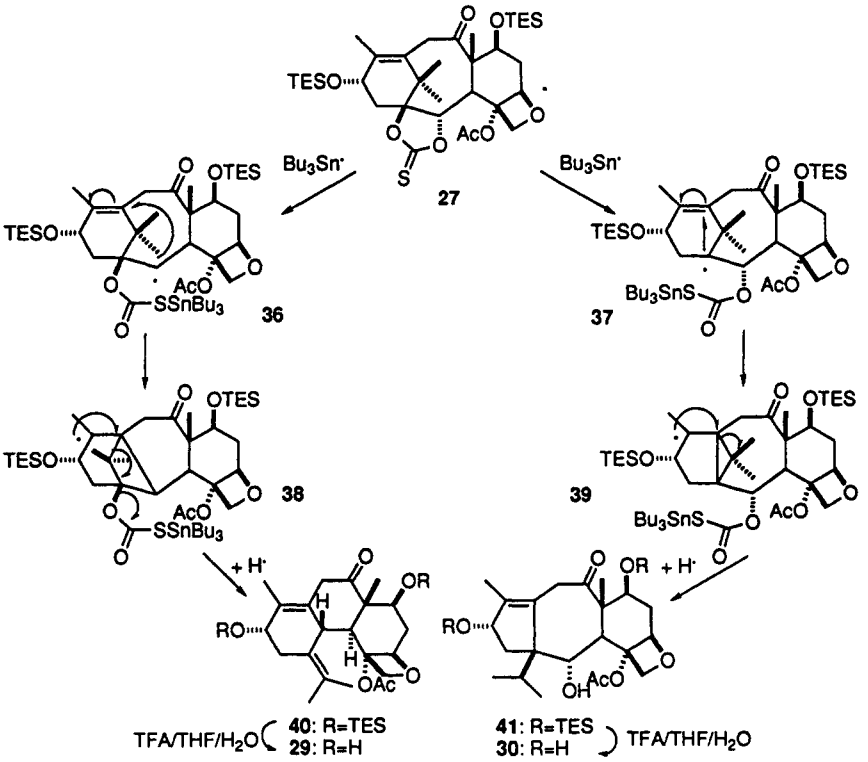
(33) Wahl, A.; Guéritte-Voegelein, F.; Guénard, D.; Le Goff, M. T.; Potier, P. *Tetrahedron* **1992**, *48*, 6965.

Scheme 7



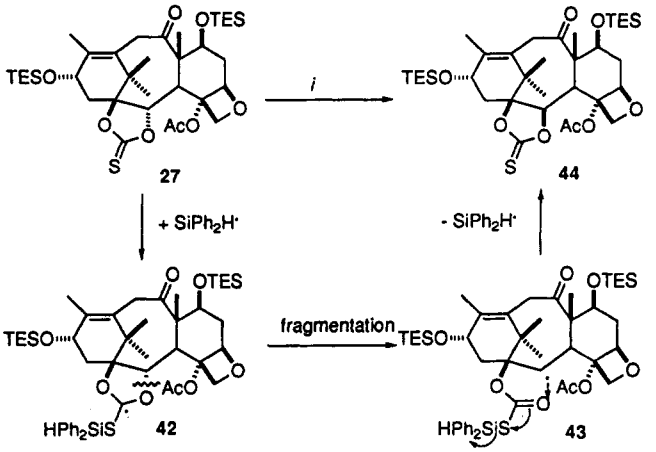
somewhat surprising. On the other hand, the tertiary radical at C-1 is at a bridgehead position and therefore pyramidalized, and this may contribute to steer the reaction toward C-2/O bond cleavage. In addition, one cannot exclude that factors such as bond angle strain, invoked previously by Ziegler,[30] may also play a role.

In order to further probe this class of interesting radical-initiated rearrangements, triphenyltin hydride and diphenylsilane were employed as the reducing agents. We reasoned that triphenyltin hydride should trap the initially formed radicals more efficiently because it is a better hydride donor.[10] This should suppress (or diminish) the formation of rearranged product. On the other hand, the use of diphenylsilane, a poorer hydride donor,[34] may lead to more extensive rearrangements.

Surpringly, treatment of C-1/C-2 *trans* cyclic thiocarbonate **27** with diphenylsilane and AIBN at 100 °C in toluene led to a clean isomeric product, the *cis* thiocarbonate **44**. The possibility of a third isomer featuring a C-2/S bond nature[29] was discounted by comparing the ^{13}C chemical shift of the relevant thiocarbonyls (δ 190 ppm in both cases), showing that both **27** and **44** possess a C=S moiety and not a carbonyl.

Mechanistically, the formation of **44** can be rationalized by invoking the initial formation of monothioacetal radical **42**, followed by fragmentation, affording **43**. Apparently, the C-2 radical, in preference to skeletal rearrangement or intermolecular quench, can rapidly attack the oxygen carbonyl in **43** and afford *cis*-1,2-thiocarbonate **44** (Scheme 8). The incomplete conversion (38% starting material was isolated) observed in this reaction may be due to the relatively short silane radical chain.[34b] On the other hand, this final conversion may simply reflect the equilibrium composition for **27** and **44**. It is quite difficult to explain

Scheme 8[a]



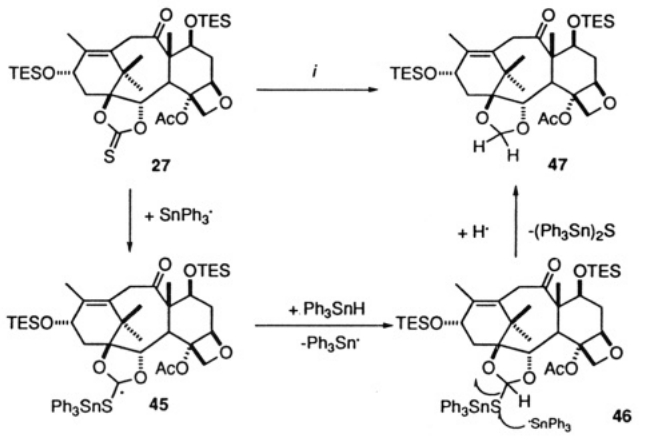
[a] Conditions: (i) Ph_2SiH_2/AIBN/toluene, 100 °C, **44** (31%); recovered **27** (38%).

why formation of **40** is not seen here or why **44** is not encountered in the reaction with tributyltin hydride. When **44** was treated with tributyltin hydride under the usual conditions, no reaction was observed. This unexpected reaction provides an interesting method for stereochemical inversion at C-2 of the taxol core.

We next turned to the examination of the reaction of **27** with triphenyltin hydride. As can be seen from Scheme 9, the initial intermediate radical **45** was trapped by this highly reactive hydride donor, much as in the formation of **9**, giving **46**. The C–S bond was further reduced by another molecule of triphenyltin hydride, affording **47**, which features a methylenedioxy moiety. It is important to note that no C–O bond cleavage (either at C-1 or C-2) was observed under these reaction conditions. Evidently, triphenyltin hydride is such a good hydride donor that not only skeletal rearrangement is prevented but even the usual C–O fragmentation process is circumvented.

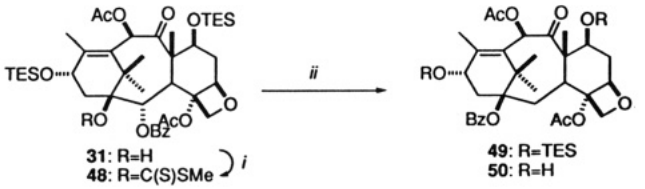
(34) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 4681. (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1993**, *49*, 2793.

Scheme 9[a]



[a] Conditions: (i) Ph_3SnH/AIBN/toluene, 100 °C (%).

Scheme 10[a]



[a] Conditions: (i) NaH/CS_2/THF/80 °C (56%); (ii) Bu_3SnH/AIBN/toluene/80 °C (84%).

In the course of our continued efforts to prepare C-1 deoxygenated analogs of baccatin and taxol, we have been able to prepare the novel C-1 xanthate of baccatin **48** (Scheme 10). This was obtained by submitting **31** to forcing conditions (NaH, CS_2 at 80 °C). *To the best of our knowledge, this is the first stable C-1 derivative of a taxane reported so far in the literature.* Unfortunately, treatment of xanthate **48** with tributyltin hydride under standard conditions led to the novel 1-benzoyl-2-deoxy derivative **49** in high yield. None of the expected C-1 deoxy product was isolated. The same product was obtained when the more reactive reducing agent triphenyltin hydride was employed. This indicates that the 1,2 acyl group migration[35] is much faster than both radical rearrangements initiated at C-1 and C-2 (Scheme 7), as well as direct C-1 radical trapping. Once again, this would not be predictable on the basis of published data. Indeed 1,2 acyl shifts should be 1 order of magnitude slower than ring closure to a cyclopropylcarbinyl radical.[32,36] This procedure, therefore, provides a novel and unexpected route to C-2 deoxy derivatives but once again underlines the synthetic difficulties associated with deoxygenation at C-1.

Our experiments, in addition to providing an illustration of the different reactivity of several radical deoxygenation reagents, nicely highlight a variety of intramolecular radical rearrangements, some of rather unusual types, and one (the oxetane fragmentation) of completely novel nature at the time of our first publication.[6] It is perhaps ironic that the C-11/C-12 double bond of the taxanes, notoriously impervious to a variety of reagents, seems to be an excellent radical trap in an intramolecular sense. Our skeletal rearrangements have implicated this double bond in 3-exo,

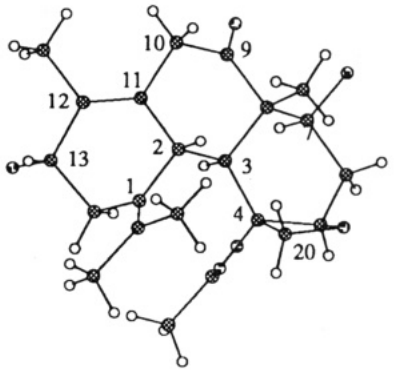


Figure 1. X-ray structure of **29**.

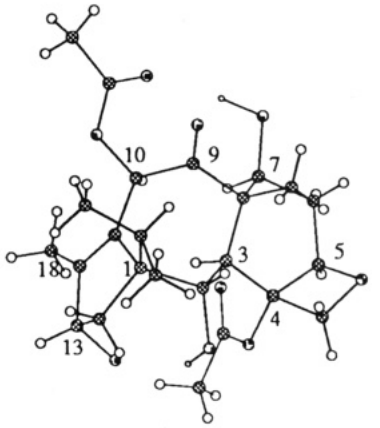


Figure 2. X-ray structure of **35**.

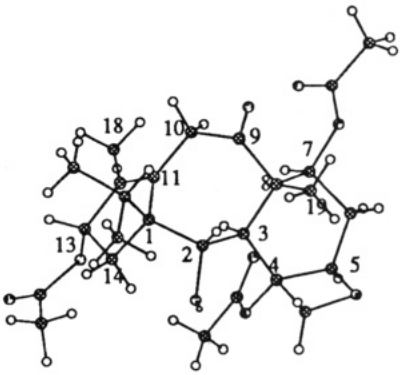


Figure 3. X-ray structure of the 7,13 diacetate of **30**.

4-exo, and 5-exo ring closures involving positions C-1, C-2, and C-7 of the baccatin core. The skeletal rearrangements of the taxol core presented here can be added to the already rich repertory of rearrangements discovered so far.[4a,j,33,37]

The structures of ring-rearranged products **29**, **35**, and the C-7/ C-13 diacetate of **30** were confirmed by X-ray analysis. The structures of these compounds are represented above. Figure 1 clearly shows the three fused six-membered A–B–C rings and the *trans* relation between H_2 and H_3. In Figures 2 and 3, the contracted five-membered A ring, the seven-membered B ring, and the (β) C-1 isopropyl group are also shown.

Experimental Section

Dichloromethane was distilled from calcium hydride. Anhydrous pyridine and methanol were obtained from Aldrich and

(35) Beckwith, A. L. J.; Duggan, P. J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1777 and references cited therein.
(36) Beckwith, A. L. J.; Tindal, P. K. *Aust. J. Chem.* **1971**, *24*, 2099.
(37) (a) Farina, V.; Huang, S. *Tetrahedron Lett.* **1992**, *33*, 3979. (b) Py, S.; Khuong-Huu, F. *Bull Soc. Chim. Fr.* **1993**, *130*, 189.

used directly. Nuclear magnetic resonance (NMR) data were obtained on a Bruker AC-300 (at 300 MHz for ^1H and 75.5 MHz for ^{13}C). Long-range carbon–proton couplings were determined by the HMBC technique of Bax and Summers.[34] Carbon-NMR spectra were partially assigned with the aid of INEPT and HETCOR experiments. Accurate mass measurements were obtained with a Kratos MS50RF mass spectrometer in the positive-ion FAB mode, with *m*-nitrobenzyl alcohol as the matrix. Sodium iodide and/or potassium iodine were added when Na(K) adducts were determined. Preparative silica chromatography was carried out according to Still.[35] X-ray diffraction data were collected on an Enraf-Nonius CAD4 Diffractometer at room temperature.

Preparation of Compound 3. Compound **2** (319 mg, 0.485 mmol) was dissolved in dry THF (5 mL), cooled to −40 °C, and treated with *n*-butyllithium (1.58 M in hexanes, 0.384 mL, 0.606 mmol). After 40 min at this temperature, pentafluorophenyl chlorothionoformate (0.086 mL, 0.536 mmol) was added neat by syringe. The reaction was stirred at −20 °C for 90 min and then quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated and the residue chromatographed (silica, 40% ethyl acetate in hexane) to afford **3** as a foam (320 mg, 74%): ^1H NMR ($CDCl_3$) δ 8.09 (d, 2H), 7.56 (t, 1H), 7.44 (m, 2H), 6.78 (s, 1H), 5.64 (d, J = 6.9 Hz, 1H), 4.96–4.89 (m, 2H), 4.49 (dd, J = 10.2 Hz, J' = 6.6 Hz, 1H), 4.12 (AB q, 2H), 3.80 (d, J = 6.9 Hz, 1H), 2.55–0.44 (m, 43H); ^{13}C NMR ($CDCl_3$) δ 199.6, 190.7, 170.7, 167.1, 146.7, 133.7, 130.9, 130.1, 129.3, 128.6, 87.3, 84.1, 80.8, 78.7, 74.5, 72.2, 67.9, 60.4, 59.0, 47.4, 42.9, 38.1, 37.2, 26.4, 22.7, 21.0, 20.1, 16.1, 14.2, 10.1, 6.7, 5.8, 5.3; HRMS calcd for $C_{42}H_{50}F_5O_{11}SSi$ (MH^+) 885.2763, found 885.2742.

Preparation of 10-Deoxybaccatin (5). Thionocarbonate **3** (119 mg, 0.135 mmol) was dissolved in dry toluene (3 mL) and treated with AIBN (2 mg). The solution was degassed with dry nitrogen, and then tributyltin hydride (0.055 mL, 0.202 mmol) was added and the solution was heated for 1 h (90 °C). Solvent evaporation and chromatography (silica, 40% ethyl acetate in hexane) gave a colorless foam **4** (87 mg, 99%). This foam (60 mg, 0.094 mmol) was dissolved in acetonitrile (2 mL), and the solution was cooled to −10 °C. Concentrated HCl (36%, 0.030 mL) was added, and the solution was stirred for 30 min. The mixture was diluted with ethyl acetate (40 mL), washed with saturated aqueous sodium bicarbonate and brine, dried, and concentrated. The residue was purified by flash chromatography (70% ethyl acetate in hexane) to afford desilylated 10-deoxybaccatin (**5**) as a foam (37.5 mg, 76% yield): ^1H NMR ($CDCl_3$) δ 8.10 (d, J = 7.3 Hz, 2H), 7.60 (m, 1H), 7.45 (m, 2H), 5.64 (d, J = 6.9 Hz, 1H), 4.97 (br d, J = 9.4 Hz, 1H), 4.81 (br t, 1H), 4.36–4.28 (m, 2H), 4.17–4.07 (m, 3H), 3.82 (d, J = 15.6 Hz, 1H), 3.43 (br d, J = 15.6 Hz, 1H), 2.60 (m, 1H), 2.28–1.73 (m, 14 H, incl. singlets at 2.27, 1.93, 1.62, 3H each), 1.11 (s, 3H), 1.04 (s, 3H); HRMS calcd for $C_{29}H_{37}O_9$ (MH^+) 529.2438, found 529.2432.

Preparation of 10-Deoxybaccatin 7-Xanthate (6). 10-Deoxybaccatin (**5**) (75 mg, 0.142 mmol) was dissolved in dry THF (2 mL) and carbon disulfide (0.5 mL). Sodium hydride (60% in mineral oil, 8.5 mg, 0.213 mmol) was then added, and the mixture was stirred at rt for 2 h. Iodomethane (0.026 mL, 0.426 mmol) was added, and the reaction was allowed to proceed overnight. The solvent was then removed and the residue chromatographed (50–70% ethyl acetate in hexane) to give **6** as a foam (46.4 mg, 53% yield): ^1H NMR ($CDCl_3$) δ 8.10 (d, J = 7.3 Hz, 2H), 7.59 (m, 1H), 7.44 (m, 2H), 6.44 (dd, J = 10.4 Hz, J' = 7.3 Hz, 1H), 5.63 (d, J = 6.8 Hz, 1H), 4.97 (br d, J = 9.4 Hz, 1H), 4.78 (br t, 1H), 4.31 (d, J = 8.4 Hz, 1H), 4.26 (d, H = 6.8 Hz, 1H), 4.13 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 15.4 Hz, 1H), 3.35 (br d, J = 15.4 Hz, 1H), 2.55 (m, 1H), 2.49 (s, 3H), 2.28 (m, 14 H, incl. singlets at 2.27, 1.95, 1.83, 3H each), 1.01 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.4, 170.9, 167.0, 137.6, 133.7, 132.0, 130.1, 129.3, 128.6, 125.0, 83.9, 80.5, 78.7, 76.5, 74.7, 67.9, 58.4, 46.7, 45.8, 43.5, 38.8, 32.2, 32.1, 29.7, 26.4, 25.7, 23.4, 22.6, 22.3, 18.4, 15.2, 11.7; HRMS calcd for $C_{31}H_{39}O_9S_2$ (MH^+) 619.2036, found 619.2017.

Reduction of 10-Deoxybaccatin 7-Xanthate (6) via Tributyltin Hydride. Xanthate **6** (36 mg, 0.058 mmol) was refluxed in benzene (1 mL) in the presence of AIBN (2 mg) and tributyltin hydride (0.079 mL, 0.290 mmol) under an argon atmosphere for 3 h at 80 °C. Evaporation and flash chromatography (40% ethyl acetate in hexanes) followed by HPLC separation (Beckman HPLC system (pump: 126 and detector: 166) together with the column (Dynamax-60A-Si) were used for this separation) from **7** (7.6 mg, 25%) afforded **8** as a foam (15.6 mg, 52%). **7**: ^1H NMR ($CDCl_3$) δ 8.10 (d, J = 7.3 Hz, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.62 (d, J = 7.2 Hz, 1H), 4.94 (br d, 1H), 4.79 (br s, 1H), 4.29 (d, J = 8.0 Hz, 1H), 4.18 (d, J = 8.0 Hz, 1H), 4.09 (d, J = 7.2 Hz, 1H), 3.83 (d, J = 16.2 Hz, 1H), 3.34 (br d, J = 16.2 Hz, 1H), 2.35–1.40 (m, 17H, incl. singlets at 2.27, 1.90, 1.67, 3H each), 1.06 (s, 3H), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 207.3, 170.6, 167.2, 136.3, 133.5, 132.3, 130.1, 129.6, 128.6, 125.0, 84.5, 82.1, 79.1, 76.8, 76.0, 67.8, 55.0, 45.1, 44.8, 43.2, 39.1, 34.9, 32.2, 27.1, 26.4, 25.3, 22.7, 15.1, 14.5; HRMS calcd for $C_{29}H_{37}O_8$ (MH^+) 513.2488, found 513.2502.

Compound **8** was further derivatized as its C13 acetate (Ac_2O/Et_3N/CH_2Cl_2/0 °C) for characterization. The proton and carbon NMR data are reported below. C_{13}-Acetate of **8**: ^1H NMR ($CDCl_3$) δ 8.05–8.02 (m, 2H), 7.49–7.25 (m, 3H), 6.01 (s, 1H), 4.94 (m, 1H), 3.77 (m, 1H), 3.24 (s, 3H), 2.75–0.96 (m, 22H, including singlets at 2.06, 1.69, 1.38, 1.26, 3H each, 1.00, 6H); ^{13}C NMR ($CDCl_3$) δ 219.0, 171.7, 168.6, 165.8, 143.0, 133.5, 130.0, 129.7, 128.7, 126.2, 79.1, 76.1, 75.5, 75.0, 56.9, 53.6, 53.1, 51.0, 43.6, 43.0, 39.6, 37.3, 32.9, 28.8, 24.9, 22.7, 21.2, 20.5, 20.3; HRMS calcd for $C_{29}H_{37}O_8$ (MH^+) 513.2488, found 513.2492.

Reduction of 10-Deoxy 7-Xanthate 6 via Triphenyltin Hydride. Compound **6** (162.8 mg, 0.260 mmol) was dissolved in dry benzene (3 mL), and a catalytic amount of AIBN was added. This solution was then degassed with dry nitrogen. Triphenyltin hydride (273.8 mg, 0.780 mmol) was added, and the reaction mixture was heated at 80 °C. After 2.5 h, the reaction mixture was subjected to silica gel chromatography (40–55% ethyl acetate in hexane) to afford a 3:1 mixture of **7** and **8** (53.6 mg, 44%) together with 34 mg (30%) of **9**. Compound **7** was further separated from **8** via preparative HPLC. **9**: ^1H NMR ($CDCl_3$) δ 8.10–8.08 (d, 2H), 7.59–7.44 (m, 3H), 5.58 (d, J = 6.8 Hz, 1H), 4.99 (d, J = 8.2 Hz, 1H), 4.81 (m, 1H), 4.21 (AB q, J = 8.3 Hz, 2H), 4.12 (d, J = 6.7 Hz, 1H), 4.00 (dd, J = 6.6 Hz, J' = 10.6 Hz, 1H), 3.73 (d, J = 15.0 Hz, 1H), 3.41 (d, j = 15.0 Hz, 1H), 3.31 (s, 3H), 2.73–1.03 (m, 19H, incl. singlet at 2.28, 1.98, 1.64, 1.13, 1.04, 3H each); ^{13}C NMR ($CDCl_3$) δ 207.6, 170.8, 166.8, 136.5, 133.4, 132.5, 129.9, 129.6, 129.3, 128.4, 84.1, 81.3, 80.0, 78.7, 74.7, 67.8, 59.0, 57.1, 47.2, 45.2, 43.6, 38.7, 32.1, 25.8, 22.7, 22.2, 14.8, 10.6; HRMS calcd for $C_{30}H_{39}O_9$ (MH^+) 543.2594, found 543.2582.

Reduction of 10-Deoxy 7-Xanthate (6) via Tris(trimethylsilyl)silane. Compound **6** (108 mg, 0.175 mmol) and a catalytic amount of AIBN were dissolved in dry toluene (2.5 mL). This solution was carefully degassed with dry nitrogen. Tris(trimethylsilyl)silane (0.27 mL, 0.874 mmol) was added. The reaction mixture was heated at 80 °C for 2.5 h, and this mixture was then subjected to silica gel chromatography (40–50–60% ethyl acetate in hexanes) to afford 50 mg (46%) of the unreacted starting material **6** and a 1:1 mixture of **8** and **10** (34 mg, 38%) plus 2% of **11**. Compound **8** was further separated from **10** via preparative HPLC (Beckman HPLC system (pump: 126 and detector: 166) together with the column (Dynamax-60A-Si) were used for this separation). **10**: ^1H NMR ($CDCl_3$) δ 8.09–8.06 (m, 2H), 7.64–7.46 (m, 3H), 6.03 (m, 1H), 3.76 (m, 1H), 3.35 (d, J = 12.2 Hz, 1H), 2.55 (AAB q, J = 16.7 Hz, 2H), 2.46–1.90 (m, 7H), 1.79 (m, 1H), 1.64 (s, 3H), 1.42 (s, 3H), 1.25 (s, 3H), 1.13 (d, J = 7.3 Hz, 3H), 0.946 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 218.4, 171.4, 166.0, 140.9, 133.7, 129.7, 128.8, 123.5, 79.5, 75.3, 72.4, 57.0, 53.1, 50.9, 46.0, 43.6, 42.6, 40.6, 32.1, 28.1, 24.6, 23.5, 22.5, 20.6, 20.5; HRMS calcd for $C_{28}H_{35}O_7$ (MH^+) 483.2383, found 483.2371. **11**: ^1H NMR ($CDCl_3$) δ 8.09–8.03 (m, 2H), 7.60–7.43 (m, 3H), 5.87 (d, J = 11.9 Hz, 1H), 5.65 (s, 1H), 5.48 (s, 1H), 5.01 (d, J = 3.7 Hz, 1H), 4.67 (m, 1H), 4.64 (AB q, J = 8.1 Hz, 2H), 3.13 (d, J = 11.8 Hz, 1H), 2.87 (d, J = 15.9 Hz, 1H), 2.65–2.26 (m, 6H), 1.85 (s, 3H), 1.82 (m, 1H), 1.39 (s, 3H), 1.31 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 219.8, 169.7, 166.3, 158.2, 133.0, 132.7, 130.2, 129.3, 128.2, 128.0, 121.8, 87.5, 80.1, 76.9, 75.3, 74.8, 68.7, 58.7, 54.0, 46.7, 44.0, 43.3,

40.5, 38.8, 29.5, 28.7, 25.8, 22.6, 20.6; HRMS calcd for $C_{29}H_{35}O_8$ (MH^+) 511.2332, found 511.2337.

Preparation of Compound (24). 7-(Triethylsilyl)-10-deoxybaccatin (4) (245 mg, 0.382 mmol) was dissolved in dry DMF (5 mL). This solution was treated at 0 °C with imidazole (130 mg, 1.91 mmol) and TESCl (0.321 mL, 1.91 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (2 × 5 mL) and brine (2 × 5 mL). The organic phase was dried and concentrated in vacuo. The residue was chromatographed (20% ethyl acetate in hexane) to afford 287 mg (100%) of the desired product 24: ^1H NMR ($CDCl_3$) δ 8.10–8.07 (m, 2H), 7.61–7.43 (m, 3H), 5.59 (d, J = 6.8 Hz, 1H), 4.93 (m, 2H), 4.49 (dd, J = 6.7 Hz, J' = 10.5 Hz, 1H), 4.20 (AB q, J = 8.2 Hz, 2H), 4.00 (d, J = 6.8Hz, 1H), 3.75 (d, J = 15.1 Hz, 1H), 3.33 (d, J = 15.0 Hz, 1H), 2.50–1.11 (m, 19H, including singlets at 2.28, 1.91, 1.60, 1.13, 3H each), 1.03–0.91 (m, 18H), 0.73–0.49 (m, 12H); HRMS calcd for $C_{41}H_{68}O_9Si_2$ (MH^+) 757.4167, found 757.4159.

Preparation of Compound 25. 7,13-Bis(triethylsilyl)-10-deoxybaccatin (24) (250 mg, 0.331 mmol) was dissolved in dry THF (6 mL). To this solution at 0 °C was added Red-Al (0.258 mL, 60% wt in toluene, 1.324 mmol). The reaction was stirred for 40 min and then quenched with a saturated solution of sodium tartrate (3 mL). The reaction mixture was extracted with EtOAc and washed with water and brine. The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (40% EtOAc/hexanes) to afford 168 mg (78%) of the desired product 25: ^1H NMR ($CDCl_3$): δ 4.97–4.91 (m, 2H), 4.57 (AB q, J = 9.0 Hz, 2H), 4.42 (dd, J = 6.7 Hz, J' = 10.4 Hz, 1H), 3.82 (d, J = 6.6 Hz, 1H), 3.66 (d, J = 15.1 Hz, 1H), 3.60 (d, J = 6.7 Hz, 1H), 3.25 (d, J = 15.2 Hz, 1H), 2.45 (m, 1H), 2.16–0.47 (m, 48H, incl. singlets at 2.16, 1.84, 1.56, 1.13, 3H each); HRMS calcd for $C_{34}H_{61}O_8Si_2$ (MH^+) 653.3905, found 653.3887.

Preparation of Compounds 26 and 27. Compound 25 (89 mg, 0.137 mmol) was dissolved in dry THF (2 mL) and CS_2 (0.5 mL). To this solution was added sodium hydride (5.5 mg, 60%, 0.137 mmol). The reaction mixture was stirred at room temperature for 2 h, and then MeI (0.042 mL, 0.685 mmol) was added. The reaction mixture was further stirred for 2 h. The solvent was removed, and the residue was chromatographed (10% ethyl acetate in hexane) to afford 69 mg (68%) of **26** together with 16 mg (17%) of **27**. **26**: ^1H NMR ($CDCl_3$) δ 6.39 (d, J = 6.5 Hz, 1H), 4.96 (d, J = 7.8 Hz, 1H), 4.89 (m, 1H), 4.46 (m,1H), 4.38 (AB q, J = 7.5 Hz, 2H), 4.04 (d, J = 6.4 Hz, 1H), 3.73 (d. J = 15.1 Hz, 1H), 3.30 (m, 1H), 2.60–1.00 (m, 22H, including singlets at 2.60, 2.18, 1.89, 1.58, 1.10, 1.09, 3H each), 0.99–0.87 (m, 18H), 0.71–0.49 (m, 12H); HRMS calcd for $C_{36}H_{63}S_2O_8Si_2$ (MH^+) 743.3503, found 743.3476.

27: ^1H NMR ($CDCl_3$) δ 4.93 (m, 2H), 4.56 (AB q, J = 8.9 Hz, 2H), 4.52 (d, J = 5.7 Hz, 1H), 4.40 (dd, J = 7.1 Hz, J' = 9.7 Hz, 1H), 3.68 (d, J = 15.2 Hz, 1H), 3.53 (d, J = 5.6 Hz, 1H), 3.31 (d, J = 15.2 Hz, 1H), 2.53–0.96 (m, 19H, including singlets at 2.13, 1.91, 1.63, 1.28, 1.12, 3H each), 0.99–0.86 (m, 18H), 0.66–0.45 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 207.4, 190.6, 170.1, 142.2, 129.1, 95.1, 84.9, 84.2, 79.4, 76.3, 70.9, 67.4, 61.3, 46.4, 43.5, 41.6, 37.8, 36.4, 24.8, 22.4, 15.4, 10.4, 6.9, 6.7, 6.5, 5.7, 5.2, 4.8; HRMS calcd for $C_{35}H_{59}SO_8Si_2$ (MH^+) 695.3469, found 695.3460.

Preparation of Compound 28. 2-Xanthate **26** (58 mg, 0.0782 mmol) was dissolved in dry toluene (2 mL). A catalytic amount of AIBN was added. The reaction mixture was carefully degassed with dry nitrogen. Tributyltin hydride (0.042 mL, 0.156 mmol) was added. The reaction was heated at 100 °C for 2 h. The reaction mixture was subjected to silica gel chromatography (20% ethyl acetate in hexanes) to afford 39.5 mg (80%) of desired product 28: ^1H NMR ($CDCl_3$) δ 4.92 (d, J = 8.5 Hz, 1H), 4.83 (m, 1H), 4.40 (m, 1H), 4.33 (AB q, J = 7.6 Hz, 2H), 3.66 (d, J = 15.3 Hz, 1H), 3.32 (d, J = 7.5 Hz, 1H), 3.26 (m, 1H), 2.49–2.28 (m, 2H), 2.15–0.48 (m, 49H, including singlets at 2.14, 1.81, 1.48, 1.01, 3H each); ^{13}C NMR ($CDCl_3$): d 208.6, 169.8, 137.0, 132.6, 83.3, 81.7, 76.5, 74.5, 71.8, 68.3, 59.6, 45.9, 44.5, 40.7, 40.6, 37.6, 23.7, 22.1, 14.5, 10.6, 6.9, 6.8, 5.2, 4.8; HRMS calcd for $C_{34}H_{61}O_7Si_2$ (MH^+) 637.3956, found 637.3941.

Reduction of Thiocarbonate 27 with Tributyltin Hydride. Preparation of Compounds 29 and 30. Thiocarbonate **27** (320 mg, 0.461 mmol) was dissolved in dry toluene (9 mL). A catalytic amount of AIBN was added. The solvent was carefully degassed. Tributyltin hydride (0.248 mL, 0.922 mmol) was then added, and the reaction mixture was heated at 100 °C for 3 h. The reaction mixture was subjected to chromatography (10% ethyl acetate in hexane) to afford 300 mg of crude product. This crude material was taken up in THF (5 mL), H_2O (1.7 mL) and TFA, (0.8 mL). The reaction was stirred for 2 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (2 × 5 mL), $NaHCO_3$ saturated solution (2 × 5 mL), and brine. The organic layer was dried and concentrated *in vacuo*. The residue was chromatographed (50–80% ethyl acetate in hexanes) to afford 75 mg (42%) of **29** together with 15 mg (8%) of **30**. **29**: ^1H NMR ($CDCl_3$) δ 4.88 (d, J = 8.6 Hz, 1H), 4.43 (AB q, J = 7.7 Hz, 2H), 4.35 (m, 1H), 4.05 (d, J = 1.6 Hz, 1H), 3.98 (m, 1H), 3.58 (d, J = 11.2 Hz, 1H), 3.30 (m, 2H), 2.91 (dd, J = 5.4 Hz, J' = 11.8 Hz, 1H), 2.55 (dd, J = 6.7 Hz, J' = 8.0 Hz, 1H), 2.46 (d, J = 11.3 Hz, 1H), 2.02–1.52 (m, 17H, incl. singlets at 1.99, 1.74, 1.72, 1.70, 1.68, 3H each); ^{13}C NMR ($CDCl_3$) δ 206.7, 132.8, 129.4, 126.6, 124.3, 85.5, 79.3, 74.7, 73.0, 68.9, 53.9, 47.1, 45.3, 39.4, 37.7, 35.9, 21.2, 20.7, 20.1, 14.2, 11.4, 7.0, 6.9, 5.2, 4.9; HRMS calcd for $C_{22}H_{31}O_6$ (MH^+) 391.2121, found 391.2121; mp 182–183 °C.

Compound **30** was further derivatized as its 7,13-diacetate ($Ac_2O/Et_3N/CH_2Cl_2$/0 °C) for characterization. The proton and carbon NMR data are reported below. 7,13-Diacetate **30**: ^1H NMR ($CDCl_3$) δ 5.50 (m, 2H), 5.02 (d, J = 8.5 Hz, 1H), 4.55 (AB q, J = 8.5 Hz, 2H), 3.86 (d, J = 17.9 Hz, 1H), 3.78 (dd, J = 8.0 Hz, J' = 10.1 Hz, 1H), 3.20 (d, J = 8.0 Hz, 1H), 2.87 (m, 1H), 2.53 (ddd, J = 7.8 Hz, J' = 14.8 Hz, J'' = 16.7 Hz, 1H), 2.19–1.54 (m, 17H, including singlets at 2.11, 2.04, 1.97, 1.63, 1.61, 3H each), 1.38 (dd, J = 5.8 Hz, J' = 14.0 Hz, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 208.9, 170.6, 170.3, 169.1, 137.9, 134.1, 83.9, 79.9, 79.5, 75.8, 73.2, 71.5, 63.7, 55.8, 45.5, 40.6, 34.6, 33.5, 32.5, 21.7, 21.2, 20.9, 18.4, 10.9, 10.3; MS calcd 492, found 492 (structure is secured by X-ray analysis); mp 193 °C.

Preparation of Compound 31. Baccatin III (3.012 g, 5.290 mmol) was dissolved in dry DMF (2.1 mL). To this solution at 0 °C was added imidazole (1.80 g, 26.50 mmol), followed by TESCl (4.45 mL, 26.5 mmol). The reaction mixture was stirred at rt for 14 h and then diluted with EtOAc (350 mL). The organic layer was washed with water (4 × 20 mL), dried and concentrated *in vacuo*. The residue was chromatographed (20% ethyl acetate in hexane) to afford 4.00 g (89.1%) of the desired 7,13-bis(TES)-baccatin 31: ^1H NMR ($CDCl_3$) δ 8.06–8.03 (d, 2H), 7.58–7.40 (m, 3H), 6.43 (s, 1H), 5.58 (d, J = 7.1 Hz, 1H), 4.88 (m, 2H), 4.44 (dd, J = 6.6 Hz, J' = 10.4 Hz, 1H), 4.16 (AB q, J = 8.3 Hz, 2H), 4.09 (d, J = 8.3 Hz, 1H), 2.49–1.03 (m, 22H, incl. singlets at 2.25, 2.14, 2.07, 1.63, 1.14, 1.06, 3H each), 1.00–0.86 (m, 18H), 0.67–0.49 (m, 12H); HRMS calcd for $C_{43}H_{67}O_{11}Si_2$ (MH^+) 815.4222, found 815.4205.

Preparation of Compound 32. 7,13-Bis(triethylsilyl)baccatin (31) (307 mg, 0.377 mmol) was dissolved in dry THF (3.7 mL). To this solution at 0 °C was added Red-Al (218.5 mg, 60% wt in toluene, 1.509 mmol). After 40 min, the reaction mixture was quenched with a saturated solution of potassium tartrate (2 mL), and the reaction mixture was extracted with EtOAc (100 mL) and washed with brine (10 mL). The organic layer was dried and concentrated *in vacuo*. The residue was chromatograhed (40% ethyl acetate in hexane) to afford 233 mg (87.2%) of the desired product 32: ^1H NMR ($CDCl_3$) δ 6.36 (s, 1H), 4.91 (m, 2H), 4.56 (AB q, J = 9.0 Hz, 2H), 4.38 (dd, J = 6.6 Hz, J' = 10.3 Hz, 1H), 3.85 (t, J = 6.8 Hz, 1H), 3.39 (d, J = 6.8 Hz, 1H), 2.50–0.50 (m, 52H, including singlets at 2.14, 2.13, 2.01, 1.60, 1.11, 1.05, 3H each); HRMS calcd for $C_{36}H_{63}O_{10}Si_2$ (MH^+) 711.3960, found 711.3941.

Preparation of Compounds 33 and 34. Compound **32** (278 mg, 0.391 mmol) was dissolved in dry THF (3 mL). To this solution was added CS_2 (0.6 mL), followed by NaH (18.8 mg, 60%, 0.469 mmol). After 90 min, MeI (71.5 uL, 1.173 mmol) was added. The reaction was complete within 40 min. The solvent was removed by a stream of N_2. The residue was chromatographed (10–15% ethyl acetate in hexane) to afford 62 mg (21%) of thiocarbonate **34** together with 190 mg (61%) of the C_2 xanthate **33**: **33**: ^1H NMR ($CDCl_3$) δ 6.41 (m, 2H), 4.93 (m, 2H), 4.43 (m, 1H), 4.38 (AB q, J = 8.5 Hz, 2H), 3.84 (d, J = 6.7 Hz, 1H), 2.59–0.51 (m, 55H, including singlets at 2.59, 2.17, 2.15, 2.08, 1.63,

1.13, 1.08, 3H each); HRMS calcd for $C_{38}H_{65}O_{10}S_2Si_2$ (MH^+) 801.3558, found 801.3532.

34: ^1H NMR ($CDCl_3$) δ 6.40 (s, 1H), 4.96 (m, 2H), 4.55 (d, J = 5.9 Hz, 1H), 4.57 (AB q, J = 8.9 Hz, 2H), 4.40 (dd, J = 7.2 Hz, J' = 9.5 Hz, 1H), 3.38 (d, J = 5.8 Hz, 1H), 2.57–2.32 (m, 2H), 2.17–1.16 (m, 20H, including singlets at 2.09, 1.70, 1.28, 1.19, 3H each, 2.14, 6H), 1.28–0.86 (m, 18H), 0.68–0.51 (m, 12H); HRMS calcd for $C_{37}H_{61}O_{10}SSi_2$ (MH^+) 753.3524, found 753.3496.

Reduction of Thiocarbonate 34 with Tributyltin Hydride. Compound **34** (116 mg, 0.155 mmol) and AIBN were dissolved in dry toluene (3.1 mL). After the mixture was degassed with dry nitrogen, tributyltin hydride (0.084 mL, 0.310 mmol) was added. The reaction mixture was heated at 100 °C for 2 h. The reaction mixture was subjected to silica gel chromatography (20% ethyl acetate in hexanes) to afford a crude product. This material was dissolved in THF (2.4 mL), H_2O (0.4 mL), and TFA (0.4 mL). The reaction mixture was stirred at rt for 2 h. The reaction was worked up the same as above to yield compound **35** (15 mg, 21%) together with many unidentified minor products: ^1H NMR ($CDCl_3$) δ 6.04 (s, 1H), 5.01 (d, J = 8.2 Hz, 1H), 4.63–4.44 (m, 4H), 3.72 (t, J = 11.5 Hz, 1H), 3.04 (d, J = 11.8 Hz, 1H), 2.87 (d, J = 10.3 Hz, 1H), 2.67 (d, J = 3.7 Hz, 1H), 2.53 (m, 1H), 2.26 (d, J = 3.8 Hz, 1H), 2.16–1.22 (m, 16H, incl. singlets at 2.16, 2.00, 1.75, 1.54, 3H each), 0.87 (d, J = 6.6 Hz, 3H), 0.69 (d, J = 6.6 Hz, 3H); HRMS calcd for $C_{24}H_{35}O_9$ (MH^+) 467.2281, found 467.2276; mp 195–197 °C.

Reduction of Thiocarbonate 27 with Diphenylsilane. Thiocarbonate **27** (173 mg, 0.249 mmol) was dissolved in toluene (4 mL). A catalytic amount of AIBN was added. The solvent was carefully degassed with nitrogen. Diphenylsilane (0.139 mL, 0.748 mmol) was then added. The reaction mixture was heated at reflux for 6 h. The crude reaction mixture was subjected to silica gel chromatography (10–20% ethyl acetate in hexane) to afford 65.8 mg (38%) of **44** together with 56 mg (32%) of remaining **27**. **44**: ^1H NMR ($CDCl_3$) δ 5.15 (d, J = 8.7 Hz, 1H), 4.93 (dd, J = 3.0 Hz, J' = 9.2 Hz, 1H), 4.69 (AB q, J = 8.3 Hz, 2H), 4.64 (m, 1H), 4.50 (dd, J = 6.9 Hz, J' = 10.7 Hz, 1H), 3.19 (AB q, J = 12.9 Hz, 2H), 2.49–1.20 (m, 20H, incl. singlets at 2.02, 1.75, 1.67, 1.58, 1.38, 3H each), 0.96–0.87 (m, 18H), 0.64–0.52 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 203.8, 189.4, 169.9, 148.9, 125.8, 95.2, 84.0, 78.8, 77.1, 76.4, 76.3, 68.4, 57.6, 55.4, 42.2, 39.8, 39.6, 37.1, 26.6, 24.9, 21.5, 12.0, 10.8, 6.9, 6.8, 5.1, 4.8; HRMS calcd for $C_{38}H_{59}O_8Si_2$ (MH^+) 695.3469, found 695.3476.

Reduction of Thiocarbonate 27 with Triphenyltin Hydride. Thiocarbonate **27** (259 mg, 0.373 mmol) was dissolved in dry toluene (6 mL). A catalytic amount of AIBN was added. The solvent was degassed by dry nitrogen. Tributyltin hydride (393 mg, 1.119 mmol) was added. The reaction mixture was heated at 100 °C for 3 h. The reaction mixture was subjected to silica gel chromatography (10% ethyl acetate in hexane) to afford 200 mg (81%) of the product **47**: ^1H NMR ($CDCl_3$) δ 4.99 (s, 1H), 4.95 (m, 2H), 4.84 (s, 1H), 4.49 (s, 2H), 4.46 (dd, J = 7.0 Hz, J' = 9.8 Hz, 1H), 3.68 (d, J = 15.0 Hz, 1H), 3.59 (d, J = 5.5 Hz, 1H), 3.41 (d, J = 5.5 Hz, 1H), 3.30 (d, J = 13.6 Hz, 1H), 2.50 (m, 1H), 2.16–0.48 (m, 48H, including singlets at 2.14, 1.90, 1.60, 1.21, 1.09, 3H each); MS calcd 694, found 694.

Preparation of Compound 48. 7,13-Bis(triethylsilyl)baccatin (**31**) (127 mg, 0.156 mmol) was dissolved in THF (1.2 mL) and CS_2 (1.2 mL). Sodium hydride (9.4 mg, 60%, 0.234 mmol) was added. The reaction mixture was stirred at rt for 1 h and then heated at 70 °C for 6 h. MeI (0.029 mL, 0.468 mmol) was then added. The reaction mixture was further stirred for 3 h. The solvent was removed, and the residue was chromatographed (20% ethyl acetate in hexane) to afford 79.0 mg (56%) of 1-xanthate **48** together with 45 mg (35%) of the remaining **31**: ^1H NMR ($CDCl_3$) δ 7.89–7.86 (m, 2H), 7.51–7.33 (m, 3H), 6.72 (d, J = 6.6 Hz, 1H), 6.45 (s, 1H), 5.09 (m, 1H), 4.95 (d, J = 7.6 Hz, 1H), 4.47 (m, 3H), 3.93 (d, J = 7.1 Hz, 1H), 3.79 (dd, J = 8.1 Hz, J' = 16.0 Hz, 1H), 2.53–1.14 (m, 24H, including singlets at 2.35, 2.18, 2.12, 2.10, 1.69, 1.33, 1.15, 3H each), 1.04–0.89 (m, 18H), 0.77–0.51 (m, 12H); HRMS calcd for $C_{45}H_{70}O_{11}S_2Si_2$ (MH^+) 905.3820, found 905.3842.

Preparation of Compound 49. 7,13-Bis(triethylsilyl)baccatin 1-xanthate (**48**) (118 mg, 0.131 mmol) was dissolved in toluene (1.3 mL). A catalytic amount of AIBN was added, and the solvent was degassed. Triphenyltin hydride (92.0 mg, 0.262 mmol) was added. The reaction mixture was heated at 80 °C for 1 h. The reaction mixture was cooled to rt and chromatographed (10% ethyl acetate in hexane) to afford 98.0 mg (94%) of desired product **49**. This material was redissolved in THF (2 mL) and treated with TBAF (0.736 mmol, 1 M, 0.736 mmol). The reaction was stirred at 0 °C for 30 min and then at rt for 2.5 h. The solvent was then removed, and the residue was chromatographed (40–60% ethyl acetate in hexane) to afford 40 mg (57%) of diol **50**. **49**: ^1H NMR ($CDCl_3$) δ 7.97–7.94 (m, 2H), 7.59–7.42 (m, 3H), 6.44 (s, 1H), 4.93 (d, J = 8.3 Hz, 1H), 4.82 (m, 1H), 4.40 (m, 1H), 4.36 (AB q, J = 8.0 Hz, 2H), 3.23 (d, J = 7.5 Hz, 1H), 2.86–1.24 (m, 24H, incl. singlets at 2.21, 2.19, 2.04, 1.54, 1.28, 1.24, 3H each), 0.98–0.80 (m, 18H), 0.67–0.51 (m, 12H); MS calcd 798, found 798.

50: ^1H NMR ($CDCl_3$) δ 7.94–7.91 (m, 2H), 7.58–7.40 (m, 3H), 6.27 (s, 1H), 4.95 (d, J = 8.4 Hz, 1H), 4.78 (m, 1H), 4.40 (m, 1H), 4.35 (AB q, J = 7.7 Hz, 2H), 3.31 (d, J = 7.7 Hz, 1H), 2.96 (dd, J = 9.7 Hz, J' = 15.7 Hz, 1H), 2.58–1.17 (m, 23H, including singlets at 2.23, 2.18, 2.03, 1.64, 1.49, 1.22, 3H each); HRMS calcd for $C_{31}H_{39}O_{10}$ (MH^+) 571.2543, found 571.2523.

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Supplementary Material Available: ^1H NMR for all the compounds and NOE data for compounds **8**, **10**, **11**, and **44** (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information. The author has deposited atomic coordinates for **29**, **30**, and **35** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.