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Facile AB Ring Cleavage Reactions of Taxoids

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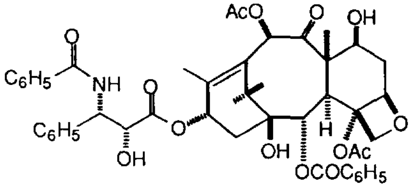
Abstract: Two facile B ring cleavage reactions of taxoids related to paclitaxel are reported. Treatment of a 13-chlorobaccatin with azide ion led to cleavage of the C-10/C-11 bond and formation of a hemiketal product. Treatment of a protected 2-debenzoyl paclitaxel with MnO_2 yielded a ketoaldehyde in which the C-1/C-2 bond had been cleaved and the side chain had been eliminated.

The structurally novel and functionally complex diterpenoid paclitaxel (Taxol®) **1** is now firmly established as a clinically active antitumor drug,[1] but interest in its chemistry and its structure-activity relationships remains high. A part of the reason for this interest is because of the expectation that the development of analogs with improved activity can be achieved, but another significant factor is that paclitaxel has a novel mechanism of action, binding to polymerized tubulin and stabilizing the polymer to disassembly. Several reviews of both the chemistry and biology of paclitaxel have appeared.[2]



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Work in our group has concentrated on modifications of the basic diterpenoid core of paclitaxel, and has included deoxygenation at C-7, C-10 and C-4,[3] opening of the oxetane ring,[4] and changes in the benzoyl group at C-2.[5] These and other studies from our group and the studies of other groups have been summarized in a recent comprehensive review.[2a] From these studies has emerged the overall conclusion that modifications of the "northern hemisphere" of paclitaxel have in general a smaller effect than modifications to the "southern hemisphere", including the oxetane ring and the C-2 and C-4 acyl groups. However, no final consensus has yet emerged as to the modifications required for optimal activity, and no predictive model of the binding of paclitaxel to polymerized tubulin has been developed.

In the course of our studies of the modification of the taxane diterpenoid skeleton of paclitaxel, we were interested in manipulating the nature of the linkage at C-13 between the diterpenoid core and the side chain. Although we were unsuccessful in this attempt, we did discover an unusual ring-opening reaction of ring B, which is reported herein. Also reported is a separate study on the oxidative cleavage of ring B.

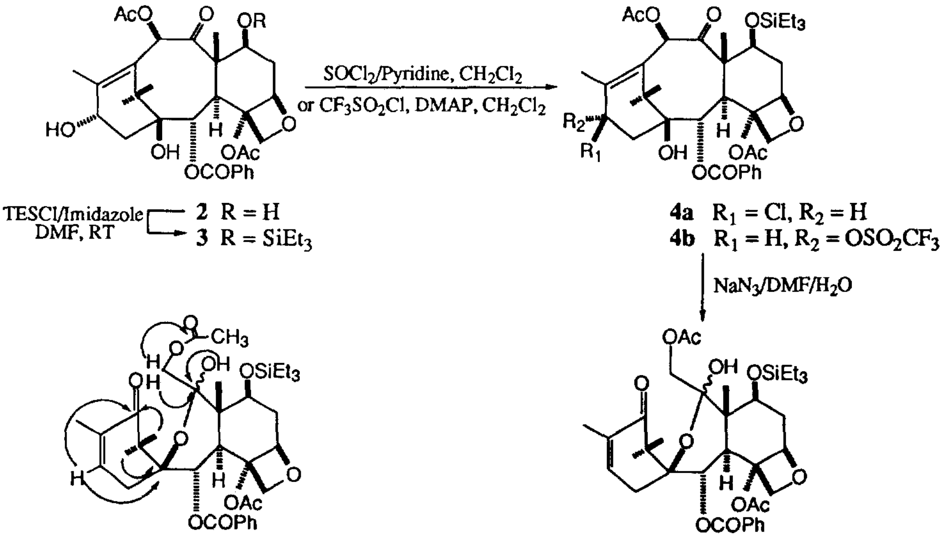
RESULTS AND DISCUSSION

Cleavage of the C-10/C-11 bond

Modifications at the C-13 position of paclitaxel have been very rare, in contrast to the extensive work that has been carried out on the synthesis of analogs with modified side chains.[6] The only example of a C-13 modification which retains the side chain is a recent report by Hoemann on the synthesis of 13-*epi*paclitaxel;[7] perhaps not surprisingly the product was much less active than paclitaxel. We were thus interested in preparing an analog of paclitaxel in which the C-13 oxygen was replaced with a nitrogen atom, in order to discern whether the greater rotational rigidity associated with an amide bond would affect the activity of the product.

Our approach centered on carrying out a nucleophilic displacement at C-13. Protection of baccatin III as its 7-triethylsilyl ether **3** was followed by treatment with thionyl chloride in pyridine to give 13-deoxy-13β-chlorobaccatin III **4a** (Scheme 1). The structure of the product was established by its ^{1}H NMR spectrum, which contained signals very similar to those of the precursor **3** except for the shift of the peak for H-13 from 4.83 to 4.18 ppm. A NOESY spectrum established the stereochemistry of the chlorine as β, since a correlation could be observed between the C-17 methyl at 1.28 ppm and H-14β at 2.88 ppm, and between H-14α at 1.58 ppm and H-13α at 4.18 ppm. Other correlations were observed between H-13α and H-3α and between H-13α and the C-4 acetate methyl group. Displacement of the C-13 hydroxyl group thus occurred with the expected inversion of stereochemistry by attack of chloride from the less hindered β-face of the molecule.

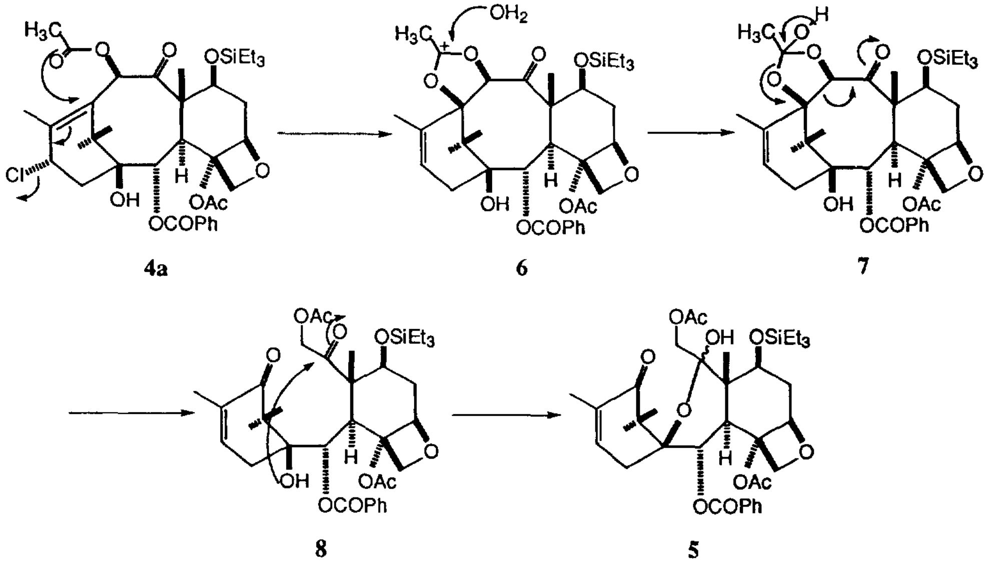
Treatment of the 13-chloro analog **4a** with sodium azide in DMF and a trace of water was then carried out in an attempt to use the good nucleophilicity of the azide ion to achieve a backside displacement of the allylic halide. The only product formed in this reaction, however, proved to be the unexpected B-seco derivative **5**. The structure **5** was assigned primarily on the basis of NMR data; key items included the shift of the signal for



Scheme 1

H-13 from a broad triplet at 4.18 ppm to a broad singlet at 6.47 ppm, and the disappearance of the characteristic sharp singlet at 6.44 ppm for H-10. The UV spectrum of **5** showed an additional peak at 238 nm, consistent with an αβ-unsaturated ketone, and HRFABMS indicated its composition to be $C_{37}H_{52}O_{11}Si$. Careful 2D-NMR experiments (COSY, HETCOR, and HMBC) confirmed the structural assignments: key HMBC correlations are shown in Scheme 1.

The formation of **5** presumably occurs by the pathway of Scheme 2. Loss of the allylic chloride with neighboring group participation by the acetate carbonyl oxygen would give the acetoxonium ion intermediate **6**, which would be trapped by water to give the hemiorthoester **7**. Opening of **7** to give **8** followed by hemiacetal formation would yield the observed product **5**.



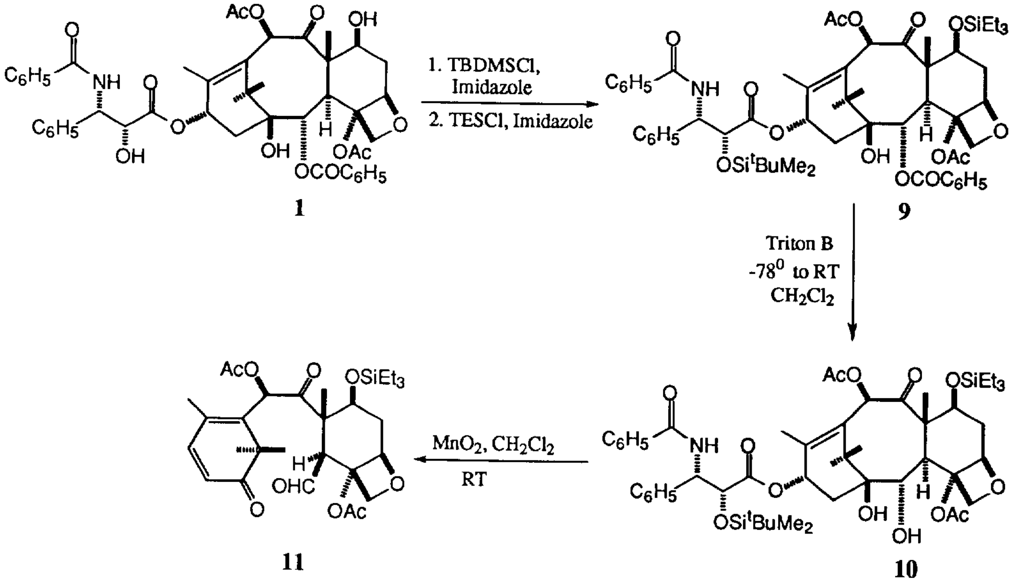
Scheme 2

Attempts at avoiding the elimination-cleavage conversion of **4a** to **5** by the use of other conditions were unsuccessful. Thus treatment of the chloro derivative **4a** with LiI and Bu_4NI in CH_2Cl_2 gave no reaction at room temperature, and the same cleavage product (albeit in low yield) at elevated temperatures. Other reagents (Bu_4NN_3, Bu_4NCN) also gave similar results. A change in the stereochemistry of the leaving group was also ineffective. Thus treatment of 7-(triethylsilyl)baccatin III with triflyl chloride and DMAP in CH_2Cl_2 yielded 7-(triethylsilyl)-13-triflylbaccatin III (**4b**), but attempted displacement of the triflate by azide ion in DMF at 60° gave 7-(triethylsilyl)baccatin III (**3**) as the major product and the B-seco derivative **5** as a minor product. The formation of **3** presumably occurs by an unusual displacement on sulfur rather than on carbon, and serves to illustrate the lack of reactivity of the C-13 position to nucleophilic displacement from either face. Attack from the top face on the backside of a C-13α substituent is prevented by the C-16 methyl group, and backside attack from the bottom face on a C-13β substituent is prevented by the C/D rings which sit directly in the line of attack.

Simple E2 elimination is also prevented by the rigid conformation of the A-ring, which prevents an anticoplanar arrangement of H-14 with either a 13α or a 13β leaving group.

Cleavage of the C-1/C-2 bond

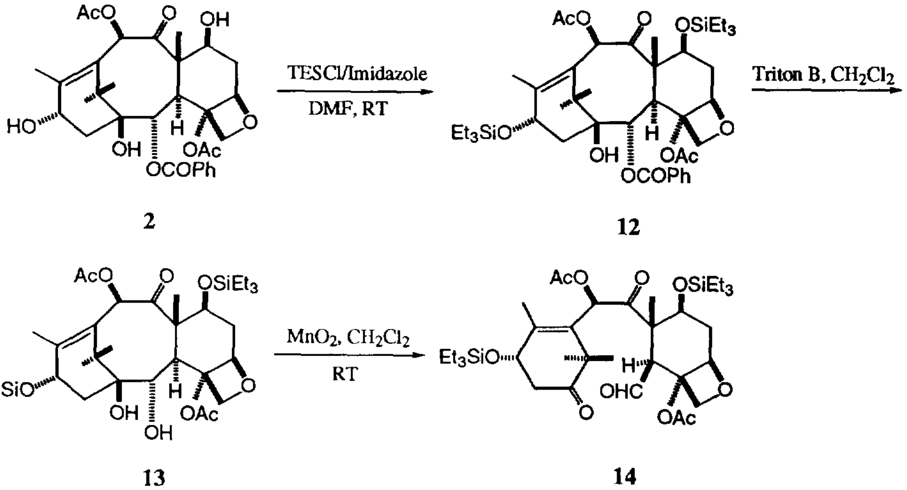
The availability of the protected 2-debenzoylpaclitaxel **10**[5] made it possible to investigate the oxidative cleavage of the C-1/C-2 bond. Treatment of **10** with MnO_2 in dichloromethane at room temperature afforded a single non-polar product **11** in good yield (Scheme 3). The ^{1}H-NMR spectrum of **11** indicated that it lacked the C-13 side chain and had instead gained an aldehyde group and an additional double bond. Detailed analysis of ^{1}H-and ^{13}C-NMR spectra, coupled with a UV absorption at 310 nm characteristic of a conjugated dienone, confirmed the assignment of structure **11**. The formation of **11** is presumably due to normal oxidative cleavage of the vicinal diol of **10**, followed by elimination of the side chain from the resulting ketone under the mildly basic conditions used.



Scheme 3

Oxidative cleavage could also be accomplished without loss of the 13-oxygen functionality if its leaving group ability was reduced. Thus conversion of baccatin III to its 7,13-bis(triethylsilyl) derivative **12** was followed by debenzoylation with Triton B to give the 2-debenzoyl derivative **13**. Treatment of **13** with MnO_2 in dichloromethane gave the B-secopaclitaxel **14** in which the 13-(triethylsiloxy) group remained intact (Scheme 4).

The cleavage of the C-1/C-2 bond is similar to that observed by Py et al.[8] except that their studies, carried out on 10-deacetylbaccatin III derivatives, yielded a cyclic hemiacetal product by internal reaction of the C-10 hydroxyl group with the C-2 aldehyde. These studies thus confirm and extend our knowledge of the chemistry of the taxane ring system, and provide a source of intermediates for studies of recyclization reactions.



Scheme 4

EXPERIMENTAL

13β-chloro-13-deoxy-7-(triethylsilyl)baccatin III (4a). To a stirred solution of 7-triethylsilylbaccatin III (3) (70 mg, 0.1 mmol) in dry CH_2Cl_2 (2.0 mL) was added dry pyridine (100 mL) followed by $SOCl_2$ (50 mL) at room temperature. The mixture was stirred at room temperature for 15 minutes, after which TLC (hexane:EtOAc, 7:3) showed that reaction was complete. The mixture was then diluted with CH_2Cl_2 (15 mL) and washed with dil. $NaHCO_3$, dil. HCl, H_2O, and brine. The organic layer was dried over sodium sulfate and evaporated to give crude product which was purified by preparative TLC (silica gel, 500m, hexane:EtOAc 4:1) to furnish the compound **4a** (55mg, 76%). ^1H NMR: δ 0.57 (6H, q, *J* = 7.7, $SiCH_2$), 0.91 (9H, t, J = 7.7, CH_2CH_3), 1.18 (3H, s, H-16), 1.28 (3H, s, H-17), 1.66 (3H, s, H-19), 1.86 (2H, m, C-6H & C-1 OH), 2.15 (3H, s, H-18), 2.20 (3H, s, C-10 OAc), 2.33 (3H, s, C-4 OAc), 2.52 (1H, m, C-6H), 2.90 (1 H, dd, *J* = 10, 16, C-14H), 3.52 (1H, d, *J* = 7.1, C-3H), 4.13 (1H, d, *J* = 8.3, 1H, C-20H), 4.18 (1H, dd, *J* = 10.3, 4.7, C-13H), 4.29 (1H, d, *J* = 8.3, C-20H), 4.42 (1H, dd, *J* = 6.8,10.4, C-7H), 4.94 (1H, d, *J* = 8.0, C-5H), 5.64 (1H, d, *J* = 7.1, C-2H), 6.44 (1H, s, C-10H), 7.44-7.64 (3H, m, ArH), 8.07 (2H, dd, *J* = 7.1,1.4, *o*-ArCO); ^{13}C NMR; δ 5.2, 6.7, 9.7, 17.7, 19.0, 20.9, 22.0, 30.0, 37.1, 37.2, 42.1, 46.9, 57.1, 59.0, 72.2, 72.6, 76.0, 76.1, 81.3, 82.6, 83.8, 128.6, 129.0, 130.0, 133.8, 139.2, 139.3, 166.9, 169.1, 170.2, 201.1; the detailed assignments of proton and carbon chemical shifts were done on the basis of 2D NMR (TOCSY, HETCOR, NOESY); FABMS: *m/z* (rel int.) 721 (10, MH^+), 719 (30, MH^+), 683 (100), 507 (40), 145 (100).

Reaction of 13β-chloro-13-deoxy-7-(triethylsilyl)baccatin III (4a) with $NaN_3/DMF/H_2O$. 13β-Chloro-13-deoxy-7-(triethylsilyl)baccatin III **4a** (20.0 mg, 0.028 mmol) was dissolved in DMF (0.5mL), and to this solution water (50μL) followed by sodium azide (20 mg, 0.30 mmol) were added. The inhomogenous mixture was heated at 60° for 2 hrs, after which TLC analysis indicated the formation of one polar product and complete consumption of starting material. The mixture was then diluted with EtOAc (10 mL) and washed successively with H_2O and finally brine. The organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure. The crude material thus obtained was purified by PTLC (silica gel, 500μm, hexane:EtOAc, 4:1) to yield compound **5** (14.0mg, 71%). UV (MeOH) λ_{max} (log ε) 238 nm (2.5); IR (nujol): ν_{max} 3500, 1739, 1735, 1723, 1720, 1670, 1663, 1654 cm^{-1}; ^1H NMR: δ 0.61 (6H, q, *J* = 7.8, Si-CH_2), 0.96 (9H, t, *J* = 7.8, CH_2CH_3), 1.06 (6H, bs, H-16 and H-17), 1.46 (3H, s, H-19), 1.71 (3H, s, H-18), 1.78 (1H, bt, *J* = 13.8, H-6), 1.91 (3H, s, C-10 OAc), 2.13 (3H, s, C-4 OAc), 2.37 (1H, m, H-6), 2.60 (1H, dd, *J* = 10,16, H-14), 2.78 (1H, bd, *J* = 16, H-14), 3.37 (1H, d, *J* = 12.5, H-3), 3.87 (1H, s, exchangeable with D_2O, OH), 4.14 (1H, d, *J* = 8.5, H-10), 4.46 (1H, d, *J* = 10.8, H-20), 4.60 (2H, m, H-10 and H-20), 4.86 (1H, d, *J* = 7.7, H-5), 5.82 (1H, d, *J* = 12.5, H-2), 6.40 (1H, bs, H-13), 7.39-7.56 (3H, m, ArH), 7.78 (2H, d, J = 7.1, *o*-ArCO); ^{13}C NMR: δ 5.2, 6.8, 9.4, 15.8, 20.5, 20.9, 21.2, 22.9, 37.0, 39.8, 41.8, 46.4, 50.9, 69.7, 69.9, 73.8, 74.3, 79.0, 81.1, 84.2, 98.0, 128.2, 128.3, 130.1, 132.9, 133.5, 139.3, 165.3, 169.5, 170.8, 202.0; the detailed assignments of proton and carbon chemical shifts were done on the basis of 2D NMR (DQCOSY, HETCOR, HMBC); FABMS: *m/z* (rel int.) 723 (75, MNa$^+$); HRFABMS: *m/z* 723.3176 ($C_{37}H_{52}O_{11}SiNa$ requires 723.3175).

Preparation of 7-(triethylsilyl)-13-(trifluoromethanesulfonyl)baccatin III (4b). 7-(Triethylsilyl)-baccatin III (3) (70.0 mg, 0.1 mmol) was dissolved in dry CH_2Cl_2 (1.0 mL) and to this solution DMAP (134.2 mg, 1.1 mmol) and triflyl chloride (100 μL, 0.94 mmol) were added and the mixture stirred at room temperature overnight (16 hrs). The reaction mixture was then diluted with EtOAc (20 mL) and washed with H_2O followed by dil. HCl, dil. $NaHCO_3$, and brine. The organic layer was dried over sodium sulfate and evaporated to give crude product. Purification of crude product by column chromatography (silica gel, hexane:EtOAc 1:1) furnished 7-(triethylsilyl)-13-triflylbaccatin III **4b** (68.2 mg, 82% yield). ^{1}H NMR: δ 0.56 (6H, q, J = 7.0, Si-CH_2), 0.91 (9H, t, *J* = 7.0, CH_2CH_3), 1.11 (3H, s, H-16), 1.25 (3H, s, H-17), 1.67 (3H, s, H-19), 1.87 (1H, bt, *J* = 12.7, H-14), 2.14 (3H, s, H-18), 2.27 (3H, s, C-10 OAc), 2.27 (3H, s, C-4 OAc), 2.49 (3H, m, H-6 and H-14), 3.82 (1H, d, *J* = 7.0, H-3), 4.11 (1H, d, *J* = 8.3, H-20), 4.30 (1H, d, *J* = 8.3, H-20), 4.47 (1H, dd, *J* = 6.5, 10.4, H-7), 4.92 (1H, d, *J* = 7.8, H-5), 5.66 (1H, d, *J* = 7.0, H-2), 5.70 (1H, t, *J* = 8.2, H-13), 6.43 (1H, s, H-10), 7.45-7.64 (3H, m, ArH), 8.07 (2H, dd, J = 1.4, 8.2, *o*-ArCO); FABMS: *m/z* (rel int.) 833 (100, MH$^+$), 699 (16).

Treatment of 4b with NaN_3. 7-(Triethylsilyl)-13-triflylbaccatin III **4b** (33.3 mg, 0.04 mmol) was dissolved in DMF (0.5mL), and to this solution water (100μL) followed by sodium azide (40 mg, 0.60 mmol) was added. The inhomogenous mixture was heated at 60° for 2 h; during this time the mixture became homogenous, and TLC analysis indicated the formation of two polar products and complete consumption of starting material. The mixture was then diluted with EtOAc (10 mL) and washed successively with H_2O and finally brine. The organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure. The crude material thus obtained was purified by PTLC (silica gel, 500μm, hexane:EtOAc, 4:1) to yield nonpolar compound **5** (7.0mg, 25%) and polar 7-(triethylsilyl)baccatin III **2** (17.0mg, 60%). Both compounds had identical ^{1}H NMR spectra to those of authentic samples.

2'-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)paclitaxel (9). To a stirred solution of paclitaxel **1** (270 mg, 0.316 mmol) in 2.5 ml anhydrous DMF, imidazole (107 mg, 1.58 mmol) and *tert*-butyldimethylsilyl chloride (238 mg, 1.58 mmol) were added. The solution was heated at 60° for 2 h. The mixture was cooled to room temperature and an additional amount of imidazole (107 mg, 1.58 mmol) and triethylsilyl chloride (265 μl, 1.58 mmol) were added. After stirring at room temperature for 1 h the reaction mixture was diluted with EtOAc and washed successively with H_2O and brine. Drying of the organic layer over Na_2SO_4 and evaporation under reduced pressure yielded crude material. Purification of this material by column chromatography over silica gel (EtOAc:hexanes, 1:2) gave 2'-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)paclitaxel (**9**) (325 mg, 95%) as an amorphous white solid, m.p.130-131°; ^{1}H-NMR: δ -0.20 (3H, s, $SiCH_3$), -0.02 (3H, s, $SiCH_3$), 0.62 (6H, q, *J* = 7.8, $SiCH_2$), 0.79 (9H, s, $(CH_3)_3C$), 0.92 (9H, t, *J* = 7.8, $SiCH_2CH_3$), 1.17 (3H, s, H-16), 1.21 (3H, s, H-17), 1.70 (3H, s, H-19), 2.02 (3H, bs, H-18), 2.16 (3H, s, C-10 OAc), 2.40 (1H, m, H-14), 2.55 (1H, m, H-6), 2.58 (3H, s, C-4 OAc), 3.83 (1H, d, *J* = 7.0, H-3), 4.19 (1H, d, *J* = 8.3, H-20), 4.30 (1H, d, *J* = 8.3, H-20), 4.48 (1H, dd, *J* = 9.4, 6.6, H-7), 4.67 (1H, d, *J* = 2.1, C-2'H), 4.04 (1H, bd, *J* = 8.8, H-5), 5.69

(1H, d, *J* = 7.0, H-2), 5.74 (1H, dd, *J* = 9.0, 2.1, H-3'), 6.26 (1H, bt, H-13), 6.45 (1H, s, H-10), 7.10 (1H, d, *J* = 8.9, C-3'NH), 7.30-7.60 (11H, m, ArH), 7.74 (2H, dd, *J* = 8.0, 1.5, *o*-ArCONH), 8.13 (2H, dd, *J* = 8.5, 1.4, *o*-ArCO); FABMS: *m/z* (rel int.) 1104 (5, MNa$^+$), 705 (3) 422 (40), 354 (12), 105 (100); HRFABMS: *m/z* 1104.4936 (MNa$^+$; $C_{59}H_{79}NO_{14}Si_2Na$ requires 1104.4937).

Reaction of 2-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)paclitaxel (9) with Triton-B. To a solution of compound **9** (110.4 mg, 0.1mmol) in anhydrous CH_2Cl_2 was added benzyltrimethyl ammonium hydroxide (Triton-B, 100 µL, 40% w/w solution in MeOH) at -78° (acetone, dry ice). The reaction mixture was stirred at -78° for 5 minutes and the cooling bath was replaced by a -10° bath (ethylene glycol, dry ice) to allow the reaction mixture to warm to -10°. Monitoring the progress of reaction by TLC over a period of 10 minutes indicated the formation of a more polar compound. The mixture was diluted with cold CH_2Cl_2 and quenched with dil. HCl (2N, 5ml). The organic layer was separated, washed successively with H_2O, dil. $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration under reduced pressure gave crude residue, which was purified by PTLC (silica gel, 1000 µm, EtOAc:hexanes, 2:3) to yield compound **10** (75.4 mg, 76%), m.p. 133-35°C; ^{1}H-NMR: δ -0.28 (3H, s, $SiCH_3$), -0.04 (3H, s, $SiCH_3$), 0.57 (6H, q, *J* = 7.8, $SiCH_2$), 0.80 (9H, s, tBu), 0.92 (9H, t, *J* = 7.8, $SiCH_2CH_3$), 1.07 (3H, s, H-16), 1.15 (3H, s, H-17), 1.62 (3H, s, H-19), 1.96 (3H, bs, H-18), 2.14 (3H, s, C-10 OAc), 2.40 (1H, m, H-14), 2.51 (1H, m, H-6), 2.42 (3H, s, C-4 OAc), 2.79 (1H, d, *J* = 5.9, C-2 OH), 3.46 (1H, d, *J* = 7.0, H-3), 3.92 (1H, t, *J* = 6.3, H-2), 4.41 (1H, dd, *J* = 9.4, 6.6, H-7), 4.60 (1H, d, *J* = 1.6, H-2'), 4.63 (2H, bs, H-20), 4.95 (1H, bd, *J* = 8.6, H-5), 5.67 (1H, dd, *J* = 9.2, 1.6, H-3'), 6.24 (1H, bt, H-13), 6.37 (1H, s, H-10), 7.05 (1H, d, *J* = 9.2, C-3'NH), 7.30-7.54 (8H, m, ArH), 7.74 (2H, dd, *J* = 8.3, 1.5, *o*-ArCONH); FABMS: *m/z* (rel int.) 1000 (3, MNa$^+$), 400 (22) 354 (84), 105 (100); HRFABMS: *m/z* 1000.4632 (MNa$^+$; $C_{59}H_{79}NO_{14}Si_2Na$ requires 1000.4675).

Reaction of 2'-(*tert*-Butyldimethylsilyl)-2-(debenzoyl)-7-(triethylsilyl)paclitaxel (10) with MnO_2. To a solution of 2'-(*tert*-butyldimethylsilyl)-2-debenzoyl-7-(triethylsilyl)paclitaxel **10** (49.0 mg, 0.05 mmol) in dry CH_2Cl_2 was added activated MnO_2 (150 mg, excess) and the mixture was stirred at room temperature for 2 h. The mixture was then diluted with CH_2Cl_2, filtered, and the solvent evaporated to obtain crude material. Purification of crude product by PTLC (silica gel, 500 µM, 4:1 hexane:EtOAc) yielded compound **11** (25.4 mg, 87%) as a thick pale yellow liquid. UV (MeOH): λ_{max} (log ε) 310 nm (0.86); IR (nujol): ν_{max} 1740, 1735, 1665, 1636, 1464 cm^{-1}; ^{1}H NMR: δ 0.62 (6H, q, *J* = 7.8, $SiCH_2$), 0.96 (9H, *J* = 7.8, CH_2CH_3), 1.14 (6H, bs, H-16, 1.25 (3H, s, H-17), 1.60 (3H, s, H-19), 1.83 (3H, s, H-18), 2.11 (3H, s, C-10 OAc), 2.18 (3H, s, C-4 OAc), 2.58 (1H, m, H-6), 3.60 (1H, s, H-3), 4.39 (1H, d, *J* = 8.2, H-20), 4.64 (1H, dd, *J* = 4.8, 10.8, H-7), 4.79 (1H, d, *J* = 8.2, H-20), 5.06 (1H, d, *J* = 7.7, H-5), 6.08 (1H, d, *J* = 8.0, H-14), 6.24 (1H, bs, H-10), 7.85 (1H, d, *J* = 8.0, H-13), 9.58 (s, 1H, H-2); ^{13}C NMR: δ 5.8, 6.9, 10.6, 21.0, 21.2, 21.3, 26.3, 37.0, 49.3, 55.2, 58.1, 74.0, 75.3, 76.0, 76.6, 83.9, 124.7, 129.9, 147.3, 169.9, 170.0, 198.8, 205.0; FABMS: *m/z* (rel int.) 599.3 (100, MNa$^+$), 329 (15) 176 (61); HRFABMS: *m/z* 599.2635 (MNa$^+$; $C_{30}H_{44}O_9SiNa$ requires 599.2652).

Reaction of 7,13-bis(triethylsilyl)baccatin III (12) with Triton-B. To a cooled (-78°C) solution of 7,13-bis(triethylsilyl)baccatin III **12**[9] (40.7 mg, 0.05 mmol) in dry CH_2Cl_2 was added Triton-B (40% w/w solution in MeOH, 25 µL, 0.59 mmol) and the mixture stirred for 15 min and allowed to warm to room temperature. The mixture was stirred at room temperature for an additional 30 minutes, diluted with EtOAc and washed thoroughly with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by PTLC (silica gel, 1000 µm, EtOAc:hexanes, 2:3) to yield compound **13** (23.8 mg, 67%) as an amorphous white solid. ^{1}H NMR: δ 0.57 (6H, q, *J* = 8.0, $SiCH_2$), 0.66 (6H, q, *J* = 8.0, $SiCH_2$), 0.90 (9H, t, *J* = 8.0, CH_2CH_3), 0.98 (9H, t, *J* = 8.0, CH_2CH_3), 1.08 (3H, s, H-16), 1.14 (3H, s, H-17), 1.63 (3H, s, H-19), 1.87 (1H, bt, *J* = 10.4, H-6), 2.04 (3H, s, H-18), 2.12 (3H, s, C-10 OAc), 2.17 (3H, s, C-4 OAc), 2.53 (1H, m, H-6), 2.88 (1H, dd, *J* = 10, 16, H-14), 3.43 (1H, d, *J* =

6.8, H-3), 3.88 (1H, t, $J = 7.8$, H-2), 4.41 (1H, dd, $J = 6.6$, 10.3, H-7), 4.59 (2H, ABq, $J = 9.0$, H-20), 4.94 (2H, bt, H-5 and H-13), 6.39 (1H, s, H-10); ^{13}C NMR: δ 4.8, 5.2, 6.7, 6.9, 10.2, 14.7, 20.9, 21.1, 22.3, 26.1, 37.2, 40.4, 42.4, 46.8, 58.2, 68.4, 72.2, 74.8, 75.7, 77.8, 79.5, 81.9, 83.8, 131.1, 145.0, 169.2, 169.5, 203.0; FABMS: *m/z* (rel int.) 711.3 (100, MH^+),

Reaction of 2-debenzoyl-7,13-bis(triethylsilyl)baccatin III (13) with MnO_2. To a solution of 2-debenzoyl-7,13-bis(triethylsilyl)baccatin III **13** (20.0 mg, 0.028 mmol) in dry CH_2Cl_2 was added activated MnO_2 (40 mg, excess) and the mixture was kept stirring at room temperature for 3 h. The mixture was then diluted with CH_2Cl_2, filtered, and the solvent evaporated under reduced pressure to yield crude material. Purification of crude product by PTLC (silica gel, 500μ, 4:1 hexane EtOAc) yielded the B-seco ketoaldehyde **14** (16.0mg, 80%). ^1H NMR: δ 0.60 (12H, m, $SiCH_2$), 0.92 (18H, m, CH_2CH_3), 1.02 (3H, s, H-16), 1.26 (3H, s, H-17), 1.59 (3H, s, H-19), 1.76 (3H, s, H-18), 1.95 (1H, m, H-6), 2.10 (3H, s, C-10 OAc), 2.15 (3H, s, C-4 OAc), 2.59 (1H, m, H-6), 2.66 (1H, dd, $J = 6.9$, 13.4, H-14), 2.78 (1H, dd, $J = 4.2$, 13.4, H-14), 3.59 (1H, s, H-3), 4.35 (1H, bt, $J = 6.7$, H-13), 4.49 (1H, d, $J = 8.0$, H-20), 4.66 (1H, dd, $J = 6.7$, 10.4, H-7), 4.77 (1H, d, $J = 8.0$, H-20), 5.05 (1H, d, $J = 7.2$, H-5), 6.10 (1H, s, H-10), 9.57 (1H, s, H-2); FABMS: *m/z* (rel int.) 731.4 (100, MNa^+).

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