Tetrahedron Vol. 49, No. 14, pp. 2805-2828, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
Pergamon Press Ltd

THE CHEMISTRY OF TAXANES: REACTION OF TAXOL AND BACCATIN DERIVATIVES WITH LEWIS ACIDS IN APROTIC AND PROTIC MEDIA

Shu-Hui Chen,* Stella Huang, Jianmei Wei and Vittorio Farina

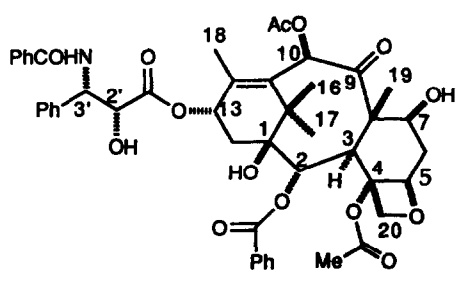
Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway
P.O.Box 5100, Wallingford CT 06492-7660

(*Received in USA 7 December* 1992)

Abstract: *Several Lewis acids were shown to cleanly open the oxetane ring of taxol and baccatin derivatives. The reaction is shown to proceed via anchimeric assistance by the C-4 acetate group. Several minor products, including a novel derivative possessing a bridged C-ring, were also isolated. A mechanistic rationale is provided for all compounds formed. When taxol derivatives were treated with Lewis acids in methanol, ester cleavage reactions were observed. We provide conditions that are selective for C-10 acetate cleavage and for C-13 side-chain methanolysis.*

INTRODUCTION

Considerable excitement is being generated in clinical trials by the anticancer agent taxol (**1**).[1] We have launched a program aimed at understanding the structural basis of the biological activity displayed by this interesting diterpenoid. The chemistry of taxol has been reviewed very recently. [2] The oxetane ring apparently plays a key role in the bioactivity of taxol since treatment of taxol with alkylating agents causes opening of the oxetane ring, which leads to loss of biological activity. [3]

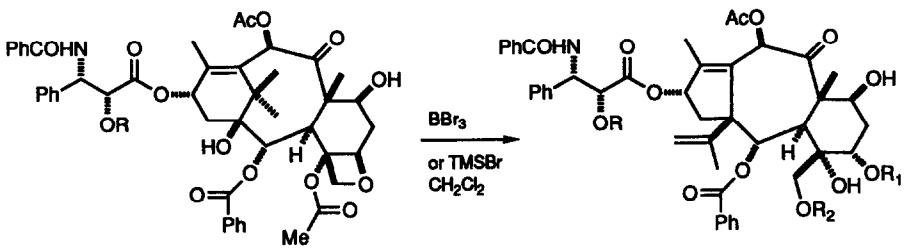


1 Taxol

When other electrophilic reagents were used, an unusual contraction of the A ring was also observed. In contrast, when electrophilic reagents were used in protic media, the favored process is deacetylation at C-10. [3] In our efforts to develop a comprehensive Structure-Activity Relationship (SAR) data-base, we decided it would be worthwhile to examine the chemistry of the oxetane moiety in more detail; specifically, we undertook a comprehensive study dealing with the reactivity of taxol with Lewis acids in aprotic media. In addition, we investigated the ability of Lewis acids in protic media to selectively deacylate specific ester groups in the taxol molecule. These two related studies form the subject of the present report.

CHEMISTRY OF THE OXETANE SYSTEM: RING OPENING WITH LEWIS ACIDS

When taxol was treated with trimethylsilyl bromide in CH_2Cl_2, a reaction took place, leading to two products in a 9:1 ratio. The major one was identified as **3b**, while the minor one was its regioisomer **3a**. The ^{1}H-NMR spectra clearly showed the formation of a terminal olefin, indication of a contracted A ring, as recently reported by Kingston (Scheme 1). [3] The opening of the oxetane was evidenced by the disappearance of the AB quartet (J=8.3 Hz) typical of the two protons at C-20.



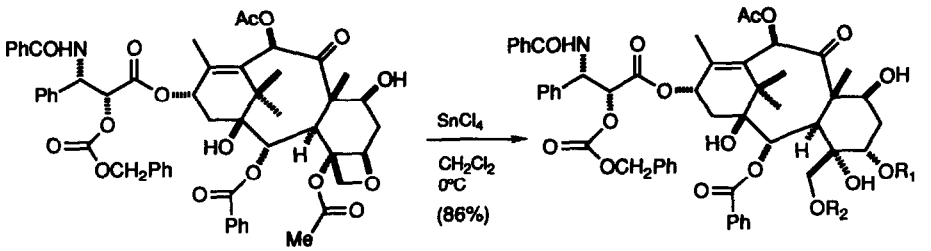
1 **R=H**
2 **R=CO_2CH_2Ph**

3 a: **R=H,R_1=Ac,R_2=H**
b: **R=H,R_1=H,R_2=Ac**
c: **R=COO_2CH_2Ph,R_1=Ac,R_2=H**
d: **R=COO_2CH_2Ph, R_1=H,R_2=Ac**

Scheme 1

Both the A ring contraction and the observed mode of oxetane cleavage were reported by Kingston, [3] although the oxetane ring-opening reaction was described to produce only the regioisomer corresponding to **3b**. Interestingly, when the Lewis acid used was boron tribromide, and the reaction was carried out in an analogous manner, **3a** and **3b** were obtained in a 7:3 ratio (i.e. the regioselectivity was reversed). Analogous results were obtained with **2**: TMSBr afforded **3d** as the only isolable product in 79% yield, while BBr_3 yielded **3c** in similar yield. In order to prepare new taxol analogs with modified C ring for SAR studies, it was important to prevent A ring contraction, and milder Lewis acids were studied. It was then found that high yields of the desired products could be obtained by treatment of **2** with $SnCl_4$, yielding a mixture of **4a** and **4b** in a 4:1 ratio. These compounds could be separated chromatographically, and were found to be somewhat unstable in organic solvents, which made the obtention of clean ^{13}C-NMR spectra under overnight conditions quite difficult. Structural assignment rests on ^{1}H-NMR spectra and accurate mass determinations, and all our data are in agreement with Kingston's recent results.[3] Different results were obtained with $TiCl_4$ (here the

regiochemistry was reversed, **4b** predominating over **4a**) and BF_3-OEt_2 (which led to a 1:1 mixture of **4a** and **4b**) (Scheme 2). Given the high yields obtained with $SnCl_4$, we selected this reagent for further study.

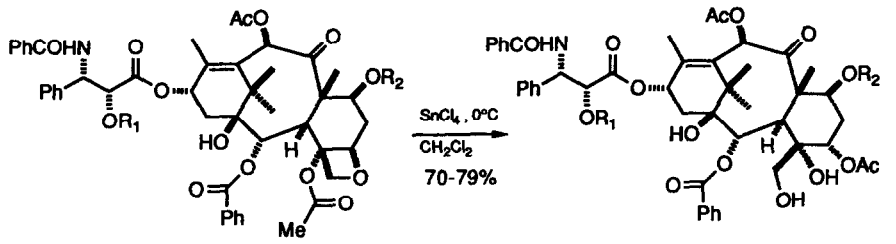


2

4 a: R_1=Ac, R_2=H
b: R_1=H, R_2=Ac

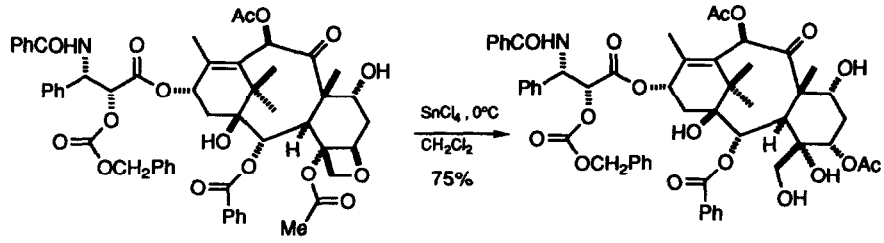
Scheme 2

We first examined the issue of the regiochemistry of ring opening by submitting a number of taxol derivatives to the above conditions. Taxol itself reacted very poorly with $SnCl_4$, and A-ring rearrangement could not be avoided. Once the alcohol function at C-2' was blocked, however, smooth reaction took place at 0°C to yield primarily one product.



5 a: R_1=CO_2Bn, R_2=OAc
b: R_1=CO_2Bn, R_2=$OCO_2CH_2CCl_3$

6 a,b



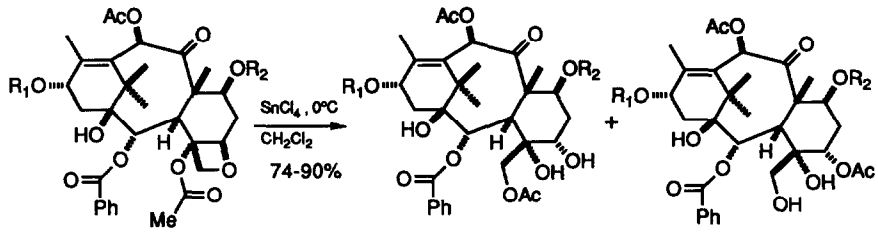
7

8

Scheme 3

The type of substitution at the C-2' or C-7 hydroxyl groups had little effect on yield, rate or regiochemistry, compounds **6a,b** being obtained as major products in high yields. Epimerization at C-7 had the effect of slowing down the reaction substantially, and cleavage only occurred at RT, with the expected regio- and stereochemistry to yield **8** (Scheme 3).

Baccatin derivatives, on the other hand, gave different results (Scheme 4). Here the opposite regioisomer was favored (ratios **10:11** were in the range 1.5-5.0 to 1).

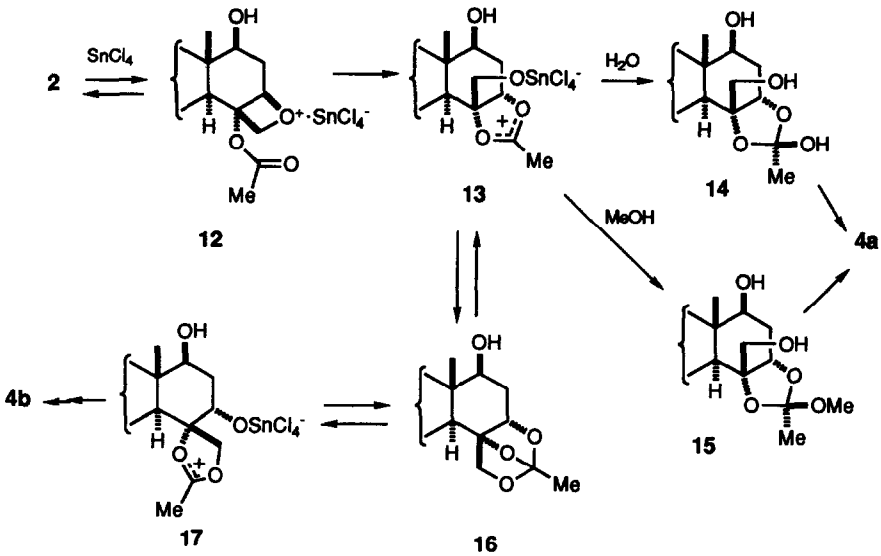


9 a: R_1=H, R_2=$CO_2CH_2CCl_3$ **10 (a,b,c)** **11 (a,b,c)**
b: R_1=H, R_2=CO_2Et
c: R_1=R_2=Ac

Scheme 4

From these experiments, it is clear that the oxetane ring can open in two regiochemically distinct ways, and that the regiochemistry depends on the Lewis acid used. The presence of the side chain at C-13 has an effect on the regiochemistry. The reactivity seems also to depend on the substitution pattern of the molecule. Specifically, an unprotected hydroxyl group at C-2' or at the α-C-7 position considerably retard the reaction with $SnCl_4$. Puzzled by these observations, we decided to study the reaction in further detail. With **2** as a substrate, and with authentic samples of products **4a** and **4b** in hand, we decided to monitor the reaction by reversed-phase HPLC. Our goal was to find out whether the ratio **4a:4b** was time-dependent, i.e. whether the final ratio was of kinetic or thermodynamic nature. The reaction was carried out at 20 mM concentration in both reactants, and sampling was carried out every 2 minutes by quenching an aliquot into acetonitrile/ammonium acetate buffer (pH=4). Interestingly, the reaction was 40% complete in 2 min, but the only product observed (Retention time= 4.1 min) was different from either **4a** (R.t.= 4.88 min) or **4b** (R.t.= 6.04 min). Indeed, as the reaction was allowed to proceed for 30 min, only traces (<10%, ratio apparently was 1:1) of **4a,b** were observed, and the major product was represented by the peak at 4.1 min. Yet, when the reaction mixture was quickly evaporated and chromatographed, **4a** was isolated in good yield as usual. No trace of the compound eluting at 4.1 in the HPLC system could be found. When the experiment was repeated and the aliquots were quenched into methanol, a completely different product, less polar than all others, was observed (R.t.= 13.5 min). Once again this was the exclusive product, and could not be isolated when chromatography or work-up (basic or slightly acidic) was attempted. It was then evident that the outcome of these reactions is dependent on the type of quench. When a bicarbonate quench was utilized, the products observed by HPLC were indeed **4a** and **4b**, but in the quenched aliquots **4a** quickly rearranged to **4b**, and indeed a bicarbonate work-up led to the isolation of **4b** in 68% yield, without traces of **4a**, in contrast with the

"silica gel" quench (direct chromatography) that yielded only **4a**. A plausible explanation for the above observations is illustrated in Scheme 5, and is consistent with the mechanism proposed by Kingston in his work with Meerwein's reagent. [3]

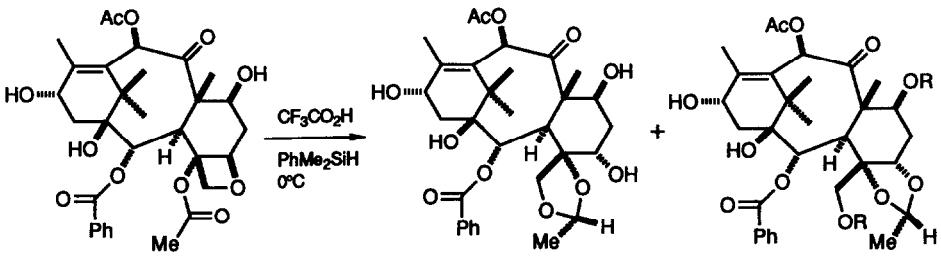


Scheme 5

The mechanism follows from Winstein's classical studies [4] on acetyl group participation in solvolysis reactions. The first step is the complexation of the Lewis acid with the oxetane oxygen which is likely the most basic atom in the molecule. [5] The acetoxy group at C-4 is positioned for backside attack onto C-5, leading to acetoxonium ion **13**. Indeed, when the 4 acetoxy group is not as readily available for nucleophilic displacement (it is hydrogen bonded to the C-7 hydroxyl in **7**, [3] and it apparently interacts with the hydroxyl group at C-2' in taxol), the overall reaction is sluggish at 0°C and only proceeds at room temperature. Intermediate **13** is the species that is trapped when the reaction is quenched after a short interval, and hemi-orthoester and orthoester **14** and **15** are the labile species that are formed on trapping with water and methanol, respectively. Their stability to the HPLC conditions attests to the mildness of the C-18 surface vs. the more traditional silica gel. While reactions that were worked up with acidic buffers at short times gave crude products that contained (by NMR) a new species, the spectra generated were too complex to allow confident structural assignments for **14**. Similar results were obtained when trying to isolate **15**. The occurrence of these intermediates is, however, very likely on the basis of Winstein's work. The stereochemistry shown is only tentative and results from likely attack on the convex face of the molecule. Also, the relative stability of **14** at acidic pH and its lability at basic ones is consistent with the assigned structure and inconsistent with other formulations (e.g. orthoester **16**). Intermediate hemi-orthoester **14** can in principle open in two ways, to produce either the observed 5-acetoxy derivative or an unobserved 4-acetoxy derivative. Based on the NMR

analysis, the 5-acetoxy in **4a** is axial, while the 4-hydroxy group is equatorial. The production of axial acetates over equatorial in similar opening reactions has been explained by invoking stereoelectronic effects.[6] We note, however, that **4a** and **4b** readily equilibrate, especially under basic conditions: indeed 1,2 acetyl migration in carbohydrate chemistry is very well precedented,[7] and the possibility exists that a 4-acetyl derivative may be too unstable (due to steric interactions with the C-2 benzoyl group) to be observed. Indeed, the formation of of **4b** could simply be explained as the result of equilibration of initially formed, and less stable, **4a**, without invoking interconversion of acetoxonium ions **13** and **17** via strained orthoester **16**.

Several observations, however, support the occurrence of a second isomeric acetoxonium ion. As the reactions with different Lewis acids were worked up in similar ways, it appears unlikely that the extent of acetate equilibration during purification can be so completely different from run to run. *More likely, it is the ability of 13 to equilibrate with 17 that strongly depends on the Lewis acid used.* For example TMSBr may lead to ready equilibration of an ion similar to **17**, affording mostly a 20-acetyl derivative. Boron tribromide, instead, probably affords slower rates of interconversion (perhaps the C-20 hydroxyl is less nucleophilic here, being strongly coordinated to the boron atom) and preferentially leads to a C-5 acetate. We sought additional evidence in favor of this mechanism, and we attempted to trap these acetoxonium ions with nucleophilic reagents. Although trapping proved unsuccessful with $SnCl_4$ using a variety of reducing agents, when we stirred baccatin III in cold trifluoroacetic acid in the presence of a large excess of phenyldimethylsilane, acetals **19** and **20a** (characterized as its diacetate **20b**) [8] were obtained in fair overall yield, suggesting that the two acetoxonium ions were indeed both present, at least under these particular conditions (Scheme 6).



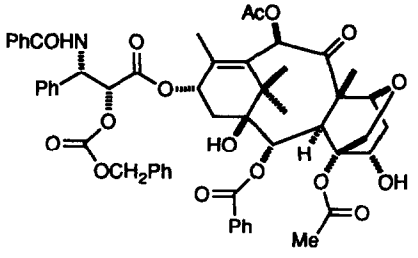
18 **19** (42%) **20** (9%)

a) R=H
b) R=Ac

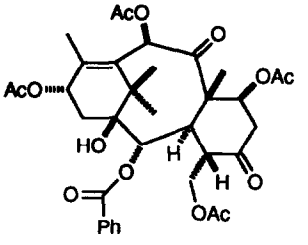
Scheme 6

Further evidence came with the observation that the reaction mixtures in the $SnCl_4$ reaction substantially deteriorated with time, suggesting that at least one of the two acetoxonium ions was unstable and was probably involved in secondary processes. When **2** was treated with $SnCl_4$ for 2 h at 0°C, an unusual product was isolated in 14% yield. It was assigned structure **21** after extensive NMR characterization (see Table 1). Proton-proton and carbon-proton connectivities for **21** were obtained by 2-D NMR, and were in agreement with the structure proposed. In addition, a three-bond coupling was observed between H-7 and C-20, thus establishing the presence of the ether bridge. Strong NOEs were observed between the C-19 methyl hydrogens and H-20(β), and between H-5 and H-20(α), thus confirming the stereochemistry at C-5. The

formation of **21** can be explained by assuming that the conformation of the C ring in **17** can flip to a boat, in which the hydroxyl at C-7 can attack C-20, to permanently lock the C ring in a boat conformation. In the reaction of **9c** with $SnCl_4$, on the other hand, the C-7 hydroxyl is blocked, and compound **22** was observed as a side product (4% yield) under prolonged reaction times. Compound **22** is the result of a hydride shift from C-5 to C-4, in an intermediate like **17**, and obviously results in inversion at C-4, as shown by NMR data (Table 1). This observation strongly supports, once again, the intermediacy of the second acetoxonium ion, as postulated in Scheme 5.

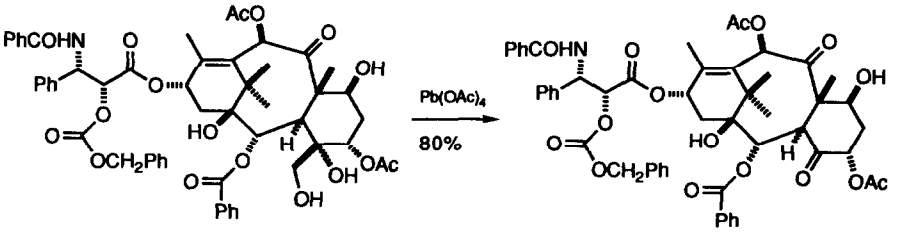


21

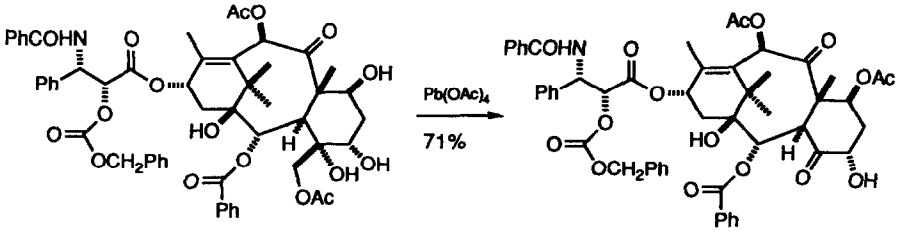


22

In order to further confirm structures **4a,b**, both diols were cleaved with lead tetraacetate in acetonitrile. While **4a** gave the expected **23** in high yield (Scheme 7), **4b**, on the other hand, cleanly produced the unexpected **24**, where the acetyl group had migrated from C-20 to C-7. [9]



4a **23**



4b **24**

Scheme 7

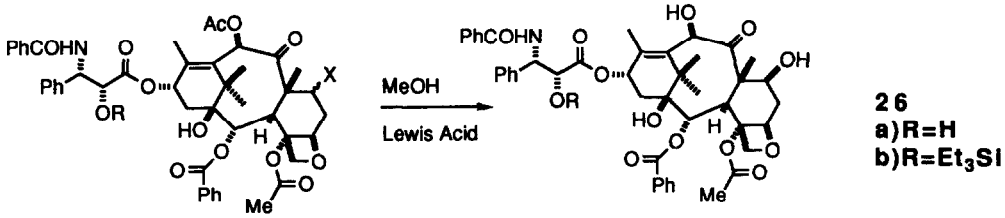
Evidently, formation of a cyclic lead (IV) intermediate at C-4 and C-5 is slow on steric grounds, and there is ample time for acetate equilibration.

Interestingly, none of the compounds described above displayed significant biological activity, either in the tubulin polymerization assay [10] or in an in vitro cytotoxicity assay.[11] This seems to confirm the importance of the oxetane ring or, just as plausibly, the necessity for a conformationally rigid C ring.

TREATMENT OF TAXOL WITH LEWIS ACIDS IN PROTIC MEDIA

Treatment of taxol with zinc bromide in methanol was reported by Kingston to produce 10-deacetyl derivative **26a** (Scheme 8) together with 7-epi product **27a**.[3] We investigated this reaction in further detail: in particular, we were interested in devising procedures for performing selective deacylation with Lewis acids, in connection with our SAR studies. When other alcoholic solvents were tried, it became clear that the reaction proceeds at acceptable rates only in methanol. The next step was to investigate other Lewis acids.

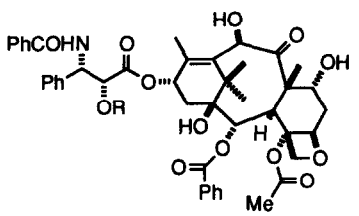
Scheme 8



25

a) R=H,X= β-OH (Taxol, 1)
b) R=H, X= α-OH
c) R=Et_3Si, X=β–OH
d) R=Et_3Si, X=β-OSiEt_3
e) R= $COOCH_2CCl_3$, X= β-$OCOOCH_2CCl_3$

26
a)R=H
b)R=Et_3Si



27
a)R=H
b)R=Et_3Si

As shown in Table 1, all zinc halides gave results that are analogous to the ones observed with zinc bromide. In particular, epimerization at C-7 could not be entirely suppressed. Of the many salts tried Ce(III) and Mg(II) salts were also effective, but caused epimerization at C-7. Obviously , in order to avoid epimerization, the C-7 hydroxyl group required protection, and the silylated derivative **25d** was examined next. Surprisingly, no reaction was observed in this case. The deacetylation also failed in the case of bis-carbonate **25e**. These results seem to imply that a free hydroxyl group at C-7 is necessary for the deacetylation at C-10 to proceed at appreciable rates. Such hydroxyl group at C-7 must be in the β configuration, as shown

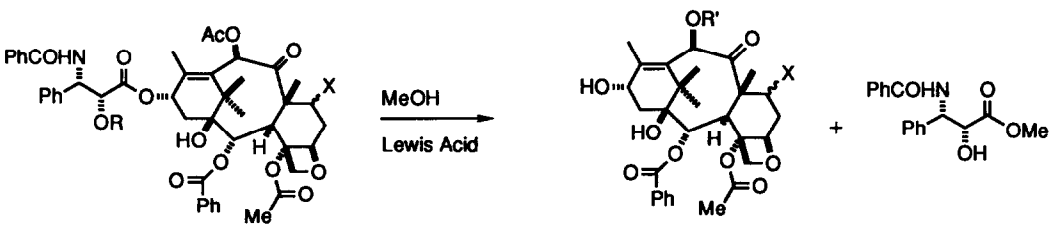
by the extremely slow conversion rate displayed by 7-epi derivative **25b** (Table 1).
A Lewis acid that did not cause side reactions is $PdCl_2(CH_3CN)_2$, but in this case the reaction was quite slow and did not reach completion under our standard conditions.

TABLE 1: Lewis acid-promoted methanolysis of taxol derivatives **25a-e** (25°C)

SUBSTRATE	LEWIS ACID (CONDITIONS)	PRODUCTS
25a	$ZnCl_2$ (4 eq., 6 days)	**26a** (32%); **27a** (40%)
25a	$ZnBr_2$ (4 eq., 2 days)	**26a** (36%);**27a** (29%);S.M. (14%)
25a	ZnI_2 (4 eq., 4.5 days)	**26a** (27%); S.M. (54%)
25a	$MgBr_2$ (.4 eq., 2 days)	**26a** (23%); **27a** (28%);S.M. (31%)
25a	$CeCl_3$ (4 eq., 2 days)	**26a** (15%); **27a** (30%);S.M. (29%)
25a	$PdCl_2(CH_3CN)_2$ (.2 eq., 1 day)	**26a** (30%); S.M. (40%)
25b	$ZnBr_2$ (4 eq., 1day)	**27a** (4%); S.M. (76%)
25c	$ZnBr_2$ (6 eq.; 1.5 days)	**26b** (31%); **27b** (40%)
25d	$ZnBr_2$ (4 eq., 2 days)	no reaction
25e	$ZnBr_2$ (4 eq., 2 days)	no reaction

Other Lewis acids (notably CsF and LiI) were found to also cleave the side chain of taxol, thereby affording an alternative to the reductive cleavage introduced by Kingston [12] (Scheme 9).

Scheme 9



25

a) R=H,X= β-OH (Taxol, 1)
b) R=H, X= α-OH
c) R=Et_3Si, X=β-OH
f) R=H, X=β-OSIEt_3

28
a)R'=OH, X=β-OH
b)R'=OH, X=α-OH
c)R'=OAc, X=β-OSIEt_3
d)R'=OAc, X=α-OH

29

The side chain was recovered as methyl ester **29**. Several substrates were examined and the results are summarized in Table 2. Once again deacylation at C-10 required a free hydroxyl group at C-7. While extensive deacylation was observed with taxol and its 2'-silyl ether **25c**, protection at C-7 allowed clean preparation of 7-triethylsilyl baccatin III , **28c**, with little or no C-10 deacetylation or C-7 epimerization.

TABLE 2: Lewis acid-promoted methanolysis of taxol derivatives **25a-d** (25°C)

SUBSTRATE	LEWIS ACID (CONDITIONS)	PRODUCTS
25a	LiI (4 eq., 16h)	**28a** (58%); **28b** (40%); **29** (82%)
25a	CsF (8 eq., 7 days)	**28a** (36%); **28b** (38%); **29** (63%)
25b	LiI (4 eq., 16h)	**28d**(56.5%); **28b**(17%); **29** (78%)
25c	LiI (4 eq., 14 days)	**28a** (22%); **28b** (34%); **29** (71%)
25f	LiI (8 eq., 36h)	**28c** (82%)

Mechanistically, the role of the β-hydroxy group at C-7 in the acetyl cleavage at C-10 is rather intriguing, and suggests that *Lewis acid chelation of the 7-OH and the C-10 acetate oxygen somehow enhances the rate of cleavage of the acetyl group.* This view is consistent with the weak hydrogen bond detected in solution between the C-7 hydroxyl group and the C-10 acetate carbonyl.[13] From the synthetic viewpoint, however, these observations point to a limitation in the efficiency of the Zn(II)-catalyzed deacetylation at C-10, which is almost always accompanied by epimerizarion at C-7. The use of LiI and CsF allows smooth cleavage of the taxol side-chain, affording baccatin derivatives in good yield. The reason for the change in selectivity with these salts is not understood. Once again, protection at the C-7 hydroxyl group retards C-10 deacetylation, and this was exploited synthetically in our new route to 7-protected baccatin from taxol. Key ^{1}H-NMR data for the more interesting compounds described in this study are collected in Table 3.

ACKNOWLEDGEMENTS

We are grateful to Dr. D.M. Vyas and Dr. T.W.Doyle for encouragement and useful discussions. We thank Ms. S.I. Hauck for preliminary experiments and Dr.S.E.Klohr for the high resolution mass spectra.

EXPERIMENTAL

Dichloromethane was distilled from calcium hydride. Anhydrous pyridine and methanol were obtained from Aldrich, and used directly. Nuclear magnetic resonance (NMR) data were obtained on a Bruker AC-300 (at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C). Long-range carbon-proton couplings were determined by the HMBC technique of Bax and Summers.[14] 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 iodide were added when Na (K) adducts were determined. Preparative silica chromatography was carried out according to Still.[15] HPLC monitoring was carried out using a Perkin-Elmer Series 410 instrument equipped with a BioLC pump, an LC-235 Diode Array Detector and LCI-100 integrator. A Jones C-18 column (150 x 4.6 mm, 5μm particle size) was used for the analyses, operating the detector at 235 nm. Elution was carried out with mixtures of acetonitrile and 10mM ammonium hydrogen phosphate (pH=6.50). Yields refer to homogeneous materials evaporated *in vacuo* to constant weight.

TABLE 3: Selected ^{1}H-NMR chemical shifts (δ) for some taxol derivatives (J values in Hertz).

Proton	4a	4b	19	20b	21	22
H-2	5.65(d,J=5.8)	5.56(d,J=5.4)	5.52 (J=7.1)	5.61(d,J=8.2)	5.59(d,J=5.5)	5.54(d,J=7.0)
H-3	3.88(d,J=5.8)	4.04(d,J=5.4)	3.71 (J=7.1)	3.20(d,J=8.2)	4.83(d,J=5.5)	3.45(dd,J=7.0 J'=9.8)
H-4	--	--	--	--	--	2.38(d,J=9.8)
H-5	5.32(br s)	3.45(br s)	3.92 (br s)	4.22 (m)	4.51 (m)	--
H-7	4.21 (m)	4.52 (m)	4.39 (m)	5.47(dd,J=11 J'=6.2)	3.49(d,J=4.8)	5.47(dd,J=7.7 J'=9.6)
H-10	6.51 (s)	6.58 (s)	6.41 (s)	6.25 (s)	6.33 (s)	6.28 (s)
H-13	6.12 (m)	5.99 (m)	4.72 (m)	4.71 (m)	6.12 (m)	6.01 (m)
H-20	3.46 (AB, J=11.3)	4.04;3.84 (AB,J=11.7)	4.22;3.33 (AB, J=8.8)	4.23;4.09 (AB, J =12.3)	4.13;4.00 (AB,J=9.3)	4.44;4.27 (AB,J=10.7)
H-2'	5.32(d,J=1.9)	5.34(d,J=1.5)	--	--	5.47(d,J=3.3)	--
H-3'	6.15(dd,J=1.9 J'=9.6)	6.16(dd.J=1.5 J'=9.3)	--	--	6.12(dd,J=3.3 J'=9.7)	--

2'-Benzyloxycarbonyl Taxol, 2.

Taxol (862 mg, 1.010 mmol) was dissolved in dry dichloromethane (10 mL) and cooled to 0°C. Diisopropylethylamine (0.528 mL, 3.030 mmol) was added, followed by benzyl chloroformate (0.433 mL, 3.030 mmol). The reaction was stirred at 0°C for 3 h, then it was diluted with ethyl acetate, and washed with water and brine. The organic phase was dried and concentrated, and the residue was chromatographed (60% ethyl acetate in hexane) to afford **2** as a white powder (991 mg, 99%). M.p. 140-8 °C (dec.).
^{1}H-NMR ($CDCl_3$) δ 8.15-7.25 (m, 20H) 7.02 (d, J=9.3 Hz, 1H) 6.31 (m, 2H) 6.00 (dd, J=7.8 Hz, J'=2.7 Hz, 1H) 5.69 (d, J=7.1 Hz, 1H) 5.47 (d, J=2.8 Hz, 1H) 5.28 (s, 1H) 5.18 (AB q, 2H) 4.97 (d, J=7.9 Hz, 1H) 4.45 (dd, J=10.7 Hz, J'=6.6 Hz, 1H) 4.26 (AB q, J=8.4 Hz, Δν= 32.3 Hz, 2H) 3.82 (d, J=7.0 Hz, 1H) 2.58-1.11 (m, 23 H incl. singlets at 2.46, 2.22, 1.94, 1.69, 1.24, 1.14, 3H each). **^{13}C-NMR** ($CDCl_3$) δ 203.8; 171.2; 169.8; 167.0; 166.9; 154.1; 142.6; 136.6; 134.2; 133.6; 133.4; 132.7; 132.0; 130.2; 129.1; 129.0; 128.8; 128.7; 128.5; 128.4; 127.1; 126.5; 84.4; 81.0; 79.1; 76.8; 76.4; 75.5; 75.0; 72.1; 72.0; 70.7; 58.4; 52.7; 45.5; 43.1; 35.5; 35.4; 26.8; 22.6; 22.1; 20.8; 14.8; 9.5. **HRMS** Calcd for $C_{55}H_{58}NO_{16}$ (MH^+): 988.3756, found 988.3713.

Reaction of Taxol with Boron Tribromide.

Taxol (12 mg, 0.0137 mmol) was dissolved in dry dichloromethane (0.5 mL) , cooled to 0°C, and treated with boron tribromide (1M in dichloromethane, 0.0165 mL, 0.0165 mmol). After 1h at 0°C, the solution was directly applied to a short silica column and quickly eluted with 80% ethyl acetate in hexane. Products **3a** (6.1 mg, 50%) and **3b** (2.6 mg, 21%) were obtained as oils. Compound **3a** had: **^{1}H-NMR** ($CDCl_3$) δ 7.78-7.05 (m, 15H) 7.04 (d, J=9.5 Hz, 1H) 6.48 (s, 1H) 6.03 (d, J=9.9 Hz, 1H) 5.52 (m, 1H) 5.40 (s, 1H) 5.28 (d, J=6.6

Hz, 1H) 5.25 (s, 1H) 4.80 (m, 2H) 4.68 (s, 1H) 4.44 (m, 1H) 3.49 (d, J=3.0 Hz, 1H) 3.35 (d, J=6.6 Hz, 1H) 3.33 (AB q, J=11.2 Hz, Δν=56.5 Hz, 2H) 2.80 (dd, J=12.9 Hz, J'=5.7 Hz, 1H) 2.40-1.24 (m, 20H, incl. singlets at 2.25, 1.85, 1.62, 1.31, 1.24, 3H each). **HRMS** Calcd for $C_{47}H_{52}NO_{14}$ (MH^+): 854.3388, found 854.3371.

Compound **3b** had: **^{1}H-NMR** ($CDCl_3$) δ 7.79-7.26 (m, 15H) 7.09 (d, J=9.3 Hz, 1H) 6.47 (s, 1H) 5.86 (d, J=9.3 Hz, 1H) 5.57 (m, 1H) 5.32 (d, J=6.9 Hz, 1H) 4.82 (s, 1H) 4.74 (s, 1H) 4.68 (s, 1H) 4.64 (m, 1H) 4.35 (s, 1H) 3.88 (AB q, J=12.1 Hz, Δν=70.7 Hz, 2H) 3.45 (d, J=6.9 Hz, 1H) 3.41 (d, J=2.4 Hz, 1H) 2.85 (dd, J=12.9 Hz, J'=5.7 Hz, 1H) 2.50 (dd, J=12.9 Hz, J'=8.0 Hz, 1H) 2.21-1.24 (m, 20 H incl. singlets at 2.18, 1.82, 1.61, 1.31, 1.24, 3H each). **HRMS** Calcd for $C_{47}H_{52}NO_{14}$ (MH^+) 854.3388, found 854.3407.

Reaction of Taxol with Trimethylsilyl Bromide.

Taxol (7 mg, 0.008 mmol) was dissolved in dry dichloromethane (0.2 mL), cooled to 0°C, and treated with trimethylsilyl bromide (0.87 μL, 0.008 mmol) for 2h at 0°C. The mixture was directly applied to a short silica column, quickly eluting with 80% ethyl acetate in hexane. Compounds **3b** (5.4 mg, 71%) and a trace of **3a** (0.6 mg, 8%) were obtained. The NMR spectra were identical to the ones described above.

Compound 3c.

2'-Benzyloxycarbonyl taxol (**2**) (19 mg, 0.0192 mmol) was dissolved in dry dichloromethane (0.4 mL), cooled to 0°C, and treated with boron tribromide (1M in dichloromethane, 0.024 mL , 0.024 mmol), stirring at 0°C for 30 min. The mixture was directly applied to a short silica column and quickly eluted with 60% ethyl acetate in hexane, to yield **3c** (14.5 mg, 75%) as the major product.

^{1}H-NMR ($CDCl_3$) δ 7.81-7.13 (m, 20H) 6.99 (d, J=10.1 Hz, 1H) 6.49 (s, 1H) 6.19 (dd, J=10.1 Hz, J'=1.2 Hz, 1H) 5.54 (m, 2H) 5.38 (m, 1H) 5.29 (d, J=6.6 Hz, 1H) 5.20 (AB q, 2H) 4.94 (s, 1H) 4.80 (s, 1H) 4.68 (s, 1H) 4.42 (m, 1H) 3.35 (d, J=6.6 Hz, 1H) 3.32 (AB q, J=11.3 Hz, Δν=54.8 Hz, 2H) 2.82 (dd, J=12.9 Hz, J'= 5.7 Hz, 1H) 2.35 (dd, J=12.9 Hz, J' =8.5 Hz, 1H) 2.28-1.28 (m, 19H, incl. singlets at 2.25, 2.23, 1.86, 1.59, 1.29, 3H each). **HRMS** Calcd for $C_{55}H_{58}NO_{16}$ (MH^+): 988.3756, found 988.3789.

Compound 3d.

2'-Benzyloxycarbonyl taxol (24.2 mg, 0.0245 mmol) was dissolved in dry dichloromethane (0.5 mL), cooled to 0°C, and treated with trimethylsilyl bromide (2.6 μL, 0.024 mmol) for 30 min. The mixture was directly applied to a silica gel column, and quickly eluted with 60% ethyl acetate in hexane, to afford **3d** as a foam (19.1 mg, 79%).

^{1}H-NMR ($CDCl_3$) δ 7.80-7.23 (m, 20H) 6.99 (d, J=9.6 Hz, 1H) 6.44 (s, 1H) 6.02 (dd, J=9.6 Hz, J'=2.0 Hz, 1H) 5.54 (m, 1H) 5.48 (d, J=2.0 Hz, 1H) 5.32 (d, J=6.9 Hz, 1H) 5.17 (m, 2H) 4.79 (s, 1H) 4.66 (s, 1H) 4.60 (m, 1H) 4.08 (m, 1H) 3.80 (AB q, J=12.1 Hz, Δν= 59.4 Hz, 2H) 3.76 (s, 1H) 3.41 (d, J=6.9 Hz, 1H) 2.85 (dd, J=13.1 Hz, J'= 5.9 Hz, 1H) 2.45 (dd, J=13.1 Hz, J'= 8.1 Hz, 1H) 2.23-1.26 (m, 19H, incl. singlets at 2.17; 1.80; 1.59; 1.52, 1.26, 3H each). **HRMS** Calcd for $C_{55}H_{58}NO_{16}$ (MH^+): 988.3756, found 988.3746.

Reaction of 2 with Tin Tetrachloride.

2'-Benzyloxycarbonyl taxol (42 mg, 0.042 mmol) was dissolved in dry dichloromethane (1 mL), cooled to 0°C, and treated with tin tetrachloride (1M in dichloromethane, 0.042 mL, 0.042 mmol) for 1h. The mixture was directly applied to a silica column, eluting with 60% ethyl acetate in hexane, affording two products, **4a** (29.6 mg, 69%) and **4b** (7.4 mg, 17%) as foams. Compound **4a** had: **^{1}H-NMR** ($CDCl_3$) δ 8.17-7.17 (m, 20H) 7.02 (d, J=9.6 Hz, 1H) 6.51 (s, 1H) 6.15 (dd, J=9.6 Hz, J'= 1.9 Hz, 1H) 6.12 (m, 1H) 5.65 (d, J=5.8 Hz, 1H) 5.32 (s, 2H) 5.18 (s, 2H) 4.23 (m, 1H) 4.11 (s, 1H) 3.88 (d, J=5.9 Hz, 1H) 3.46 (AB q, J=11.3 Hz, Δν=28.6 Hz, 2H) 3.02 (dd, J=15.6 Hz, J'= 6.0 Hz, 1H) 2.37 (dd, J=15.6 Hz, J'= 9.9 Hz, 1H) 2.24-1.13 (m, 23H, incl. singlets at 2.25, 2.15, 1.67, 1.25, 1.17, 1.14, 3H each). **HRMS** Calcd for $C_{55}H_{60}NO_{17}$ (MH^+): 1006.3861, found 1006.3849.
Compound **4b** had: **^{1}H-NMR** ($CDCl_3$) δ 8.08-7.12 (m, 20H) 7.04 (d, J=9.3 Hz, 1H) 6.58 (s, 1H) 6.16 (dd, J=9.3 Hz, J'= 1.5 Hz, 1H) 5.99 (m, 1H) 5.56 (d, J=5.4 Hz, 1H) 5.34 (d, J=1.5 Hz, 1H) 5.16 (m, 2H) 4.52 (m, 1H) 4.29 (s, 1H) 4.04 (d, J=5.4 Hz, 1H) 3.94 (AB q, J=11.7 Hz, Δν=54.7 Hz, 2H) 3.89 (br s, 1H) 3.45 (br s, 1H) 3.02 (dd, J=15.6 Hz, J'= 4.2 Hz, 1H) 2.43 (dd, J=15.6 Hz, J'=9.9 Hz, 1H) 2.23-1.10 (m, 22H, incl. singlets at 2.23, 2.13, 1.59, 1.26, 1.16, 1.13, 3H each). **HRMS** Calcd for $C_{55}H_{60}NO_{17}$ (MH^+): 1006.3861, found 1006.3857.

Reaction of 2 with Tin Tetrachloride: Bicarbonate Quench.

Compound **2** (170 mg, 0.172 mmol) was dissolved in dry dichloromethane (5 mL), cooled to 0°C, and treated with tin tetrachloride (1.0 M in dichloromethane, 0.190 mL, 0.190 mmol) for 40 min, monitoring disappearance of starting material by HPLC. The cold solution was quenched with 5% aqueous sodium carbonate solution, and stirring of the two-phase mixture was continued at RT for 10 min. After addition of more dichloromethane, phase separation, and further washing of the organics with water and brine, drying and evaporation gave a crude oil, which was purified by silica gel flash chromatography (50-70% gradient of ethyl acetate in hexane), to leave **4b** as a colorless foam (120.5 mg, 68%). No trace of **4a** was detected by TLC or HPLC.

Reaction of 2 with Titanium Tetrachloride.

Compound **2** (114 mg, 0.116 mmol) was dissolved in dry dichloromethane (2.2 mL), cooled to 0°C, and treated with titanium tetrachloride (1M in dichloromethane, 0.139 mL, 0.139 mmol), and stirred 1h at 0°C and 30 min at RT. The mixture was directly applied to a short silica column, and eluted with a gradient of 50-70% ethyl acetate in hexane, to afford **4a** (18.6 mg, 15%) and **4b** (65 mg, 57%).

Reaction of 2 with Boron Trifluoride Etherate.

Compound **2** (76 mg, 0.077 mmol) was dissolved in dry dichloromethane (1.5 mL), cooled to 0°C, and

treated with boron trifluoride etherate (9.5 μL, 0.077 mmol) for 1h at 0°C. The solution was directly applied to a short silica column, and eluted as above to yield **4a** (33 mg, 43%) and **4b** (33 mg, 43%).

2'-Benzyloxycarbonyl-7-Acetyl Taxol, 5a.

Compound **2** (76 mg, 0.077 mmol) was dissolved in dichloromethane (1.5 mL) and treated at RT with acetic anhydride (0.036 mL, 0.385 mmol), dicyclohexylcarbodiimide (48 mg, 0.231 mmol) and 4-dimethylaminopyridine (2 mg). After 5h at RT, the mixture was diluted with ethyl acetate, the organic layer was washed with saturated aqueous sodium bicarbonate, water and brine. Drying and evaporation were followed by silica chromatography (40% ethyl acetate in hexane), to afford **5a** as a white solid (73 mg, 92%), m.p. 116-8°C (EtOAc-hexane).
^{1}H-NMR ($CDCl_3$) δ 8.14-7.25 (m, 20H) 6.92 (d, J=9.3 Hz, 1H) 6.25 (m, 2H) 5.97 (dd, J=9.3 Hz, J'=2.7 Hz, 1H) 5.69 (d, J=6.9 Hz, 1H) 5.59 (dd, J=10.5 Hz, J'=7.0 Hz, 1H) 5.46 (d, J=2.7 Hz, 1H) 5.16 (m, 2H) 4.96 (d, J=8.0 Hz, 1H) 4.25 (AB q, J=8.4 Hz, Δν=42.0 Hz, 2H) 3.95 (d, J=6.8 Hz, 1H) 2.61 (m, 1H) 2.44-1.75 (m, 19H, incl. singlets at 2.45, 2.16, 2.03, 2.00, 1.81, 3H each) 1.21 (s, 3H) 1.17 (s, 3H). **^{13}C-NMR** ($CDCl_3$) δ 202.2; 170.4; 169.7; 169.0; 168.1; 167.3; 167.0; 154.1; 141.2; 136.8; 134.4; 133.8; 132.6; 132.1; 130.3; 129.2; 128.8; 128.6; 127.3; 126.7; 84.1; 81.0; 78.8; 75.4; 74.6; 72.1; 71.5; 70.9; 57.1; 56.1; 52.9; 49.7; 47.0; 43.4; 35.5; 33.4; 32.8; 30.9; 26.5; 25.6; 25.4; 24.8; 24.3; 22.7; 21.4; 21.2; 20.8; 14.6; 10.9. **MS** ($C_{57}H_{59}NO_{17}$): 1029.

Compound 6a.

Compound **5a** (57 mg, 0.055 mmol) was dissolved in dry dichloromethane (1.2 mL), cooled to 0°C, and treated with tin tetrachloride (1M in dichloromethane , 0.061 mL, 0.061 mmol) for 1h at 0°C, then another portion of tin tetrachloride was added (0.0275 mL, 0.0275 mmol) and stirring was continued for another 30 min. The mixture was directly applied to a silica column, eluting with 50% ethyl acetate in hexane, yielding **6a** as the major product (40.8 mg, 70%, foam).
^{1}H-NMR ($CDCl_3$) δ 8.17-7.25 (m, 20H) 7.06 (d, J=9.6 Hz, 1H) 6.42 (s, 1H) 6.17 (dd, J=9.6 Hz, J'=2.1 Hz, 1H) 6.17 (m, 1H) 5.61 (d, J=5.7 Hz, 1H) 5.46 (dd, J=12.0 Hz, J'= 4.5 Hz, 1H) 5.32 (d, J=2.1 Hz, 1H) 5.29 (s, 1H) 5.26 (m, 2H) 4.18 (s, 1H) 4.00 (d, J=5.4 Hz, 1H) 3.43 (AB q, J=11.1 Hz, Δν=24.6 Hz, 2H) 3.05 (dd, J=15.4 Hz, J'= 5.7 Hz, 1H) 2.40-1.10 (m, 26H, incl. singlets at 2.23, 2.15, 1.99, 1.84, 1.32, 3H each, and 1.22, 6H). **MS** ($C_{57}H_{61}NO_{18}$): 1047.

2'-Benzyloxycarbonyl-7-(2,2,2)-Trichloroethoxycarbonyl Taxol , 5b.

Compound **2** (229 mg, 0.232 mmol) was dissolved in dry dichloromethane (4.6 mL), cooled to 0°C, and treated with pyridine (0.056mL, 0.696 mmol), followed by trichloroethyl chloroformate (0.096 mL, 0.696 mmol). After 1h at 0°C and 16 h at RT, the mixture was worked up with dichloromethane/water, and the organics were dried. Evaporation and chromatography of the crude residue (40% ethyl acetate in hexane) left **5b** as a white solid (220.3 mg, 82%), m.p. 155-7°C (EtOAc-hexane).

^{1}H-NMR ($CDCl_3$) δ 8.14-7.24 (m, 20H) 6.90 (d, J=9.3 Hz, 1H) 6.38 (s, 1H) 6.27 (m, 1H) 5.97 (dd, J=9.3 Hz, J'=2.5 Hz, 1H) 5.70 (d, J=6.9 Hz, 1H) 5.59 (dd, J=10.7 Hz, J'= 7.1 Hz, 1H) 5.45 (d, J= 2.5 Hz, 1H) 5.16 (m, 2H) 4.98 (d, J=8.1 Hz, 1H) 4.84 (AB q, J=8.4 Hz, Δν=42.4 Hz, 2H) 4.27 (m, 2H) 3.97 (d, J=7.0 Hz, 1H) 2.62 (m, 1H) 2.46-1.16 (m, 23H, incl. singlets at 2.46, 2.16, 2.02, 1.84 1.73, 1.22, 1.17, 3H each). **^{13}C-NMR** ($CDCl_3$) δ 201.6; 169.8; 169.1; 167.9; 167.2; 167.0; 154.1; 153.2; 141.4; 136.7; 134.3; 133.8; 133.5; 132.6; 132.0; 130.2; 129.1; 129.0; 128.9; 128.8; 128.7; 128.5; 127.2; 126.6; 94.6; 83.8; 80.7; 78.7; 77.3; 76.8; 76.4; 76.3; 75.3; 74.5; 72.0; 70.8; 60.4; 56.0; 52.8; 46.9; 43.3; 35.4; 33.2; 26.5; 22.6; 21.4; 20.7; 14.5; 10.8. **HRMS** Calcd for $C_{58}H_{59}NO_{18}Cl_3$ (MH^+): 1162.2798, found 1162.2766.

Compound 6b.

Compound **5b** (34.5 mg, 0.0296 mmol) was dissolved in dry dichloromethane (1.0 mL), cooled to 0°C and treated with tin tetrachloride (1M in dichloromethane, 0.033 mL, 0.033 mmol) . After 1 h at 0°C, another portion of tin tetrachloride solution was added (0.011 mL), and stirring continued for 1 h. The mixture was then directly applied to a silica column and eluted with 1:1 ethyl acetate / hexane. Yield: 27.7 mg (79%) of **6b** as a foam.
^{1}H-NMR ($CDCl_3$) δ 8.16-7.24 (m, 20H) 7.02 (d, J=9.4 Hz, 1H) 6.50 (s, 1H) 6.15 (dd, J=9.4 Hz, J'=1.9 Hz, 1H) 6.09 (m, 1H) 5.61 (d, J= 5.5 Hz, 1H) 5.35 (m, 3H) 5.17 (m, 2H) 4.78 (AB q, 2H) 4.20 (s, 1H) 3.99 (d, J=5.5 Hz, 1H) 3.46 (AB q, J=11.2 Hz, Δν=33.0 Hz, 2H) 3.04 (dd, J=15.6 Hz, J'=6.0 Hz, 1H) 2.36 (dd, J=15.6 Hz, J'= 9.9 Hz, 1H) 2.30-1.14 (m, 22 H, incl. singlets at 2.23, 2.18, 2.16, 1.67, 1.35, 3H each, and 1.14, 6H). **HRMS** Calcd for $C_{58}H_{61}NO_{19}Cl_3$ (MH^+): 1180.2903, found 1180.2859.

2'-Benzyloxycarbonyl-7-epi -Taxol, 7.

7-epi -Taxol [16] (138 mg, 0.162 mmol) was dissolved in dry dichloromethane (3.5 mL), cooled to 0°C, and treated with diisopropylethylamine (0.085 mL, 0.485 mmol) and benzyl chloroformate (0.070 mL, 0.485 mmol). After 3h at 0°C, the solvent was removed *in vacuo*, and the residue chromatographed (50% ethyl acetate in hexane) to afford **7** as a white solid (160 mg, 99%), m.p. 157-9°C (EtOAc-hexane).
^{1}H-NMR ($CDCl_3$) δ 8.12-7.19 (m, 20H) 6.88 (d, J=9.5 Hz, 1H) 6.76 (s, 1H) 6.20 (m, 1H) 5.94 (dd, J=9.5 Hz, J'=2.7 Hz, 1H) 5.69 (d, J=7.5 Hz, 1H) 5.40 (d, J=2.7 Hz, 1H) 5.09 (m, 2H) 4.86 (dd, J= 12.3 Hz, J'=3.6 Hz, 1H) 4.65 (s, 2H) 4.52 (s, 2H) 3.86 (d, J=7.5 Hz, 1H) 3.65 (s, 1H) 2.48-1.01 (m, 22H, incl. singlets at 2.48, 2.12, 1.83, 1.60, 1.14, 1.06, 3H each). **^{13}C-NMR** ($CDCl_3$) δ 207.3; 171.8; 169.2; 167.5; 167.0; 166.9; 153.9; 140.1; 136.6; 134.2; 133.5; 133.4; 132.9; 131.9; 130.1; 129.2; 129.0; 128.8; 128.7; 128.6; 128.5; 128.35; 128.3; 127.0; 126.4; 82.6; 81.9; 79.1; 78.0; 76.8; 75.7; 75.3; 71.8; 70.6; 53.4; 52.6; 42.5; 40.2; 35.9; 35.1; 25.8; 22.5; 21.3; 20.7; 16.1;14.7. **HRMS** Calcd for $C_{55}H_{58}NO_{16}$ (MH^+): 988.3756, found 988.3732.

Compound 8.

Compound **7** (47 mg, 0.048 mmol) was dissolved in dry dichloromethane (1 mL), cooled to 0°C, and treated with tin tetrachloride (1M in dichloromethane, 0.052 mL, 0.052 mmol). The mixture was stirred at 0°C for 1

h and at RT for 2 h. The solution was directly applied onto a silica column, eluting with 1:1 ethyl acetate/hexane. Yield: 36 mg (75%) of **8** as a foam.
^{1}H-NMR ($CDCl_3$) δ 8.12-7.15 (m, 20H) 7.05 (d, J=9.6 Hz, 1H) 7.02 (s, 1H) 6.15 (dd, J=9.6 Hz, J'=2.1 Hz, 1H) 6.05 (m, 1H) 5.77 (d, J=6.3 Hz, 1H) 5.36 (d, J=2.1 Hz, 1H) 5.33 (s, 1H) 5.17 (s, 2H) 4.20 (s, 2H) 4.02 (d, J=6.2 Hz, 1H) 3.51 (m, 2H) 3.31 (m, 1H) 3.16 (d, J=7.5 Hz, 1H) 3.00 (dd, J=15.5 Hz, J'= 6.3 Hz, 1H) 2.37 (dd, J=15.5 Hz, J'= 9.6 Hz, 1H) 2.19-1.08 (m, 21H, incl.singlets at 2.19, 2.11, 2.08, 1.29, 1.14, 1.13, 3H each).
HRMS Calcd for $C_{55}H_{60}NO_{17}$ (MH^+): 1006.3861, found 1006.3838.

7-(2,2,2)-Trichloroethoxycarbonyl Baccatin III, 9a.

Baccatin III (135 mg, 0.230 mmol) was dissolved in dry dichloromethane (1.5 mL) and treated with pyridine (0.065 mL, 0.804 mmol) and trichloroethyl chloroformate (0.065 mL, 0.748 mmol). A catalytic amount of 4-dimethylaminopyridine (2 mg) was added, and the mixture stirred for 3h. The solution was diluted with ethyl acetate, and washed with saturated aqueous cupric sulfate, water and brine, then dried and concentrated. Chromatography (1:1 ethyl acetate/hexane) afforded **9a** as a white solid (150 mg, 87%), m.p. 220-4°C (dec.).
^{1}H-NMR ($CDCl_3$) δ 8.08-8.05 (m, 2H) 7.61-7.24 (m, 3H) 6.36 (s, 1H) 5.57 (m, 2H) 4.95 (d, J=8.4 Hz, 1H) 4.83 (m, 1H) 4.81 (m, 2H) 4.21 (AB q, J=8.4 Hz, Δν=51.3 Hz, 2H) 3.98 (d, J=6.9 Hz, 1H) 2.60 (m, 1H) 2.30-1.64 (m, 17H, incl. singlets at 2.28, 2.14, 2.04, 1.79, 3H each) 1.10 (s, 3H) 1.05 (s, 3H). **^{13}C-NMR** ($CDCl_3$) δ 202.0; 170.8; 169.3; 167.0; 153.3; 145.1; 133.8; 131.7; 130.2; 129.3; 128.7; 94.7; 83.9; 80.5; 78.7; 77.3; 76.4; 76.0; 74.3; 67.9; 56.3; 47.4; 42.8; 38.5; 33.3; 26.7; 22.6; 20.9; 20.2; 15.3; 10.7.
MS ($C_{34}H_{39}O_{13}Cl_3$) : 760.

Reaction of 9a with Tin Tetrachloride.

Compound **9a** (39 mg, 0.0512 mmol) was dissolved in dry dichloromethane (1.3 mL), cooled to -78°C, and treated with tin tetrachloride (1 M in dichloromethane, 0.073 mL, 0.073 mmol), stirred at -78°C for 15 min, then stirred in an ice bath for a further 15 min. The mixture was then directly applied onto a silica column, and eluted with 75% ethyl acetate in hexane, yielding **10a** (foam, 30 mg, 75%) and **11a** (oil, 6 mg, 15%).
Compound **10a** had:
^{1}H-NMR ($CDCl_3$) δ 8.16-8.13 (m, 2H) 7.62-7.32 (m, 3H) 6.61 (s, 1H) 5.61 (dd, J=11.4 Hz, J'=4.6 Hz, 1H) 5.48 (d, J=4.0 Hz, 1H) 4.80 (AB q, J=11.9 Hz, Δν= 103.2 Hz, 2H) 4.75 (m, 1H) 4.16 (d, J=4.0 Hz, 1H) 4.10 (AB q, J=12.0 Hz, Δν=27.1 Hz, 2H) 3.87 (m, 1H) 3.29 (s, 1H) 3.07 (dd, J=15.1 Hz, J'=4.2 Hz, 1H) 2.40-1.05 (m, 24H, incl. singlets at 2.30, 2.14, 1.75, 1.38, 1.10, 1.05, 3H each).
HRMS Calcd for $C_{34}H_{41}O_{14}Cl_3Na$ (MNa^+) : 801.1460, found 801.1443.
Compound **11a** had:
^{1}H-NMR ($CDCl_3$) δ 8.09 (m, 2H) 7.63-7.43 (m, 3H) 6.52 (s, 1H) 5.48 (m, 2H) 5.24 (m, 1H) 4.81 (AB q, J=11.9 Hz, Δν= 113.1 Hz, 2H) 4.60 (m, 1H) 4.09 (d, J=5.4 Hz, 1H) 3.96 (s, 1H) 3.61 (dd, J=10.9 Hz, J'=4.7 Hz, 1H) 3.40 (dd, J=10.9 Hz, J'= 5.7 Hz, 1H) 3.20 (d, J=9.8 Hz, 1H) 2.73 (dd, J=15.7 Hz, J'=2.6 Hz, 1H) 2.47 (dd, J=15.7 Hz, J'=10.9 Hz, 1H) 2.36-1.04 (m, 20H, icl. singlets at 2.33, 2.30, 2.17, 1.30, 1.12, 1.05 , 3H each). **MS** ($C_{34}H_{41}O_{14}Cl_3$) : 778.

7-Ethoxycarbonyl Baccatin III, 9b.

Baccatin III (46 mg, 0.078 mmol) was dissolved in dry dichloromethane (1.5 mL) and treated with pyridine (0.019 mL, 0.234 mmol) and ethyl chloroformate (0.0224 mL, 0.234 mmol). A catalytic amount of 4-dimethylaminopyridine (2 mg) was also added. The solution was stirred at RT for 2h, then another portion of pyridine (0.019 mL) and ethyl chloroformate (0.0224 mL) was added. After a total of 18 h at RT, ethyl acetate was added, and the organics were washed with water, saturated aqueous sodium bicarbonate, water, then brine. After drying and evaporation, the crude product was purified by chromatography (50-60% ethyl acetate in hexane) to yield **9b** as a white solid (27 mg, 52%), m.p. 238-42°C (dec.), together with some starting material (15 mg, 33%).
^{1}H-NMR ($CDCl_3$) δ 8.11-8.08 (m, 2H) 7.63-7.45 (m, 3H) 6.40 (s, 1H) 5.61 (d, J=6.9 Hz, 1H) 5.51 (dd, J=10.5 Hz, J'= 7.2 Hz, 1H) 4.97 (d, J=8.5 Hz, 1H) 4.85 (m, 1H) 4.22 (m, 2H) 4.21 (AB q, J=8.3 Hz, Δν=40.3 Hz, 2H) 3.99 (d, J= 6.9 Hz, 1H) 2.60 (m, 1H) 2.27-1.60 (m, 17H, incl. singlets at 2.20, 2.14, 2.08, 1.77, 3H each) 1.28 (t, J=7.2 Hz, 3H) 1.12 (s, 3H) 1.06 (s, 3H). **^{13}C-NMR** ($CDCl_3$) δ 202.2; 170.7; 168.9; 166.9; 154.2; 144.7; 133.7; 131.7; 130.1; 129.2; 128.6; 83.9; 80.6; 78.7; 76.3; 75.9; 75.6; 75.4; 74.3; 67.9; 64.5; 56.2; 47.4; 42.8; 38.4; 33.4; 26.6; 22.6; 20.8; 20.2; 15.3; 14.1; 10.6. **HRMS** Calcd for $C_{34}H_{43}O_{13}$: 659.2704, found 659.2701.

Reaction of 9b with Tin Tetrachloride.

Compound **9b** (26 mg, 0.040 mmol) was dissolved in dry dichloromethane (1 mL), cooled to 0°C, and treated with tin tetrachloride (1 M in dichloromethane, 0.043 mL, 0.043 mmol) for 1h, then the mixture was directly applied onto a silica column, eluting with 80% ethyl acetate in hexane, to yield **10b** (foam, 14 mg, 52%) and **11b** (oil, 2.8 mg, 10%). Compound **10b** had: **^{1}H-NMR** ($CDCl_3$) δ 8.05-8.03 (m, 2H) 7.60-7.42 (m, 3H) 6.57 (s, 1H) 5.53 (m, 2H) 4.70 (m, 1H) 4.20 (AB q, 2H) 4.05 (AB q, J=11.9 Hz, Δν=22.9 Hz, 2H) 3.81 (s, 1H) 3.75 (s, 1H) 3.58 (s, 1H) 3.10 (d, J=7.5 Hz, 1H) 2.79 (dd, J=15.7 Hz, J'=3.5 Hz, 1H) 2.43 (dd, J=15.7 Hz, J'= 10.2 Hz, 1H) 2.30-1.34 (m, 16H, incl. singlets at 2.30, 2.15, 1.64, 1.30, 3H each) 1.28 (t, J=7.2 Hz, 3H) 1.21 (s, 3H) 1.11 (s, 3H). **HRMS** Calcd for $C_{34}H_{45}O_{14}$ (MH^+): 677.2809, found 677.2808.
Compound **11b** had: **^{1}H-NMR** ($CDCl_3$) δ 8.09-8.05 (m, 2H) 7.61-7.42 (m, 3H) 6.52 (s, 1H) 5.47 (d, J=5.0 Hz, 1H) 5.38 (dd, J= 11.7 Hz, J'=4.4 Hz, 1H) 5.20 (m, 1H) 4.58 (m, 1H) 4.22 (q, J=7.1 Hz, 2H) 4.08 (d, J=5.3 Hz, 1H) 3.96 (s, 1H) 3.58 (dd, J=10.9 Hz, J'= 4.8 Hz, 1H) 3.38 (dd, J=10.9 Hz, J'=5.9 Hz, 1H) 3.24 (d, J=9.8 Hz, 1H) 2.73 (dd, J=15.9 Hz, J'= 2.6 Hz, 1H) 2.46 (dd, J=15.9 Hz, J'=10.5 Hz, 1H) 2.33 - 1.03 (m, 25H, incl. singlets at 2.33, 2.28, 2.17, 1.26, 1.11, 1.03, 3H each, and triplet at 1.30, J=7.1 Hz, 3H). **HRMS** Calcd for $C_{34}H_{45}O_{14}$ (MH^+): 677.2809, found 677.2795.

7,13-Diacetyl Baccatin III, 9c.

This compound, reported in the literature, [12] was prepared under much milder conditions and in higher yield than previously described, as follows:
Baccatin III (826.5 mg, 1.409 mmol) was dissolved in dry dichloromethane (2 mL) and pyridine (2 mL), and

acetic anhydride (1.33 mL, 14.089 mmol) were added, followed by a catalytic amount of 4-dimethylaminopyridine (18 mg). The solution was stirred at RT for 15 h, then it was diluted with water and ethyl acetate, and the organics were extensively washed with aqueous cupric sulfate (5% w/v), water and brine. Drying and evaporation afforded a crude product that was purified by chromatography (40% ethyl acetate in hexane). Yield: 921 mg (99%) of **9c** as a white solid, m.p. 230-3°C (lit.[12] : 234-6°C). The NMR spectrum was identical to the literature one.[12] **HRMS** Calcd for $C_{35}H_{43}O_{13}$ (MH^+): 671.2704, found 671.2715.

Reaction of 9c with Tin Tetrachloride.

Compound **9c** (45 mg, 0.067 mmol) was dissolved in dry dichloromethane (3 mL), cooled to 0°C, and treated with tin tetrachloride (1M in dichloromethane, 0.074 mL, 0.074 mmol) for 1h at 0°C. The mixture was directly applied onto a silica column, and quickly eluted with ethyl acetate (gradient 40% to 60%) in hexane, to yield **10c** (oil, 20.4 mg, 44%), **11c** (oil, 13.6 mg, 29%) and **22** (oil, 2.0 mg, 4%).
Compound **10c** had: **^{1}H-NMR** ($CDCl_3$) δ 8.00-7.98 (m, 2H) 7.60-7.55 (m, 3H) 6.44 (s, 1H) 5.93 (m, 1H) 5.66 (dd, J=11.4, J'= 4.5 Hz, 1H) 5.50 (d, J=5.4 Hz, 1H) 4.03 (d, J=5.4 Hz, 1H) 4.02 (AB q, J=11.9 Hz, Δν=46.1 Hz, 2H) 3.75 (m, 1H) 3.39 (s, 1H) 2.91 (s, 1H) 2.88 (dd, J=15.6 Hz, J'= 4.8 Hz, 1H) 2.42 (dd, J=15.6 Hz, J'= 9.9 Hz, 1H) 2.20-1.11 (m, 27H, incl. singlets at 2.17, 2.16, 2.15, 1.99, 1.62, 1.34, 1.13, 1.11, 3H each). **HRMS** Calcd for $C_{35}H_{45}O_{14}$ (MH^+) : 689.2809, found 689.2816.
Compound **11c** had: **^{1}H-NMR** ($CDCl_3$) δ 8.05-8.02 (m, 2H) 7.75-7.43 (m, 3H) 6.39 (s, 1H) 6.01 (dd, J=8.3 Hz, J'=6.5 Hz, 1H) 5.51 (d, J=5.6 Hz, 1H) 5.42 (dd, J=11.9 Hz, J'=4.5 Hz, 1H) 5.19 (m, 1H) 3.82 (d, J=5.6 Hz, 1H) 3.52 (d, J=11.1 Hz, J'=3.9 Hz, 1H) 3.38 (m, 1H) 3.35 (s, 1H) 2.92 (dd, J=15.3, J'=6.3 Hz, 1H) 2.50-1.10 (m, 29H, incl. singlets at 2.29, 2.17, 2.14, 2.01, 1.70, 1.28, 1.16, 1.13, 3H each). **HRMS** Calcd for $C_{35}H_{45}O_{14}$ (MH^+) : 689.2809, found 689.2828.
Compound **22** had: **^{1}H-NMR** ($CDCl_3$) δ 7.94-7.91 (m, 2H) 7.64-7.45 (m, 3H) 6.28 (s, 1H) 6.01 (m, 1H) 5.54 (d, J=7.0 Hz, 1H) 5.47 (dd, J=9.6 Hz, J'=7.7 Hz, 1H) 4.44 (dd, J=10.7 Hz, J'=3.1 Hz, 1H) 4.27 (dd, J=10.7 Hz, J'=2.7 Hz, 1H) 3.45 (dd, J=9.8 Hz, J'=7.0 Hz, 1H) 2.95 (dd, J=20.0 Hz, J'=7.6 Hz, 1H) 2.58 (dd, J=15.7 Hz, J'=10.1 Hz, 1H) 2.38 (d, J=9.8 Hz, 1H) 2.33-1.18 (m, 27H, incl. singlets at 2.19, 2.17, 2.10, 2.06, 2.04, 1.31, 1.20, 1.18, 3H each). **MS** ($C_{35}H_{42}O_{13}$): 670.

Reaction of Baccatin III with Dimethylphenylsilane in Trifluoroacetic Acid.

Baccatin III (175 mg, 0.298 mmol) was suspended in dimethylphenylsilane (1.00 mL, 6.467 mmol) and chilled to 0°C. While stirring vigorously with a stirring bar, trifluoroacetic acid (0.8 mL) was added slowly by syringe over 10 min. The slurry was stirred at 0°C for 45 min, then the reaction was quenched by pouring into aqueous saturated sodium bicarbonate, extracted exhaustively with ethyl acetate, dried and evaporated. The crude liquid was diluted with acetonitrile, and washed three times with equal volumes of hexane, in order to remove the excess silane. The acetonitrile phase was evaporated, and the residue chromatographed (silica, gradient of 30-70% acetonitrile in dichloromethane) to yield some unreacted baccatin III (29 mg, 16%), acetal **19** (foam, 74 mg, 42%), and acetal **20a** (oil, 16 mg, 9%).

Compound **19** had: **^{1}H-NMR** ($CDCl_3$) δ 7.90 (d, J=7.3 Hz, 2H) 7.55-7.38 (m, 3H) 6.41 (s, 1H) 5.52 (d, J=7.1 Hz, 1H) 4.78 (m, 1H) 4.72 (m, 1H) 4.39 (m, 1H) 4.22 (d, J=8.8 Hz, 1H) 3.92 (br s, 1H) 3.71 (d, J=7.1 Hz, 1H) 3.46 (s, 1H) 3.33 (d, J=8.8 Hz, 1H) 2.81 (br d, J=5.7 Hz, 1H) 2.62 (m, 1H) 2.42 (m, 1H) 2.23-1.10 (m, 13H, incl. singlets at 2.21, 1.94, 1.41, 3H each) 1.11 (s, 3H) 1.03 (s, 3H) 0.92 (d, J=4.7 Hz, 3H). **HRMS** Calcd for $C_{31}H_{40}O_{11}Na$ (MNa^+) : 611.2468, found 611.2460.

Compound **20a** had: **^{1}H-NMR** ($CDCl_3$) δ 8.13 (d, J=7.3 Hz, 2H) 7.66-7.43 (m, 3H) 6.26 (s, 1H) 5.85 (d, J=11.6 Hz, 1H) 5.17 (m, 1H) 4.35 (dd, J=11.0 Hz, J'=6.2 Hz, 1H) 4.24-4.19 (m, 2H) 4.11 (s, 1H) 3.58 (s, 1H) 3.55-3.47 (m, 3H) 2.47-1.03 (m, 24H, incl. singlets at 2.18, 1.93, 1.53, 1.30, 1.08 , 3H each, and doublet at 1.50, J=4.9 Hz, 3H). **HRMS** Calcd for $C_{31}H_{40}O_{11}Na$ (MNa^+) : 611.2468, found 611.2475.

Compound **20a** was further characterized as a diacetate: **20a** (30 mg, 0.051 mmol) was dissolved in dichloromethane (1 mL) and treated with acetic anhydride (0.048 mL, 0.510 mmol) and triethylamine (0.071 mL, 0.510 mmol) for 16 h at RT. Evaporation and chromatography (silica, 60% ethyl acetate in hexane) gave **20b** (foam, 13.7 mg, 40%). **^{1}H-NMR** ($CDCl_3$) δ 8.04 (d, J=7.4 Hz, 2H) 7.56-7.40 (m, 3H) 6.25 (s, 1H) 5.61 (d, J=8.2 Hz, 1H) 5.47 (dd, J=11.0 Hz, J'=6.2 Hz, 1H) 5.00 (q, J=4.9 Hz, 1H) 4.71 (m, 1H) 4.23 (d, J=12.3 Hz, 1H) 4.22 (m, 1H) 4.09 (d, J=12.3 Hz, 1H) 3.20 (d, J=8.2 Hz, 1H) 2.63-2.36 (m, 3H) 2.11 (s, 3H) 2.02-1.52 (m, 18H, incl. singlets at 2.00, 1.92, 1.65, 1.40, 3H each , and doublet at 1.57, J=4.9 Hz, 3H) 1.06 (s, 3H) 1.01 (s, 3H). **HRMS** Calcd for $C_{35}H_{44}O_{13}Na$ (MNa^+) : 695.2680, found 695.2700.

Compound 21.

2'-Benzyloxycarbonyl taxol, **2,** (286 mg, 0.290 mmol) was dissolved in dry dichloromethane (6 mL). To this solution at 0°C was added tin tetrachloride (1 M in dichloromethane, 0.319 mL, 0.319 mmol). The solution was stirred at 0°C for 2 hr. The solution was directly applied to a silica column and the product was eluted with a gradient of 40-70% ethyl acetate in hexanes, to afford **21** (40.4 mg, 14%, m.p. 136-8°C from EtOAc-hexane), together with **4a** (151 mg, 52%). **21** had: **^{1}H-NMR** ($CDCl_3$) δ 8.02-7.20 (m, 20H) 7.07 (d, J=9.7 Hz, 1H) 6.33 (s, 1H) 6.10 (m, 2H) 5.59 (d, J=5.5 Hz, 1H) 5.47 (d, J=3.3 Hz, 1H) 5.12 (AB q, 2H) 4.83 (d, J=5.5 Hz, 1H) 4.65 (s, 1H) 4.51 (m, 1H) 4.07 (m, 2H) 3.96 (s, 1H) 3.50 (d, J=4.8 Hz, 1H) 2.79 (dd, J=15.4 Hz, J'=7.9 Hz, 1H) 2.57 (m, 2H) 2.19 (s, 3H) 2.00 (s, 3H) 1.94 (s, 3H) 1.65 (s, 3H) 1.46 (dd, J=14.6 Hz, J'=4.2 Hz, 1H) 1.19 (s, 3H). **^{13}C-NMR** ($CDCl_3$) δ 206.9 (C-9); 170.2; 169.6; 167.2; 167.1; 166.7 (amide, ester carbonyls); 154.4 (carbonate carbonyl); 140.9 (C-12); 137.0 (C-11); 136.2; 134.1; 133.6; 133.4; 132.1; 129.8.; 129.0; 128.7; 128.5; 128.4; 127.6; 127.1; 126.9; 126.7 (aromatics); 83.8 (C-4); 78.7 (C-2); 77.4 (C-2'); 76.8 (C-10); 74.7 (C-7); 73.1 (C-13); 70.8 (CBZ $\underline{CH_2}$); 68.1 (C-5); 63.1 (C-20); 58.8 (C-8); 52.8 (C-3'); 42.0 (C-15); 37.8 (C-14); 34.9 (C-6); 33.8 (C-3); 27.9 (C-16); 24.4 (C-19); 22.4 (acetate $\underline{CH_3}$); 20.8 (C-17 and acetate $\underline{CH_3}$); 15.9 (C-18). **HRMS** Calcd for $C_{55}H_{58}NO_{16}$ (MH^+): 988.3756, found 988.3721.

Compound 23.

Compound **4a** (131 mg, 0.130 mmol) was dissolved in dry acetonitrile (3 mL). To this solution at 0°C was added lead tetraacetate (63.6 mg, 0.143 mmol). After 10 min the solvent was removed *in vacuo*, and the residue was chromatographed on silica (60% ethyl acetate in hexanes) to afford **23** (101.5 mg , 80%) as a

white solid, m.p. 145-8°C (EtOAc-hexane). **^{1}H-NMR** ($CDCl_3$) δ 8.10-7.24 (m, 20H) 7.11 (d, J=9.0 Hz, 1H) 6.42 (s, 1H) 6.24 (m, 1H) 5.90 (dd, J=9.0 Hz, J'=2.5 Hz, 1H) 5.59 (d, J=8.2 Hz, 1H) 5.33 (d, J=2.7 Hz, 1H) 5.14 (m, 2H) 4.54 (s, 1H) 4.31 (m, 1H) 4.17 (d, J=8.1 Hz, 1H) 2.59-1.08 (m, 24H, incl. singlets at 2.22, 2.14, 1.86, 1.10, 3H each, and 1.23, 6H). **^{13}C-NMR** ($CDCl_3$) δ 201.9 (C-9); 201.1 (C-4); 170.8; 169.7; 168.2; 166.8; 166.6 (carbonyls); 154.3 (carbonate carbonyl); 140.5 (C-12); 137.0 (C-11); 134.2; 134.0; 133.6; 133.0; 132.0; 130.2; 129.9; 129.1; 129.0; 128.7; 128.6; 128.4; 127.1; 127.0; 126.7 (aromatics); 78.0 (C-10); 77.2 (C-2'); 77.1 (C-1); 74.7 (C-5); 73.4 (C-2); 72.1 (C-13); 70.8 (CBZ $\underline{CH_2}$); 69.1 (C-7); 61.5 (C-8); 53.0 (C-3'); 49.5 (C-3); 42.5 (C-15); 36.5 (C-6); 35.3 (C-14); 26.3 (C-16); 21.6 (C-17); 21.1; 20.8 (acetate $\underline{CH_3}$'s); 15.0 (C-18); 10.6 (C-19). **HRMS** Calcd for $C_{54}H_{56}NO_{16}$ (MH^+): 974.3599, found 974.3597.

Compound 24.

Compound **4b** (630 mg, 0.627 mmol) was dissolved in dry acetonitrile (6 mL). To this solution at 0°C was added lead tetraacetate (305 mg, 0.690 mmol). After 30 min, the solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography (50% ethyl acetate in hexanes) to afford **24** as a foam (433 mg, 71%).

^{1}H-NMR ($CDCl_3$) δ 8.11-7.19 (m, 20H) 7.05 (d, J=9.3 Hz, 1H) 6.45 (s, 1H) 6.09 (m, 1H) 6.00 (dd, J=9.2 Hz, J'=2.3 Hz, 1H) 5.32 (d, J=2.4 Hz, 1H) 5.27 (d, J=6.1 Hz, 1H) 5.20 (m, 1H) 5.12 (m, 2H) 4.75 (d, J=6.1 Hz, 1H) 3.82 (s, 1H) 3.03 (dd, J=15.7 Hz, J'=6.9 Hz, 1H) 2.79 (m, 1H) 2.41-1.68 (m, 16H, incl. singlets at 2.12, 1.82, 1.69, 1.68, 3H each) 1.13 (s, 3H) 1.05 (s, 3H). **^{13}C-NMR** ($CDCl_3$) δ 207.2 (C-9); 200.2 (C-4); 169.8; 169.1; 167.8; 166.8; 166.75; 166.7 (carbonyls); 154.1 (carbonate carbonyl); 139.9 (C-12); 137.3 (C-11); 135.7; 134.6; 134.0; 133.3; 131.7; 130.1; 129.3; 129.0; 128.7; 128.6; 128.4; 128.3; 128.2; 127.2; 127.0 (aromatics); 77.9 (C-10); 77.3 (C-2'); 77.2 (C-1); 74.8 (C-5); 74.6 (C-2); 72.0 (C-13); 70.5 (C-7 and CBZ $\underline{CH_2}$); 57.2 (C-8); 53.1 (C-3'); 49.5 (C-3); 42.0 (C-15); 36.6 (C-6); 36.2 (C-14); 30.0 (C-16); 20.8; 20.5 (acetate $\underline{CH_3}$'s); 20.4 (C-17); 19.5 (C-18); 15.2 (C-19). **HRMS** Calcd for $C_{54}H_{56}NO_{16}$ (MH^+): 974.3599, found 974.3596.

2'-Triethylsilyl Taxol , 25c.

Taxol **1** (493 mg, 0.578 mmol) was dissolved in dry dichloromethane (2 mL). To this solution was added dry pyridine (3 mL), followed by triethylsilyl chloride (0.485 mL, 2.890 mmol). The mixture was stirred at RT overnight, then it was diluted with dichloromethane, washed with water, saturated cupric sulfate and brine. The organic phase was dried and concentrated *in vacuo*. The residue was purified by silica gel chromatography (40-70% ethyl acetate in hexanes) to afford **25c** (451 mg, 81%), together with taxol (86 mg, 17.4%).

^{1}H-NMR ($CDCl_3$) δ 8.11-8.06 (m, 2H) 7.73-7.20 (m, 13H) 7.08 (d, J=8.9 Hz, 1H) 6.25 (m, 2H) 5.66 (m, 2H) 4.92 (d, J=7.7 Hz, 1H) 4.66 (d, J=2.1 Hz, 1H) 4.38 (m, 1H) 4.23 (AB q, J=8.4 Hz, Δν=31.6 Hz, 2H) 3.79 (d, J=7.0 Hz, 1H) 2.45-1.10 (m, 22H, incl. singlets at 2.42, 2.20, 1.82, 1.66, 1.18, 1.11, 3H each) 0.80 (m, 9H) 0.42 (m, 6H). **HRMS** Calcd for $C_{53}H_{66}NSiO_{14}$ (MH^+): 968.4253, found 968.4284.

7-Triethylsilyl Taxol, 25f.

2'-Benzyloxycarbonyl taxol (222.0 mg, 0.225 mmol) was dissolved in dry pyridine (2 mL). To this solution was added triethylsilyl chloride (0.189 mL, 1.125 mmol). The reaction mixture was heated (55°C) for 15 h, then cooled and diluted with ethyl acetate. The organic layer was washed with saturated aqueous cupric sulfate, water, then dried and concentrated *in vacuo*. The residue was purified by silica gel chromatography (40% ethyl acetate in hexanes) to afford the desired 2'-benzyloxycarbonyl-7-triethylsilyl taxol (178.5 mg, 72%). This product (137.8 mg, 0.125 mmol) was dissolved in ethyl acetate (2.5 mL). A catalytic amount of palladium on charcoal (10%, 40 mg, 0.0375 mmol) was added. The reaction was stirred under a hydrogen atmosphere for 4 h. Then the suspension was filtered, the filtrate was evaporated *in vacuo* and the residue was chromatographed (silica, 40% ethyl acetate in hexanes) to afford **25f** as a foam (120 mg, 99%).
^{1}H-NMR ($CDCl_3$) δ 8.11-8.08 (m, 2H) 7.74-7.23 (m, 13H) 7.02 (d, J=8.9 Hz, 1H) 6.40 (s, 1H) 6.16 (m, 1H) 5.77 (dd, J=8.9 Hz, J'=2.5 Hz, 1H) 5.65 (d, J=7.0 Hz, 1H) 4.88 (d, J=7.9 Hz, 1H) 4.77 (s, 1H) 4.01 (dd, J=10.4 Hz, J'=6.7 Hz, 1H) 4.22 (AB q, J=8.3 Hz, Δν=34.5 Hz, 2H) 3.77 (d, J=7.0 Hz, 1H) 3.59 (s, 1H) 2.54-1.11 (m, 23H, incl. singlets at 2.35, 2.15, 1.88, 1.67, 1.20, 1.15, 3H each) 0.89 (m, 9H) 0.53 (m, 6H). **HRMS** Calcd for $C_{53}H_{66}NSiO_{14}(MH^+)$ 968.4253, found 968.4273.

Reaction of Taxol, 1, with Zinc Bromide and Other Lewis Acids.

Taxol **1** (1.118 g, 1.310 mmol) was dissolved in dry methanol (13 mL). To this solution was added anhydrous zinc bromide (1.771g, 7.861 mmol) . The reaction was stirred overnight at RT. The solvent was removed *in vacuo*, the residue was taken up in ethyl acetate and washed with water and brine. The organic phase was dried and concentrated *in vacuo* to give a residue which was purified by silica gel chromatography (60% - 100% ethyl acetate in hexanes) to afford 10-deacetyl taxol, **26a** (368 mg, 36%), [3] 10-deacetyl-7-epi taxol , [3] **27a,** (316 mg, 29%) together with unreacted taxol (155 mg, 14%).
The reactions with magnesium bromide, zinc iodide, zinc chloride, and cerium chloride were carried out analogously. The results are reported in Table 1.

Reaction of Taxol, 1 , with $PdCl_2(CH_3CN)_2$.

Taxol, **1** (59 mg, 0.069 mmol) was dissolved in dry methanol (1.4 mL), and to this solution was added $PdCl_2(CH_3CN)_2$ (35.9 mg, 0.138 mmol). The reaction mixture was stirred at roomtemperature for 24 h. The solvent was then removed in vacuo, and the residue purified by silica gel chromatography (60-85% ethyl acetate in hexanes) to afford unreacted taxol (24 mg, 40%) together with the desired 10-deacetyl taxol, **26a** (15.5 mg, 30%).

Reaction of 7-epi Taxol , 25b, with Zinc Bromide.

7-Epi taxol, **25b,** [16] (46 mg, 0.054 mmol) was dissolved in dry methanol (1 mL), and to this solution was added anhydrous zinc bromide (48.5 mg, 0.216 mmol). The reaction mixture was stirred at RT overnight. The

solvent was removed *in vacuo* and the residue was chromatographed (55% ethyl acetate in hexanes) to afford unreacted **25b** (35 mg, 76%) and 10-deacetyl-7-epi taxol **27a** (2.0 mg, 4%).

Reaction of 2'-Triethylsilyl Taxol, 25c, with Zinc Bromide.

2'-Triethylsilyl taxol, **25c**, (600 mg, 0.621 mmol) was dissolved in dry methanol (6 mL), and to this solution was added zinc bromide (558 mg, 2.480 mmol). After a period of 24 h at RT, then another portion of zinc bromide (279 mg, 1.240 mmol) was added. The reaction was stirred for another 24 h, the solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate, washed with water and brine, and dried. After evaporation *in vacuo*, the residue was chromatographed (30-50% ethyl acetate in hexanes) to give **26b** (180 mg, 31%) together with **27b** (230 mg, 40%).
Compound **26b** had: ^{1}**H-NMR** ($CDCl_3$) δ 8.14-8.11 (m, 2H) 7.76-7.25 (m, 13H) 7.15 (d, J=8.8 Hz, 1H) 6.26 (m, 1H) 5.67 (m, 2H) 5.19 (d, J=1.5 Hz, 1H) 4.95 (d, J=7.7 Hz, 1H) 4.67 (d, J=2.0 Hz, 1H) 4.27 (AB q, J=8.4 Hz, Δν=31.1 Hz, 2H) 4.21 (m, 2H) 3.92 (d, J=7.0 Hz, 1H) 2.64-1.73 (m, 15H, incl. singlets at 2.53, 1.92, 1.74, 3H each) 1.21 (s, 3H) 1.09 (s, 3H) 0.80 (m, 9H) 0.47 (m, 6H). **HRMS** Calcd for $C_{51}H_{64}NO_{13}Si$ (MH^+): 926.4147, found 926.4123.
Compound **27b** had: ^{1}**H-NMR** ($CDCl_3$) δ 8.18-8.14 (m, 2H) 7.75-7.25 (m, 13H) 7.11 (d, J=8.9 Hz, 1H) 6.30 (m, 1H) 5.72 (m, 2H), 5.45 (s, 1H) 4.93 (dd, J=8.4 Hz, J'= 4.4 Hz, 1H) 4.80 (d, J=12.0 Hz, 1H) 4.69 (d, J=2.1 Hz, 1H) 4.41 (m, 2H) 4.11(s, 1H) 3.93 (d, J=7.4 Hz, 1H) 3.69 (m, 1H) 2.64-1.08 (m, 20H, incl. singlets at 2.64, 1.87, 1.69, 1.21, 1.09, 3H each) 0.79 (m, 9H), 0.43 (m, 6H). **HRMS** Calcd for $C_{51}H_{64}NO_{13}Si$ (MH^+): 926.4147, found 926.4117.

Reaction of Taxol, 1, with Lithium Iodide.

Taxol , **1**, (1.054 g, 1.240 mmol) was dissolved in methanol (24 mL). This solution was treated with lithium iodide (662 mg, 4.941 mmol) at RT. After 10 h, the solvent was removed *in vacuo*, the residue was dissoved in EtOAc and washed with water and brine . The organic phase was then dried and concentrated *in vacuo*. The residue was chromatographed (40-80% ethyl acetate in hexanes) to afford 10-deacetyl baccatin **28a** [11] (382 mg, 58%) together with 10-deacetyl-7-epi baccatin **28b** [11] (269 mg, 40.0%) and the side chain methyl ester **29** (303 mg, 82%). Compound **29** had: m.p. 182-3°C (lit.[17] 183-5°C). ^{1}**H-NMR** ($CDCl_3$) δ 7.78-7.25 (m, 10H) 7.01 (d, J=9.1 Hz, 1H) 5.74 (dd, J=9.1 Hz, J'=1.8 Hz, 1H) 4.32 (dd, J=4.0 Hz, J'=1.8 Hz, 1H) 3.84 (s, 3H),3.39 (d, J=4.0 Hz, 1H). **MS** ($C_{17}H_{17}NO_4$): 299.

Reaction of Taxol, 1 , with Cesium Fluoride.

Taxol, **1** , (91 mg, 0.107 mmol) was dissolved in dry methanol (2 mL). To this solution was added cesium fluoride (130 mg, 0.853 mmol). The reaction mixture was stirred at room temperature for 1 week, then diluted with EtOAc , and washed with brine . The organic phase was dried and concentrated *in vacuo*. The residue was purified by silica gel chromatography (50-90% ethyl acetate in hexanes) to afford the side chain methyl ester **29** (20 mg, 63%) together with 10-deacetyl-7-epi baccatin **28b** (22 mg, 38%) and 10-deacetyl baccatin

28a (21.2 mg, 36%).

Reaction of 2'-Triethylsilyl Taxol, 25c , with Lithium Iodide.

2'-Triethylsilyl taxol, **25c,** (40 mg, 0.043 mmol) was dissolved in dry methanol (1 mL), and to this solution was added lithium iodide (23.6 mg, 0.173 mmol). The reaction mixture was stirred for 2 weeks at RT. The solvent was then removed *in vacuo,* and the residue was purified by silica gel chromatography (40-90% ethyl acetate in hexanes) to afford 10-deacetyl baccatin **28a** (5.2 mg, 22%) , together with 10-deacetyl-7-epi baccatin **28b** (8 mg, 34%) and the side chain methyl ester **29** (10 mg, 71%).

Reaction of 7-Triethylsilyl Taxol , 25f, with Lithium Iodide.

7-Triethylsilyl taxol, **25f,** (39 mg, 0.040 mmol) was dissolved in dry methanol (1 mL). This solution was treated with lithium iodide (22 mg, 0.161 mmol) and the reaction mixture was stirred overnight at room temperature. After work up, the residue was chromatographed (40% ethyl acetate in hexanes) to afford 7-triethylsilyl baccatin **28c** (23.1 mg, 82%).

Reaction of 7-epi Taxol , 25b, with Lithium Iodide.

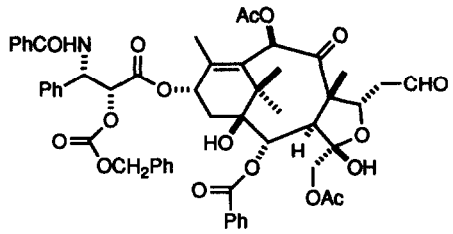
7-Epi taxol, **25b** , (103 mg, 0.121 mmol) was dissolved in methanol (2.1 mL). To this solution was added lithium iodide (64.5 mg, 0.483 mmol), and the reaction was stirred at RT for 14 h, and evaporated to dryness *in vacuo.* The residue was chromatographed as above to afford 7-epi baccatin **28d** (40 mg, 56%) together with 10-deacetyl-7-epi baccatin **28b** (11 mg, 17%). Compound **28d** had: **^{1}H-NMR** ($CDCl_3$) δ 8.10-8.07 (m, 2H) 7.59-7.43 (m, 3H) 6.79 (s, 1H) 5.68 (d, J=7.4 Hz, 1H) 4.91 (dd, J=9.0 Hz, J'=3.6 Hz, 1H) 4.80 (m, 2H) 4.34 (m, 2H) 3.98 (d, J=7.4 Hz, 1H) 3.64 (m, 1H) 2.35-1.60 (m, 19H, incl. singlets at 2.33, 2.16, 1.96, 1.60, 3H each) 1.08 (s, 3H), 1.02 (s, 3H). **HRMS** Calcd for $C_{31}H_{39}O_{11}$ (MH^+): 587.2492, found 587.2471.

REFERENCES AND NOTES

1. Slichenmeyer, W.J.; Von Hoff, D.D. *Anti-Cancer Drugs* **1991**, *2*, 519.
2. Kingston, D.G.I. *Pharmac. Ther.* **1991**, *52*, 1.
3. Samaranayake, G.; Magri, N.F.; Jitrangsri, C.; Kingston, D.G.I. *J.Org.Chem.* **1991**, *56*, 5114.
4. Roberts, R.M.; Corse, J.; Boschan, R.; Seymour, D.; Winstein, S. *J.Am.Chem.Soc.* **1958**, *80*, 1247 and references therein.
5. Thermodynamic data suggest that oxetanes have enhanced enthalpy of hydrogen bond formation *vs.* acyclic or other cyclic ethers. See, for example : Bellon, L.; Taft, R.W.; Abboud, J.L.M. *J.Org.Chem.* **1980**, *45*, 1166.
6. Deslongchamps, P. "*Stereoelectronic Effects in Organic Chemistry*", Pergamon Press, Oxford, **1983.**
7. Sugihara, J.M. *Adv.Carbohydr.Chem.* **1953**, *8*, 1.
8. The stereochemistry at the acetal carbon in **19** and **20** is only tentative and is based on the assumption

that hydride attack occurs from the much less hindered convex face of the molecule.

9. We have later run these reactions again while the manuscipt was being reviewed. On employing fresh batches of lead tetraacetate and **4b** as a starting material, a second product, whose ^{1}H- and ^{13}C-NMR spectra are in agreement with structure **i** below, was isolated. We are currently trying to pinpoint whether impurities in the reagent are responsible for this variability.



i

10. Performed as described in: Swindell, C.S.; Krauss, N.E.; Horwitz, S.B.; Ringel, I. *J.Med.Chem.* **1991,** *34,* 1176. We thank Dr. S.Mamber for performing this test.

11. We are grateful to Dr.C.Fairchild for performing the assay.

12. Magri, N.F.; Kingston, D.G.I.; Jitrangsri, C.; Piccariello, T. *J.Org.Chem.* **1986,** *51*, 3239.

13. Baker, J.K. *Spectr.Lett.* **1992,** *25*, 31.

14. Bax, A.; Summers, M.F. *J.Am.Chem.Soc.* **1986,** *108*, 2093.

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

16. Huang, C.H.O.; Kingston, D.G.I.; Magri, N.F.; Samaranayake, G.; Boettner, F.E. *J.Nat.Prod.* **1986,** *49*, 665.

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