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REARRANGEMENT REACTIONS OF TAXANES: STRUCTURAL MODIFICATIONS OF 10-DEACETYLBACCATIN III.

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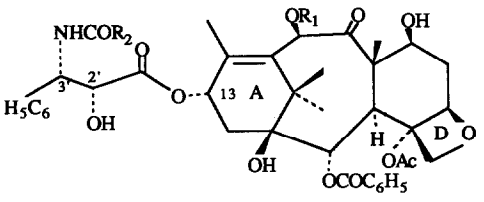
Abstract- 10-Deacetylbaccatin III **2** is a taxane diterpenoid isolated from the plant genus *Taxus*, which has been used for the partial synthesis of the antitumor compounds taxol and taxotere®. A number of structural modifications have been performed on **2** under acidic and basic conditions in order to obtain new synthetic precursors of taxol and taxotere® analogues.

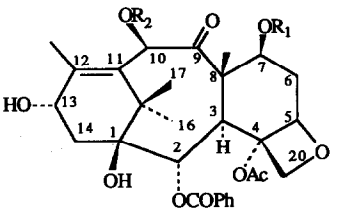
Introduction

Today, taxol **1** , a diterpene isolated in 1971 from the trunk bark of *Taxus brevifolia* Nutt. (Taxaceae)[1] , is one of the most promising new drugs studied in the field of cancer chemotherapy. In phase I clinical trials, taxol has shown antitumor activity in several malignant neoplasms and has demonstrated in phase II studies, clear efficacy in the treatment of refractory ovarian cancer [2]. Another point of interest is that taxol belongs to a new series of antimitotic agents having an unusual mode of action on the tubulin - microtubules system [3]. A major drawback of taxol is however its limited availability from natural sources. Consequently several teams have put their efforts into the total [4] and partial synthesis [5] of this complex molecule.

Some years ago, we found in the leaves of the European yew tree, *Taxus baccata* L., a suitable precursor of taxol (10-deacetylbaccatin III **2** [6, 5b]) which is more naturally abundant than taxol. This compound has been transformed into taxol [5] and a number of structural analogues [7]. Screening of these new products by use of the "tubulin test" [8] led us to select a new analogue, taxotere® **3** [7c-d,9] which has then been shown to be more potent than taxol as a promotor of tubulin assembly as well as an inhibitor of cell replication [10]. Recent investigations on the structure-activity relationships in the taxol **1** and taxotere® **3** series showed the importance of the nature and the configuration of the side chain at C-13 [7a, 7c, 11]. While the critical role played by the C-13 ester group is well known [1], no studies have been published on the role of the ester groups at C-2 and C-4. Moreover, 10-deacetylbaccatin III **2** contains a tetracyclic system that includes the A ring with a hydroxyl function α to a *gem*-dimethyl group and, in contrast to other taxane compounds such as taxine [12], an oxetane group. Such functionalities are susceptible to undergo significant structural modifications which could lead to new potentially active derivatives after esterification of the C-13 hydroxyl group with suitable acids. It is with this in mind that, some years ago, we began to study the chemical reactivity of 10-deacetylbaccatin III **2** [7a-b]. Moreover a recent publication [13] concerning the rearrangement of taxol derivatives with electrophilic reagents has prompted us to describe our own work on the reactivity of 10-deacetylbaccatin III under acidic and basic conditions.



1: R_1= CH_3CO, R_2= Ph
3: R_1= H, R_2= OtBu

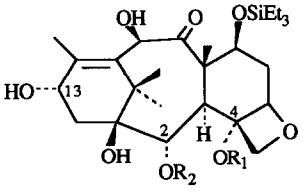


2: R_1=R_2=H
4: R_1= $SiEt_3$, R_2=H
5: R_1= R_2= $CO_2CH_2CCl_3$

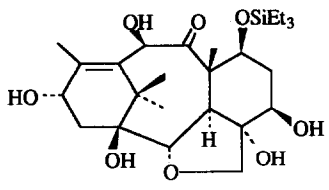
We thus report herein the synthesis of 10-deacetylbaccatin III analogues from the suitably protected compounds **4** or **5**.

Results and Discussion

Alkaline hydrolysis as well as metal hydride reduction of 7-triethylsilyl-10-deacetylbaccatin III 4 [5b] has been studied. Four compounds (**6-9**) were isolated whose ratios depended on the experimental conditions.



	R_1	R_2
6:	H	COC_6H_5
7:	$COCH_3$	H
8:	H	H



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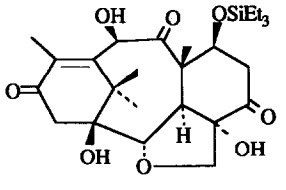

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Alkaline hydrolysis (NaOH, room temp., 5 h), methanolysis (NaOMe, 40°C, 1h) or metal hydride reduction ($LiAlH_4$, room temp., 30 min.) of **4** provided a 3:1 mixture of two products **8** and **9**. The 2-hydroxy derivative **7** was isolated using the same reagents under milder conditions (NaOH, room temperature, 10min.; NaOMe, room temp, 3h.; $LiAlH_4$, -30°C, 3h.). In the case of $LiAlH_4$ reduction this compound was accompanied by a small amount of the 4-deacetyl compound **6**.

The structures of compounds **6**, **7**, and **8** were attributed readily from their spectral characteristics. In the ^1H NMR spectra of **6** and **8** the observed change of the C-13 proton signal (bd, J=9Hz) in comparison with that of **4** and **7** (t, J=9Hz) results from a conformational change in the A ring. Molecular modelling (MM2) studies show that compounds lacking the acetyl group at C-4 (**6** and **8**) have a more folded conformation inducing a twist conformation in the A ring instead of the usual boat conformation. Compound **9** gave a mass spectrum having a molecular ion peak (the same as for **8**) at m/z 512 corresponding to the cleavage of the two ester groups at C-2 and C-4. ^{13}C-^1H 2D NMR spectrum, NOESY and ^1H-^1H

COSY 2D NMR spectra of **9** were obtained in order to clarify specific structural features and confirm the assignments. The chemical shifts and the coupling constants of the C-20 protons change from 4.48 and 4.79 (J = 8Hz) in **8** to 3.73 and 3.85ppm (J = 10 Hz) in **9**. The dd at d 4.26 ppm (J=9Hz) was assigned to H-5α NOe's of **9** were found to be very similar to that of compounds **1** and **8** except that no interaction was observed between H-5 and H-20α. Moreover, the ^{13}C NMR data for **9** showed changes in the chemical shifts of carbons 2 and 5. These NMR features indicate that structural modifications have occurred at C-2 and on the oxetane ring. The structure of this new rearranged compound **9** was then confirmed by Jones oxidation which led to the 5, 13-dioxo compound **10**.

The above results showed that the cleavage of the ester groups was not selective. It was rather surprising to isolate, even in low yield, compound **6** resulting from cleavage of the hindered tertiary acetate group. Since this compound was only formed after $LiAlH_4$ reduction, cleavage of the ester group at C-4 must occur by intramolecular hydride attack based on assistance by the neighboring C-13 alkoxy hydride complex. A similar mechanism leading to the hydrolysis of the tertiary C-4 acetoxy group was recently reported by Kingston[14] during the methanolysis of 7-(triethylsilyl)-hexahydrobaccatin III.

Isomerisation of **8** to **9**, also obtained under acidic conditions, is due to the intramolecular opening of the oxetane group by the C-2 hydroxyl group, thus preserving the β-configuration of the C-5 oxygen function. Molecular modelling studies of compound **8** show a distance of 2.8 Å between the methylene C-20 group of the oxetane ring and the hydroxyl group at C-2 consistent with this chemical transformation.

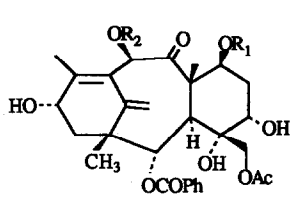
Preliminary results on the inhibitory activity of these compounds on microtubules disassembly, show that, when compared with 10-deacetylbaccatin III, loss of the acetyl group at C-4 has little effect on activity, while the presence of the benzoyl group at C-2 seems to be essential.

In organic or Lewis acid, 7,10-"ditroc"-10-deacetylbaccatin III **5** [7b] gave products in which the A and D (oxetan) rings were seen to have undergone structural modifications (Table).

Compound **5** treated with anhydrous $ZnCl_2$ in dry toluene gave a rearranged taxane product which we had considered previously to be **11** [15]. As was observed by Kingston and coll.[11b,13] during the course of their studies on taxol rearrangement in the presence of electrophilic reagents, this latter structure has to be corrected to **12**. Assignment of the majority of the proton and carbon NMR signals of **12** has been achieved by NOESY and ^{1}H / ^{13}C COSY 2D NMR long range experiments.

Entry	Reagent	Reaction conditions	Yield (%)					
			5	**12**	**13**	**14**	**15**	**16**
1	$ZnCl_2$	Toluene, 80°C,3h		50				
2	HCl	AcOH, room temp, 4h				20	17	30
3	CF_3COOH	Toluene, H_2O, room temp, 2h	27			55		8
4	CF_3COOH	Toluene, room temp, 8h		12	5	20	7	40

Table



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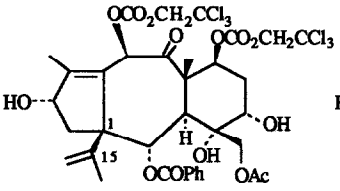

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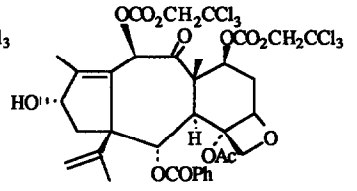

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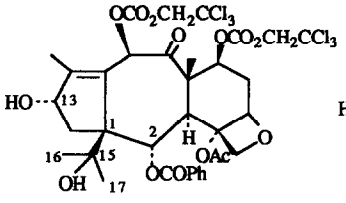

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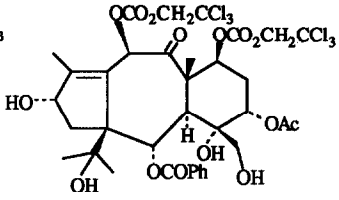

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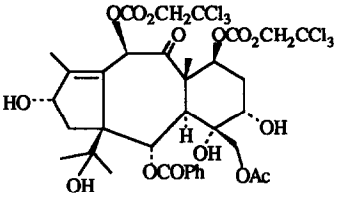
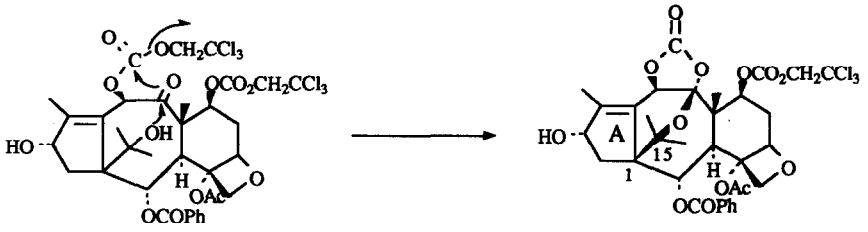


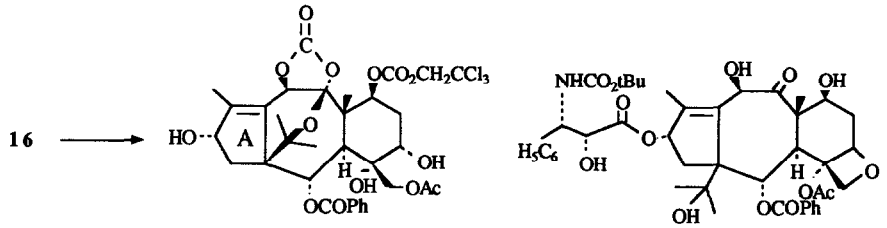
16

Treatment of **5** with organic acids led to the formation of compounds **12, 13, 14, 15** and **16**. Compound **14** obtained in trifluoroacetic acid (Table, entry 3 and 4) or hydrochloric acid (Table, entry 2) gave a mass spectrum that showed the same molecular ion as that of the starting material **5**. This product showed unusual chemical shifts for C-1 (68.2 ppm) and C-15 (74.8 ppm) when compared to those of compound **5** (respectively 78.40 and 42.10 ppm). Additionally, methyl groups at C-16 and C-17 displayed nOe interactions simultaneously with H-2 and H-13. This data taken together with the chemical transformations discussed below, are consistent with structure **14**. The resonances of the C-5 and C-20 protons at 5.33 ppm (bs) and 3.53 ppm (dd, J=12) in the ^{1}H NMR spectrum of compound **15**, indicated that C-5 was substituted with an acetyl group. The ^{1}H NMR spectrum of **16** showed the presence of the acetyl group at C-20 with the C-5 and C-20 protons appearing respectively at 3.94 ppm (bs) and 4.20 ppm (d, J=12). Treatment of **5** in dry trifluoroacetic acid for 8h (Table, Entry 4), led to a major product **16** (corresponding to the opening of the oxetane ring of compound **14**) together with compounds **12, 13, 14** and **15**. The unstable compound **15** is readily transformed into **16** by treatment with Al_2O_3 in CH_2Cl_2. Based on the above results, the following mechanism can be proposed: acid treatment of 7,10 "ditroc"-10-deacetylbaccatin III **5** first gives a cation at C-1 generated by the loss of the hydroxyl group on C1. Depending on the experimental conditions, this cation can either rearrange into the exo-methylenic compounds **12** or **13**, as noted by Kingston and coll.[11a,13], or into the gem-dimethylhydroxy compound **14**. This Wagner-Meerwein type rearrangement which leads to the contraction of the A ring is similar to the well-known transformation of A ring of the 3-hydroxy triterpenes[16]. Compound **15** is then formed from **14** as a result of the opening of the oxetane ring with assistance by the neighboring C-4 acetyl group. Compound **15** is converted into **16** via intramolecular acetyl transfer from C-5 to C-20. Structural assignments of **14** and **16** were then confirmed after noting an unusual transformation when these two compounds were treated with Al_2O_3 in CH_2Cl_2. Products **17** and **18** were obtained and IR analysis of each showed a characteristic absorption of a cyclic carbonate group at 1825 cm^{-1}. Mass spectra of **17** and **18** gave molecular ions at m/z 744 and 762 corresponding to the loss of trichloroethanol. Moreover, the ^{13}C-NMR data indicates that the C-9 ketone was no longer present. This information, and the ^{1}H-NMR data

which shows a conformational change in ring B ($J_{2,3}$=10), are consistent with structure **17** and **18**. The resonances of the C-5 proton at 3.82 ppm (bs) in compound **18** indicated that C-5 was substituted with an hydroxyl group.



14 **17**



16 **18** **19**

Formation of these cyclic ketals can be accounted for by the attack of the C-15 tertiary hydroxyl group on the C-9 keto group followed by intramolecular nucleophilic attack of the resulting hydroxyl group on the carbonyl of the troc group at C-10. Such protective group reactivity has previously been noticed in the taxol series[7b] and has been used to prepare new water soluble taxotere analogues.

As with 10-deacetylbaccatin III **2**, we have found that treating taxotere® **3** with trifluoroacetic acid gave the major rearranged compound **19**. Interestingly, this product is as active as taxotere® in the tubulin disassembly assay. The activity of product **19** which contains a cyclopentene ring system is rather surprising but can be explained by the maintenance of a conformation which is similar to that of taxotere. Indeed, the use of molecular mechanics calculations show that the most stable conformation of compound **19** indeed possesses a shape very similar to that of taxotere. It should be noted that the taxol derivative related to **12** obtained by Kingston et *al* was also reported to be a good inhibitor of tubulin assembly[13].

Most of the 10-deacetylbaccatin III derivatives obtained under basic and acidic conditions are currently being studied in order to obtain new analogues of taxol and taxotere®. These compounds should give us additional information regarding the structure-activity relationships resulting from structural modifications of the ester groups at C-2 and C-4.

Experimental

Thin and thick layer chromatography were performed on precoated silica gel plates (Merck 60F, 0.25 or 2mm thick). Optical rotations (c, g/100ml) were determined on a Perkin-Elmer 141MC polarimeter using a 10 cm path length cell. Infrared spectra (cm-1, $CHCl_3$) were recorded on a Nicolet 205 apparatus. ^1H and ^{13}C spectra were recorded at 250 MHz or at 400 MHz on a Brucker AM 250 or AM400. Chemical shifts are expressed in parts per million (ppm). Coupling constants (J) are given in Hertz; s,bs, d, bd, t, dd and m indicate singlet, broad singlet, doublet, broad doublet, triplet, doublet of doublet and multiplet.

Mass spectra were measured on a Kratos MS80 (FAB) or on an AEI MS9 (CI). Molecular mechanics calculations were performed on a 4D25 work station (Silicon Graphics) with Macromodel as software using the MM_2 force field with MonteCarlo methods to generate conformers.

Deacylation of 7-triethylsilyl-10-deacetylbaccatin III 4:

- 7-Triethylsilyl-10-deacetylbaccatin III [5b] **4** (200 mg, 0.3 mmole) was added to a solution of NaOH (79 mg, 1.97 mmole) in MeOH (11 ml). This mixture was stirred at room temp for 10 min. The pH of the solution was then adjusted to 7.0 with 0.1N HCl and the mixture was extracted with CH_2Cl_2 and AcOEt. The organic extract was washed with water, dried and the solvent was removed. The residue was purified by thick layer chromatography (cyclohexane / AcOEt, 10:90) to give **4** (77%), **7**(9%) and **8**(10%).

When the mixture was stirred for 5h under the same conditions, compounds **8** (64%) and **9** (23%) were obtained.

- To a solution of sodium (10mg) in dry methanol (6ml) was added 7-triethylsilyl-10-deacetylbaccatin III **4** (75 mg, 0.11 mmole), and the mixture was stirred at room temp for 3h, then neutralized with acetic acid and extracted with AcOEt to yield **4** (42%), **7** (14%) and **8** (6%).

When the mixture was stirred at 40°C for 1h, compounds **8** and **9** were obtained in 60% and 20% yield respectively.

- To 7-triethylsilyl-10-deacetylbaccatin III **4** (300 mg, 0.45 mmole) in 6 ml of anhydrous THF was added a solution of 160 mg of lithium aluminum hydride in 6 ml of anhydrous THF, at room temp over a period of 10 min. After standing at room temperature for 30 min., water and 10% aqueous sodium hydroxide were added. The mixture was then filtered and the solution evaporated. The residue was purified by thick layer chromatography (AcOEt) to give **8** (60%) and **9** (20%).

-To 7-triethylsilyl-10-deacetylbaccatin III **4** (700 mg, 1,06 mmole) in 14 ml of anhydrous THF was added a solution of 160 mg of lithium aluminum hydride in 14 ml of anhydrous THF at -30°C over a period of 10 min. After standing at room temperature for 3 h, water and 10% aqueous sodium hydroxide were added. After the usual work-up, the residue was chromatographed on silica gel using cyclohexane / AcOEt (1:1) as eluant to give **4** (51%), **6** (6%) and **7** (29%).

- **Compound 6.** FABMS m/z 639 (M+Na), 599 (M+H-H_2O); I.R. ($CHCl_3$): 3440, 2900, 1700, 1610 cm-1; ^1H NMR ($CDCl_3$+10%C_5D_5N): 0.57 (6H, 3xCH_2 of the 7-SiEt_3 group), 0.93 (9H, 3xCH_3 of the 7-SiEt_3 group), 1.12, 1.23, 1.70 and 2.17 (4x3H, 4 s, C-17H_3, C-16H_3,C-19H_3 and C-18H_3), 2.02 and 2.40 (2H,m,C-6H_2), 2.57 and 2.90 (2H,2dd,J=1.5 and 14, J=9.5 and 14,C-14H_2), 3.87 (1H,d,J=6,C-3H), 4.13 (1H,dd,J=6 and 11,C-7H), 4.40 and 4.48 (2H,2d,J=8,C-20H_2), 4.63 (1H,bd,J=9,C-13H), 4.95 (1H,dd,J=4 and 10,C-5H), 5.30 (1H,s,C-10H), 5.67 (1H,d,J=6,C-2H), 7.23, 7.44, 8.07 (5H,OBz).

- **Compound 7.** FABMS m/z 577 (M + Na), 555 (M + H), 237, 115; I.R. ($CHCl_3$): 3450, 2900, 1730, 17à0, 1610 cm-1; ^1H NMR ($CDCl_3$+10%C_5D_5N): 0.44 (6H, 3xCH_2 of the 7-SiEt_3 group), 0.82 (9H, 3xCH_3 of the 7-SiEt_3 group), 0.92 (3H,s,C-16H_3), 1.07 (3H,s,C-17H_3), 1.57 (3H,s,C-19H_3), 1.98 (3H,s,C-18H_3), 2.09 (3H, s, OAc), 1.81, 2.16 and 2.38 (4H,m,C-6H_2 and C-14H_2), 3.56 (1H,d,J=7,C-3H), 3.83 (1H,d,J=7,C-2H), 4.60 and 4.67 (2H,2d,J=8,C-20H_2), 4.30 (1H,dd,J=6 and 10,C-7H), 4.82 (1H,t,J=8,C-13H), 4.90 (1H,dd,J=2 and 9,C-5H), 5.05 (1H,s,C-10H). ^{13}C NMR ($CDCl_3$) : 5.24 ($\underline{CH_2}Si$), 6.78 ($\underline{CH_3}CH_2Si$), 10.17 (C19), 15.16 (C18), 19.55 (C16), 22.62 (CH_3-acetate), 26.73 (C17), 37.42 (C6), 39.22 (C14), 42.32 (C15), 46.97 (C3), 58.06 (C8), 67.96 (C13), 73.09 (C-2), 74,37 (C10), 74.78 (C7), 76.60 (C1), 78.08 (C20), 84.09 (C5), 81.95 (C4), 84.09 (C5), 135.36 (C11), 141.77 (C12), 170.58 (C=O of Ac), 210.97 (C9).

- **Compound 8.** FABMS m/z 535 (M + Na), 517 (M + Na - H_2O), 495 (M + H - H_2O), 477, 459, 115; I.R. ($CHCl_3$): 3430, 2960, 1715, 1600 cm-1; ^1H NMR ($CDCl_3$+10%C_5D_5N): 0.52 (6H, 3xCH_2 of the 7-SiEt_3 group), 0.84 (9H, 3xCH_3 of the 7-SiEt_3 group), 1.00 (3H, s, C-16H_3), 1.06 (3H, s, C-17H_3), 1.60 (3H, s, C-19H_3), 2.00 (1H, m, C-6H), 2.08 (3H, s, C-18H_3), 2.29 (1H, dd, J=2 and 16, C-14H_α), 2.39 (1H, m, C-6H), 2.45 (1H, m, C-14β), 3.39 (1H,d,J=6,C-3H), 3.82 (1H,d,J=6,C-2H), 4.00 (1H,dd,J=6 and 11,C-7H), 4.48 and 4.79 (2H,2d,J=8,C-20H_2), 4.56 (1H,bd,J=9,C-13H), 4.84 (1H,dd,J=3 and 10,C-5H), 5.16 (1H,s,C-10H); ^{13}C NMR ($CDCl_3$) : 5.12 ($\underline{CH_2}Si$), 6.68 ($\underline{CH_3}CH_2Si$), 9.75 (C19), 17.11 (C18), 18.07 (C16), 29.39 (C17), 37.56 (C6), 38.19 (C14), 41.58 (C15), 50.98 (C3), 58.09 (C8), 68.46 (C13), 73.32 (C-2), 73.50 (C7), 75.29 (C10), 76.04 (C1), 76.53 (C4), 81.20 (C20), 86.14 (C5), 137.41 (C11), 140.36 (C12), 210.77 (C9).

- **Compound 9.** FABMS m/z 535 (M + Na), 513 (M + H), 495 (M + H - H_2O), 477, 459, 363, 345, 327, 115; I.R. ($CHCl_3$): 3430, 2960, 1695, 1600 cm-1; ^1H NMR ($CDCl_3$+10%C_5D_5N): 0.37 (6H, 3xCH_2 of the 7-protect. group), 0.78 (9H, 3xCH_3 of the 7-protect. group), 0.85 (3H, s, C-16H_3), 0.98 (3H, s, C-17H_3), 1.23 (3H, s, C-19H_3), 1.75 (1H, m, C-6Hβ), 1.91 (3H, s, C-18H_3), 2.13 (1H, m, C-6Hα), 2.41 (1H, dd, J=9 and 15, C-14H), 2.58 (1H, dd, J=1 and 15, C-14H), 3.49 (1H,d,J=7,C-3H), 3.70 and 3.85 (2H,2d,J=10,C-20H_2), 3.76 (1H,dd,J=5 and 11,C-7H), 4.04 (1H,d,J=7,C-2H), 4.26 (1H,t,J=9,C-5H), 4.34 (1H,bd,J=9,C-13H), 4.93 (1H,s,C-10H).;^{13}C NMR ($CDCl_3$) : 4.87 ($\underline{CH_2}Si$), 6.71 ($\underline{CH_3}CH_2Si$), 14.83 (C19), 16.89 (C18), 18.65 (C16), 28.26 (C17), 38.07 (C6), 38.07 (C14), 42.41 (C15), 52.47 (C3), 56.60 (C8), 68.59 (C13), 71.86 (C7), 73.61 (C5), 74.46 (C20), 75.84 (C1), 76.48 (C10), 84.51 (C4), 84.92 (C-2),139.32 (C11), 141.12 (C12), 211.47 (C9).

Isomerization of 8 to 9:

Compound **8** (10 mg, 0.02mmole) in 1 ml of acetic acid was stirred for 24h. The mixture was evaporated and the resulting residue purified by tlc (AcOEt) to give 90% of compound **9**.

Oxidation of compound 9:

To a solution of compound **9** (40 mg, 0.078 mmole) in 2 ml pyridine was added 60 mg of CrO_3. The mixture was stirred at room temperature for 3 h. The reaction mixture was treated with water and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and evaporated. Purification of the residue by thick layer chromatography (CH_2Cl_2 / MeOH, 90/10) gave 90% of compound **10**.

- **Compound 10.**FABMS m/z 531 (M + Na), 509 (M + H), 491 (M + H - H_2O), 473; I.R. ($CHCl_3$): 3360, 2940, 1775, 1670, 1650, 1600 cm-1; 1H NMR ($CDCl_3$+10%C_5D_5N): 0.47 (6H, 3xCH_2 of the 7-protect. group), 0.87 (9H, 3xCH_3 of the 7-protect. group), 1.00 (3H, s, C-16H_3), 1.03 (3H, s, C-17H_3), 1.20 (3H, s, C-19H_3), 2.00 (3H, s, C-18H_3), 2.23 (1H, dd, J=8 and 19, C-6H), 2.65 (1H, d, J=19, C-14H), 3.10 (1H, d, J=8, C-3H), 3.17 (1H, dd, J=8 and 19), 3.37 (1H, d, J=19, C-14H), 3.50 and 4.00 (2H,2d,J=11,C-20H_2), 4.04 (1H,d,J=8,C-2H), 4.31 (1H, m,C-7H), 5.10 (1H,s,C-10H).;^{13}C NMR ($CDCl_3$) : 4.69 ($\underline{CH_2}Si$), 6.68 ($\underline{CH_3}CH_2Si$), 12.00 (C19), 13.16 (C18), 17.99 (C16), 31.29 (C17), 43.92 (C6), 43.92 (C14), 43.26 (C15), 54.61 (C3), 55.94 (C8), 71.23 (C7), 74.38 (C20), 75.89 (C10), 81.69 (C4), 84.53 (C-2),137.40 (C11), 155.35 (C12), 200.60 and 205.90 (C-5 and C-13), 211.47 (C9).

Reaction of 7,10-di (2,2,2-trichloroethyloxycarbonyl) 10-deacetylbaccatin III 5 with $ZnCl_2$ and organic acids.

- To a solution of 7,10-di (2,2,2-trichloroethyloxycarbonyl) 10-deacetylbaccatin III **5** [7b] (50 mg, 0.056 mmole) in 2 ml dry toluene was added 60 mg of anhydrous $ZnCl_2$. The mixture was stirred at 80°C for 15 h under argon. After filtration the reaction mixture was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and evaporated. Purification by thick layer chromatography (CH_2Cl_2 / MeOH, 98/2) gave 50% of compound **12**.

- To a solution of 7,10-di (2,2,2-trichloroethyloxycarbonyl) 10-deacetylbaccatin III **5** (100 mg, 0.11 mmole) in 2 ml acetic acid was added drop by drop 0.20 ml of 1N aqueous HCl. The mixture was stirred at room temp for 4 h. The reaction mixture was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and evaporated. Purification by thick layer chromatography (CH_2Cl_2 / MeOH, 95/5) gave compounds **14** (20%), **15** (17%) and **16** (30%).

- To a solution of 7,10-di (2,2,2-trichloroethyloxycarbonyl) 10-deacetylbaccatin III **5** (2 g, 2.24 mmole) in 10 ml toluene were added 1.1 ml of trifluoroacetic acid and 0.26 ml of water. The reaction mixture was stirred for 2h and washed with water. Evaporation of the solvent and purification of the residue by column chromatography with 40% AcOEt in cyclohexane gave 27% of starting material **5** together with compounds **14** (55%) and **16** (8%).

- To a solution of 7,10-di (2,2,2-trichloroethyloxycarbonyl) 10-deacetylbaccatin III **5** (200 mg, 0.22 mmole) in 1.5 ml toluene were added 0.10 ml of dry trifluoroacetic acid. After stirring for 8h at room temperature, the mixture was washed with water. Evaporation of the solvant and purification by thick layer chromatography (Heptane / AcOEt, 35/65) gave compounds **12**, **13**, **14**, **15** and **16** in 12, 5, 20, 7 and 40% yields respectively.

- **Compound 12.** FABMS m/z 915 (M + Na), 893 (M + H), 881, 831, 793, 759, 725, 703, 669.; I.R. (KBr): 3500, 1760, 1735, 1720, 1600 cm-1; ^{1}H NMR ($CDCl_3$): 1.63 (3H,s,C-16H_3), 1.54 (3H,s,C-19H_3), 1.68 (3H,s,OAc), 1.95 (3H,s,C-18H_3), 2.00 and 2.37 (2H,m,C-6H_2), 2.71 (1H,m,C-14H), 3.62 (1H,d,J=7,C-3H), 3.96 (1H,bs,C-5H), 4.09 and 4.20 (2H,2d,J=12,C-20H_2), 4.72 and4.38 (2H, 2bs, C-17H_3), 4.63 (1H, m, C-13H), 4.68, 4,70, 4.82 and 4.84 (4H,4d,J=12,CH_2 of the troc groups), 5.46 (1H,d,J=7,C-2H), 5.62 (1H,dd,J=5 and 12,C-7H), 6.37 (1H,s,C-10H), 7.61, 7.48, 8.03 (5H, OBz);^{13}C NMR ($CDCl_3$): 11.71 (C18), 11.90 (C19), 20.17 (CO$\underline{C}H_3$), 21.07 (C16), 30.67 (C6), 41.82 (C14), 44.05 (C3), 55.80 (C8), 63.96 (C1), 64.30 (C20), 70.55 (C5), 72.45 (C-2), 73.98 (C4), 75.31 (C10), 75.43 (C7), 75.83 (C13), 77.35 (2xCO$\underline{C}H_2CCl_3$), 94.38 and 94.52 (2xCOCH$_2\underline{C}Cl_3$), 113.15 (C17), 129.66, 128.86, 129.93 and 133.77 (Ph), 132.83 (C11), 144.75 (C12), 152.00 (C15), 153.42 and 153.13 (2x$\underline{C}OCH_2CCl_3$), 165.88 ($\underline{C}$OPh), 170.50 ($\underline{C}$OCH$_3$), 201,50 (C9).

- **Compound 13.** FABMS m/z 899, 897 (M + Na); I.R. (KBr): 3500, 1760, 1730, 1600 cm-1; ^{1}H NMR ($CDCl_3$): 1.57 and 1.83 (3H and 6H,2s,C-16H_3, C-18H_3 and C-19H_3), 1.67 (1H,m,C-14H), 1.94 (1H,dd,J=15 and 10,C-6H), 2.20 (3H,s,OAc), 2.57 (1H,m,C-14H), 2.73 (1H,m,C-6H), 3.53 (1H,d,J=7,C-3H), 4.17 (2H,2d,J=8,C-20H_2), 4.43 (1H,t,J=8,C-13H), 4.56, 4,59 and 4.73 (4H,3d,J=12,CH_2 of the troc groups), 4.66 and 4.79 (2H,2bs,C-17H_3), 4.98 (1H,d,J=9,C-5H), 5.52 (1H,d,J=7,C-2H), 5.54 (1H,m,C-7H), 6.10 (1H,s,C-10H), 7.37, 7.50, 7.93 (5H, OBz);^{13}C NMR ($CDCl_3/C_5D_5N$): 9.03 and 11.01 (C19 and C18), 20.28 (CO$\underline{C}H_3$), 21.01 (C16), 33.30 (C6), 41.51 (C14), 43.83 (C3), 53.92 (C8), 62.92 (C1), 70.19, 73.46, 75.29 and 77.14 (C2, C7, C10 and C13), 73.67 (C20), 77.68 (C4), 83.72 (C5), 77.92 (2xCO$\underline{C}H_2CCl_3$), 92.89 (2xCOCH$_2\underline{C}Cl_3$), 112.21 (C17), 128.11, 128.80, 128.84 and 133.07 (Ph), 129.21 (C11), 144.61 (C12), 151.82 and 151.85 (2x$\underline{C}OCH_2CCl_3$), 152.15 (C15), 164.40 ($\underline{C}$OPh), 169.70 ($\underline{C}$OCH$_3$), 200.00 (C9).

- **Compound 14.** FABMS m/z 917, 915 (M + Na), 895, 893 (M + H); I.R. (KBr): 3570, 2970, 1765, 1735, 1600 cm-1; ^{1}H NMR ($CDCl_3$): 1.03 and 1.09 (2x3H,2s,C-16H_3 and C-17H_3), 1.95 (6H,s,C-18H_3 and C-19H_3), 2.00 (1H,dd,J=7 and 15,C-14H_α), 2.10 (1H,dd,J=10 and 15,C-6H), 2.29 (3H,s,OAc), 2.44 (1H,dd,J=7 and 15,C-14Hβ), 2.75 (1H,m,C-6H), 3.81 (1H,d,J=8,C-3H), 4.19 and 4.40 (2H,2d,J=8,C-20H_2), 4.71 (1H,m,C-13H), 4.69, 4,72, 4.84 and 4.88 (4H,4d,J=12,CH_2 of the troc groups), 5.05 (1H,d,J=9,C-5H), 5.53 (1H,dd,J=8 and 10,C-7H), 5.80 (1H,d,J=8,C-2H), 6.25 (1H,s,C-10H), 7.48, 7.64 and 8.03 (5H, OBz);^{13}C NMR ($CDCl_3$): 9.42 (C19), 11.34 (C18), 21.80 (CO$\underline{C}H_3$), 25.24 and 26.92 (C16 and C17), 33.78 (C6), 39.00 (C14), 44.83 (C3), 54.25 (C8), 68.17 (C1), 68.98 (C2), 74.53 (C20), 74.77 (C15), 75.68 (C10), 76.17 (C13), 76.35 (2xCO$\underline{C}H_2CCl_3$), 76.89 (C7), 78.84 (C4), 84.21 (C5), 94.09 (2xCOCH$_2\underline{C}Cl_3$), 128.51, 129.54 and 133.49 (Ph), 132.15 (C11), 152.63 (C12), 152.95 (2x$\underline{C}OCH_2CCl_3$), 165.60 ($\underline{C}$OPh), 170.58 ($\underline{C}$OCH$_3$), 199.56 (C9).

- **Compound 15.** FABMS m/z 933 (M + Na), 911 (M + H); I.R. ($CHCl_3$): 3450, 1760, 1735, 1600 cm-1; ^{1}H NMR ($CDCl_3$): 1.00 and 1.10 (2x3H,2s,C-16H_3 and C-17H_3), 1.51 (3H,s,C-19H_3), 2.03 (3H,s,C-18H_3), 2.15 (2H,m,C-6H and C-14H), 2.20 (3H,s,OAc), 2.25 and 2.50 (2H,m,C-6H and C-14H)), 3.53 (2H,dd,J=12,C-20H_2), 3.69 (1H,d,J=7,C-3H), 4.65 (1H, m, C-13H), 4.64, 4,70, 4.82 and 4.88 (4H,4d,J=12,CH_2 of the troc groups), 5.33 (1H,bs,C-5H), 5.35 (1H,m,C-7H), 5.67 (1H,d,J=7,C-2H), 6.38 (1H,s,C-10H), 7.40, 7.53, 8.03 (5H, OBz).

- **Compound 16.** FABMS m/z 933 (M + Na), 911 (M + H), 757, 743, 709, 685; I.R. (KBr): 3530, 2970, 1760, 1725, 1600 cm-1; ^{1}H NMR ($CDCl_3$): 1.01 and 1.10 (2x3H,2s,C-16H_3 and C-17H_3), 1.58 (3H,s,C-19H_3), 1.61 (3H,s,OAc), 2.00 (1H,m,C-6H), 2.01 (3H,C-18H_3), 2.29 (1H,m,C-6H), 2.52 (1H,m,C-14H), 3.74 (1H,d,J=7,C-3H), 3.94 (1H,bs,C-5H), 4.07 and 4.20 (2H,2d,J=12,C-20H_2), 4.72 (1H,m,C-13H), 4.67, 4,69, 4.79 and 4.85 (4H,4d,J=12,CH_2 of the troc groups), 5.48 (1H,dd,J=4 and 11,C-7H), 5.71 (1H,d,J=7,C-2H), 6.37 (1H,s,C-10H), 7.37, 7.60 and 8.04 (5H, OBz).

- **Compound 17.** To a solution of compound **14** (50 mg) in 2ml methylene chloride was added 200 mg of Al_2O_3. The reaction mixture was stirred at room temperature for 5h. After filtration, evaporation of the solvant and purification by thick layer chromatography (Cyclohexane / AcOEt 70/30), compound **17** was obtained in 40% yield. CIMS m/z 745 (M + H), 683 (M-CO_2-HO), 571, 511,509; I.R. ($CHCl_3$): 3600, 2940, 1820, 1735, 1600 cm-1; ^{1}H NMR ($CDCl_3$): 1.20, 1.56, 1.83, 1.98, 1.99 (5x3H,5s,C-16H_3,C-17H_3,C-18H_3,C-19H_3 and OAc), 1.93, 2.13, 2.62 (4H,m,C-6H_2 and C-14H_2), 2.49 (1H,d,J=10,C-3H), 4.30 and 4.35 (2H,2d,J=8,C-20H_2), 4.47 (1H,m,C-13H), 4.55 and 4.93 (2H,2d,J=12,CH_2 of the troc group), 4.88 (1H,d,J=9,C-5H), 5.51 (1H,t,J=9,C-7H), 5.58 (1H,s,C-10H), 6.01 (1H,d,J=10,C-2H), 7.46, 7.61 and 8.10 (5H, OBz);^{13}C NMR ($CDCl_3$): 9.50 (C19), 12.20 (C18), 21.40, 25.00, 26.32 (C16, C17 and CO$\underline{C}H_3$), 34.22 (C6), 37.07 (C14), 44.99 (C3), 46.57 and 62.85 (C8 and C1), 70.28, 71.34, 75.95 and 78.89 (C2,C7,C10 and C13), 73.52 (C-20), 77.44 (2xCOO$\underline{C}H_2CCl_3$), 78.99 (C15), 80.26 (C4), 84.53 (C5), 94.35 (2xCOOCH$_2\underline{C}Cl_3$), 106.29 (C9), 128.51, 129.54 and 133.49 (Ph), 130.20 (C11), 147.66 (C12), 154.46 (CO (cyclic carbonate and $\underline{C}$OOCH$_2$CCl$_3$), 165.60 ($\underline{C}$OPh), 170.10 ($\underline{C}$OCH$_3$).

- **Compound 18:** A solution of compound **16** (50 mg) and Al_2O_3 (200 mg) in 3 ml methylene chloride was stirred at room temperature for 5h. After filtration and evaporation, the residue was purified by thick layer chromatography (Heptane / AcOEt 10/90) to give 20% of compound **18**. FABMS m/z 785 (M + Na), 740; I.R. ($CHCl_3$): 3560, 2960, 1825, 1750, 1600 cm-1; 1H NMR ($CDCl_3$): 1.19, 1.39, 1.57, 1.93, 2.05 (5x3H,5s,C-16H_3,C-17H_3,C-18H_3,C-19H_3 and OAc), 1.87, 1.98, 2.25 (4H, 3m,C-6H_2 and C-14H_2), 2.45 (1H,d,J=10,C-3H), 3.82 (1H,s,C-5H), 4.05 and 4.29 (2H,2d,J=10,C-20H_2), 4.50 (1H,m,C-13H), 4.67 and 4.89 (2H,2d,J=12,CH2 of the troc group), 5.47 (1H,dd,J=5 and 11,C-7H), 5.60 (1H,s,C-10H), 6.13 (1H,d,J=10,C-2H), 7.48, 7.63 and 8.08 (5H, OBz);

- **Compound 19.** To a solution of taxotere **3** (500mg, 0.62 mmole) in 15 ml dry methylene chloride was added 0,1 ml of trifluoroacetic acid. The reaction mixture was stirred at room temp for 4 h, then neutralised with aqueous sodium bicarbonate. The mixture was extracted, dried over $MgSO_4$ and evaporated. Purification by thick layer chromatography (CH_2Cl_2:CH_3CN:MeOH 16/3/1) yielded 20% of compound **19**. $[\alpha]_D^{20}$=-37° (c=1, EtOH),FABMS m/z 830 (M + Na), 808 (M + H), 770, 672, 549, 509; I.R. (KBr): 3570, 2970, 1735, 1600 cm-1; 1H NMR ($CDCl_3$/CD_3OD): 0.92, 0.97, 1.29 and 1.73 (4x3H,4s,C-16H_3,C-17H_3,C-18H_3 and C-19H_3), 1.79, 2.13 and 2.47 (4H,m,C-6H_2 and C-14H_2), 2.18 (3H,s,OAc), 3.52 (1H,d,J=7,C-3H), 3.94 and 4.29 (2H,2d,J=8,C-20H_2), 4.01 (1H,m,C-7H), 4.44 (1H,bs,C-2'H), 4.84 (1H,d,J=9,C-5H), 4.97 (1H,s,C-10H), 5.10 (1H,bs,C-3'H), 5.52 (1H,d,J=7,C-2H), 5.71 (1H,m,C-13H), 7.20 (5H,Ph), 7.28, 7.34 and 7.85 (5H, OBz);^{13}C NMR ($CDCl_3$): 9.34 (C19), 11.37 (C18), 22.82 (CO<u>C</u>H_3), 25.16 and 27.53 (C16 and C17), 28.71 (CH_3tBu), 36.58 (C6), 38.32 (C14), 46.51 (C3), 57.47 (C8), 58.40 (C3'), 69.04 (C1), 71.15, 72.76, 75.41 and 80.83 (C-2', C2, C7, C10 and C13)), 75.74 (C-20, C15), 80.61 (C4 and C-tBu), 86.41 (C5), 128.09, 128.53, 129.46, 129.89, 130.80 and 140.39 (COPh and Ph), 134.84, 145.88, 157.58, 167.30, 171.80, 174.23 (C11, C12, <u>C</u>OtBu, <u>C</u>OPh, <u>C</u>OCH_3 and C1').

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REFERENCES

1. Wani, M.C.; Taylor, H.L.; Wall, M.E.; Coggon, P.; McPhail, A.T. *J.Am.Chem.Soc.*, **1971**, *93*, 2325-2327.

2. Rowinsky E.K.; Cazenave L.A and Donehower R.C. *J.Natl.Cancer.Inst.*, **1990**, *82*, 1247-1259.

3. a) Schiff, P.B.; Fant, J.; Horwitz, S.B. *Nature*, **1979**, *277*, 665-667. b) Manfredi J.J. and Horwitz, P.B. *Pharmac.Ther.*, **1984**, *25*, 83-125.

4. a) Blechert, S. and Guénard, D. in *"The Alkaloids"* (A.Brossi, ed.), **1990**, *39*, 195-238. Academic Press, Inc., b) Swindell, C.S., *Org.Prep.Proc.Int.*, **1991**, *4*, 467-542.

5. a) Mangatal, L; Adeline, M-T.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Tetrahedron*, **1989**, *42*, 4451. b) Denis, J-N.; Greene, A.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J.Am.Chem.Soc.*, **1988**, *110*, 5917-5919.

6. Chauvière,G.; Guénard, D.; Picot, F.; Sénilh, V.; Potier, P. *C.R.Acad.Sc.Paris*, **1981**, *293*, 501-503.

7. a) Sénilh, V.; Guéritte, F.; Guénard, D.; Colin, M.; Potier, P. *C.R.Acad.Sc.Paris*, **1984**, *299*, Série II, 1039-1049. b) Guéritte-Voegelein, F.; Sénilh, V.; David, B.; Guénard, D.; Potier, P. *Tetrahedron*, **1986**, *42*, 4451-4460. c) Guéritte-Voegelein, F.; Guénard, D.; Lavelle, F.; Le Goff, M-T.; Mangatal, L. and Potier, P. *J.Med.Chem.*, **1990**, *34*, 992-998. d) Colin, M.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. Eur.Pat.Appl.EP 253,738 (Cl.C07D305/14), 20 Jan 1988, FR Appl.86/10,400, 17 Jul 1986; Chem.Abstr., 1988, 109, 22762w.

8. Shelanski, M.L.; Gaskin, F. and Cantor, C.R. *Proc.Natl.Acad.Sci. USA*, **1973**, *70*, 765-768.

9. Bissery, M-C; Guénard, D.; Guéritte-Voegelein, F.; Lavelle, F *Cancer Research*, **1991**, *51*, 4845-4852.

10. Ringel, I. and Horwitz, S.B. *J.Natl.Cancer.Inst.*, **1991**, *83*, 288-291.

11. a) Swindell, C.S.; Krauss, N.E.; Horwitz, S.B.; Ringel, I. *J.Med.Chem.*, **1991**, *34*, 1176-1184. b) Kingston, D.G.I.; Samaranayake, G.; Ivey, C.A. *J.Nat.Prod.*, **1990**, *53*, 1-12.

12. Miller, R.W. *J.Nat.Prod.*, **1980**, *43*, 425-436.

13. Samaranayake, G.; Magri, N.F.; Jitrangsri, C. and Kingston, D.G.I. *J.Org.Chem.*, **1991**, *56*, 5114-5119.

14. Kingston, D.G.I. Pharm.Ther., **1991**, *52*, 1-34.

15. Guéritte-Voegelein, F., Guénard, D., Potier, P.*J.Nat.Prod.*, **1990**, *50*, 9.

16. Biellmann, J-F. and Ourisson, G. *Bull.Soc.Chim.Fr.*, **1962**, 341-344.