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Baccatin III Derivatives: Reduction of the C-11, C-12 Double Bond

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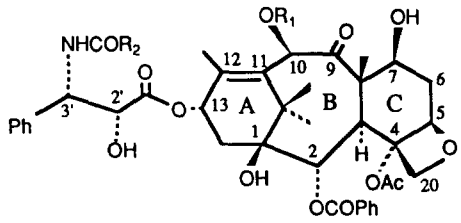
Abstract : Zinc-promoted reduction of 13-oxobaccatin III derivatives leads to 11,12-dihydro analogs. The reduced products are unstable and a skeleton rearrangement occurs leading to the cleavage of the C-10, C-11 bond. The 11, 12-dihydrobaccatin III derivatives do not retain antitubulin activity.

Introduction

The antitumor clinical effects of Taxol® (paclitaxel) **1** and Taxotere® (docetaxel) **2** [1] have led to an intensive effort in the synthesis and chemistry of taxoids[2]. These two compounds and their bioactive analogues bind to microtubules and prevent spindle formation and cell division[3]. A number of derivatives bearing modifications on the taxane skeleton have been prepared in order to study the structure-activity relationships in that series[2]. These studies showed that deletion of the substituents in the south part of the molecule led to a larger reduction in the bioactivity than deletion in the north part. However, nothing is known about the contribution of the A-ring double bond to tubulin binding. Swindell *et al* [4] reported that the presence of the Δ^{11} double bond has little influence on the strain energy of the taxene system. But it is clear that the double bond contributes to the A-ring conformation and consequently to the side chain orientation.



1 R_1= Ac, R_2= Ph **2** R_1= H, R_2= $OC(CH_3)_3$

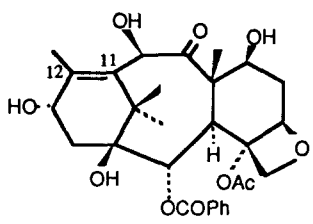
As part of our study on the chemistry of taxoids and structure-activity relationships in this series, we wish to report herein the results obtained in the reduction of the C-11, C-12 double bond of 10-deacetylbaccatin III **3** derivatives.

Results and discussion

With the exception of taxagifines and some taxinines, most of naturally occurring taxoids possess the A-ring double bond[2d]. Earlier studies showed that the C-11, C-12 double bond of paclitaxel was resistant to

hydrogenation. However, 11,12-dihydro-compounds were obtained from taxicin derivatives bearing a keto group at C-13, such as 4[2d,5]. We thus studied the reduction of the activated olefin of 13-oxo-10-deacetylbaccatin III **5**. Compound **5** was obtained from the readily available 10-deacetylbaccatin III 3[6,7] after treatment with chromium trioxide in pyridine[8] or pyridinium chlorochromate. Hydrogenation of **5** with palladium or platinum oxide failed to give the dihydro derivative. The zinc-promoted reduction of the α, β-unsaturated ketone was then investigated in acidic and basic solution.

Treatment of **5** with zinc in a solution of aqueous acetic acid and methanol led to the dihydro compound **6** and to the rearranged product **7** with a yield of 29 and 35% respectively. The reaction has also been accomplished with other metals, but only the zinc containing reagents afforded detectable amount of reduced derivatives: treatment of **5** with a zinc-copper couple under acidic conditions in methanol led mainly to the rearranged aldehyde **7**. On the other hand, reduction of **5** with a zinc-nickel couple in ethyl acetate and aqueous acetic acid afforded the reduced derivative **6** together with 13-oxo-10-deacetoxybaccatin III **8**. In that case, there was no detectable amount of **7** formed in the course of the reaction.



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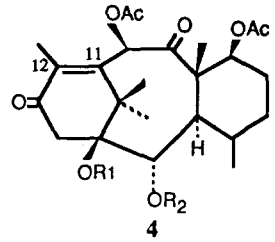

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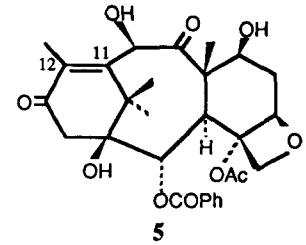

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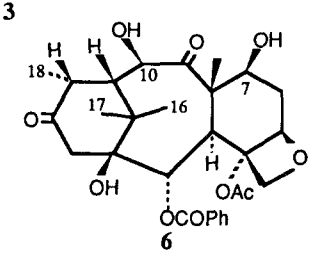

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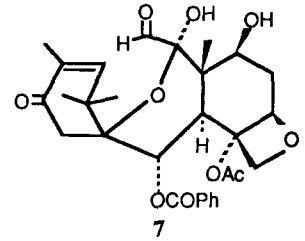

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The comparison of ^{1}H nmr spectra of compound **6** with those of 13-oxo-10-deacetylbaccatin III **5** showed that the A-ring double bond in **6** was reduced (Table 1). The singlet corresponding to the methyl at C-18 was replaced by a doublet at δ 1.25 (J= 6Hz), and new signals appeared at 2.30 and 3.23 (each 1H) due to the protons at C-11 and C-12. The protons at C-11 and C-12 were assigned to be β orientated, judging from the coupling constants between H-10, H-11 and H-12 ($J_{10ax,11eq}$= 4 Hz, $J_{11eq,12ax}$= 5 Hz). Moreover, the NOESY correlations between the Me-18 and the protons at C-3 and C-10 confirmed the α-orientation of the methyl group at C-18. Other nOe cross-peaks were also observed between H-12 and Me-17 and between H-11 and Me-16.

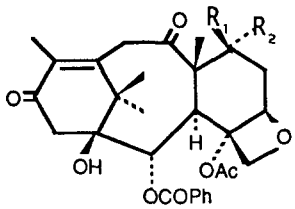
The FAB mass spectral analysis of compound **7** indicated the presence of a $\{MH\}^+$ at *m/z* 543 corresponding to the same molecular formula of the starting material. Its ir spectrum indicated the presence of an aldehyde group at 2560 cm^{-1}. The analysis of the ^{13}C- and ^{1}H-NMR spectra of **7** (Table I) and comparison with **5** showed the lack of the keto group at C-9 and of the secondary hydroxyl group at C-10,

and the presence of an olefinic proton at C-11 as well as an aldehyde group. In addition, the signal at δ 95.32 in the ^{13}C-NMR spectrum of **7** indicated the presence of a quaternary carbon corresponding to an hemiacetal. Moreover, the coupling constant of 12Hz between C-2H and C-3H suggests a rearrangement of the B ring. From these data, structure **7** was assigned to this new product.

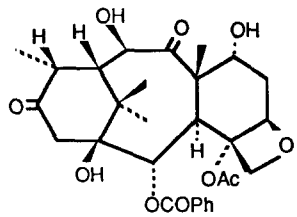
TABLE 1. ^{1}H and ^{13}C-NMR Data ($CDCl_3$) at selected positions of Compounds **5**, **6** and **7**. (J (Hz) values are shown in parentheses)

Position	Compound **5**		Compound **6**		Compound **7**	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
2	5.66 d (7)	71.32	5.68 d (7)	73.30	5.93 d (12)	73.46
3	3.98 d (7)	45.79	2.72 d (7)	41.70	3.45 d (12)	40.41
8		58.46		56.37		47.80
9		208.56		209.98		95.32
10	5.43 s	75.69	4.15 d (4)	70.15	9.56 s	194.80
11		157.57	2.30 dd (4, 5)	62.13	6.23 s	157.63
12		138.57	3.23 m	45.03		132.11
18	2.10 s	12.97	1.25 d (6)	12.04	1.80 s	25.93

We then studied the zinc reduction of 13-oxo-10-deacetylbaccatin III under basic conditions (Zn, NH_3/H_2O-NH_4Cl, MeOH). The two main products obtained were the dihydro derivative **6** and 13-oxo-10-deacetoxybaccatin III **8** with a yield of 26% and 21% respectively. Because of the basic conditions[2d], epimerization also occurred at carbon 7 leading to epimers **9** (3% yield) and **10** (4% yield).



8 R_1 = OH, R_2 = H
10 R_1 = H, R_2 = OH



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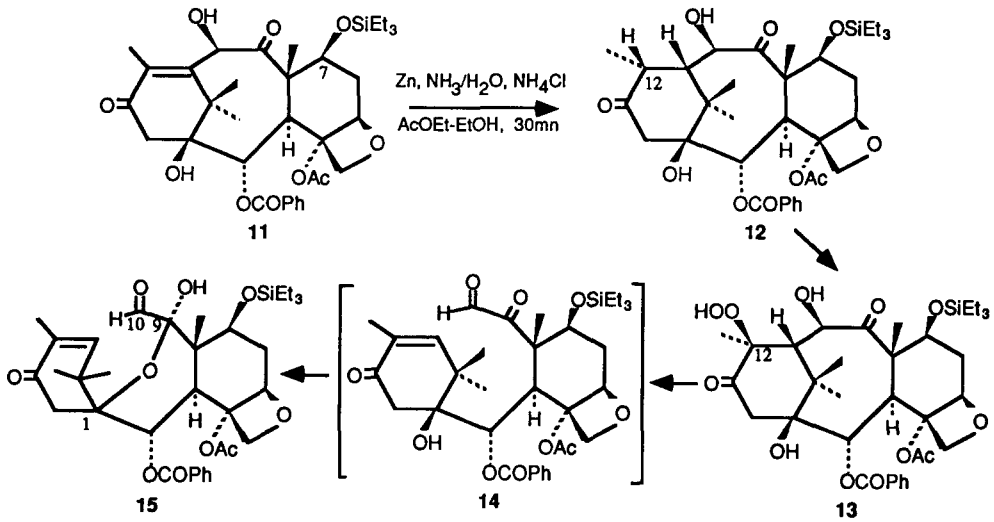
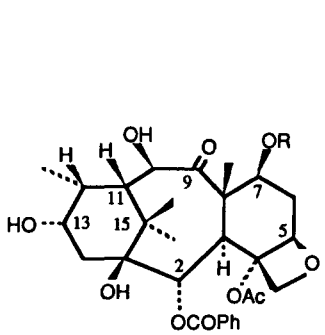
In order to avoid epimerization at C-7, reduction of the α, β-unsaturated ketone was investigated under basic conditions using the 7-protected 10-deacetylbaccatin III derivative **11** as starting material (Scheme 1). The dihydro derivative **12** was obtained with a yield of 95% when a solution of **11** in ethanol and ethyl acetate was treated under argon with zinc in a buffered solution of ammonia-ammonium chloride. No dehydroxylation at C-10 was observed. When the reaction was carried out in air, compound **12** (70%) was isolated together with the hydroperoxide **13** (20%) which rearranged readily in compound **15** (Scheme 1). ^{1}H NMR and ^{13}C NMR spectra of compound **15** were similar to those of the 7-deprotected compound **7**. The presence in **13** of an hydroperoxide group at C-12 was suggested by the mass spectra which showed a molecular ion corresponding to the addition of two oxygen atoms from the dihydro derivative **12**, and by the

resonance of the quaternary C-12 at δ 89.39. The unexpected formation of the rearranged aldehyde compound **15** can now be rationalized. First, oxidation occurs on the tertiary C-12 of compound **12** leading to the hydroperoxide **13**. Then, cleavage of the hydroperoxyde takes place giving the intermediate **14** in which the hydroxyl group at C-1 reacts immediately with the keto group at C-9 to produce the hemiacetal **15**. It should be pointed out that a different oxidative cleavage involving the C_{12}-C_{13} bond, have been previously reported in dihydrotaxinol derivatives [9]. Such as compound **6**, the dihydro derivative **12** is rather unstable and rearranged spontaneously in the solid state to give **13**, **15** and other unidentified compounds.



Scheme 1

The reduction of the C-13 keto group in compound **12** was cleanly achieved with sodium borohydride in methanol affording the stable triol **16** with a yield of 80%.



16 R= Si(Et)$_3$ **17** R= H

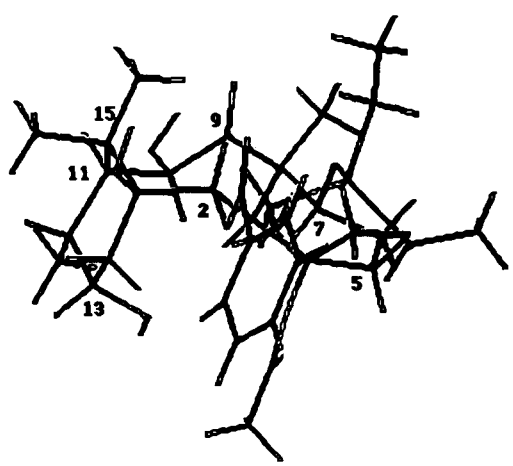


Figure 1 Molecular structure of **16**

The 13α-OH configuration was assigned by the observation of a nOe from H-13 to H-12. Moreover, crystals of **16** were subjected to X-ray crystallography[10], which confirmed the structure of the 11,12-dihydro derivative and showed that the A ring change from a boat conformation in the taxene type structure to a chair conformation in the reduced analogue. Deprotection of compound **16** with 0.5% hydrochloric acid in ethanol led to 11,12-dihydro-10-deacetylbaccatin III **17**.

Next, we studied the coupling of compound **16** with the 2-protected acid side chain of docetaxel, following the procedures described in the literature[6,11]. Unfortunately, the hydroxyl group at C-13 was resistant to acylation under any conditions. Surprisingly, the hydroxyl group at carbon 10 does not react either with acetylating agents even under forcing conditions (Ac_2O, DMAP, Pyridine; Ac_2O, NaH, THF; AcCl, pyridine; AcCl, AgCN, toluene at various temperatures). With respect to the 7-protected derivative of 10-deacetylbaccatin III **3**, the loss of reactivity of the hydroxyl groups at C-10 and C-13 in **16** can be explained by significant steric hindrance around these positions. On one hand, the C-10 hydroxyl group is in a close proximity of the C-7 triethylsilyl and C-18 methyl group. On the other hand, when compared to 10-deacetylbaccatin III **3**, the axial C-13 hydroxyl group in **16** becomes closer to the C-4 acetyl group and consequently difficultly accessible to acylating agents.

In order to know if the presence of the A-ring double bond was biologically important, the microtubule disassembly inhibitory activity of compound **17** was evaluated and compared to those of paclitaxel **1** and 10-deacetylbaccatin III **3**. Although 50 times less active than paclitaxel, 10-deacetylbaccatin III does interact with microtubules[8,12]. A major reduction of antitubulin activity was noted for compound **17** (IC_{50} (**17**) / IC_{50} (taxol) = 200) and the silylated derivative **16** was inactive on the microtubules disassembly assay. The rearranged taxoids **7** and **15** were also found inactive.

In summary, reduction of the C-11, C-12 double bond of 13-oxo-10-deacetylbaccatin III, using zinc in acidic or basic conditions, leads to the dihydro derivative which was less active than 10-deacetylbaccatin III in the microtubule disassembly assay. Because of its extremely folded structure and the closeness of the C-13 hydroxyl and C-4 acetyl group (see figure 1), the 11,12-dihydro derivative was resistant to esterification at C-13. To overcome this problem, we studied the esterification process with 11,12-dihydro derivatives that lack the acetyl group at C-4. These results will be reported in due course.

Experimental Section

General Methods. Thin and thick layer chromatographies were performed on precoated silica gel plates (Merck 60F, 0.25 or 2mm thick). Infrared spectra were recorded on a Nicolet 205 spectrophotometer. Ultraviolet spectra (EtOH, max nm) were recorded on a Perkin-Elmer lambda 5 apparatus. ^1H, ^{13}C and 2D NMR spectra were recorded on a Brucker AM 200, AM 250 or AM 300 spectrometer using tetramethylsilane as the internal standard. 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). 10-deacetylbaccatin III was isolated from the leaves of *Taxus baccata* and the acid side chain of docetaxel was a gift from Rhône-Poulenc Rorer S.A..

13-oxo-10-deacetylbaccatin III 5: To a solution of 10-deacetylbaccatin III **3** (2.96 g, 5.5 mmol) in CH_2Cl_2 was added 2 eq. of pyridinium chlorochromate. The solution was stirred for 45 min. at room

temperature and then filtrated. After addition of water, the mixture was extracted with methylene chloride. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified on a silica gel column using methylene chloride/methanol (97/3) as the eluant to give 13-oxo-10-deacetylbaccatin III (2.35g) with a yield of 79%: mp 205-207°C; IR ($CHCl_3$) γmax 3440, 1725, 1710, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.18 (s, 3H, $C_{16}H_3$, 1.24 (s, 3H, $C_{17}H_3$), 1.72 (s, 3H, $C_{19}H_3$), 1.88 (m, 1H, C_6H), 2.1 (s, 3H, $COCH_3$), 2.2 (s, 3H, $C_{18}H_3$), 2.50 (m, 1H, C_6H), 2.68 and 2.95 (2d, J=20, 2H, $C_{14}H_2$), 3.98 (d, J=7, 1H, C_3H), 4.14 and 4.31 (2d, J=9, 2H, $C_{20}H_2$), 4.26 (m, 1H, C_7H), 4.95 (d, J=9, 1H, C_5H), 5.43 (s, 1H, $C_{10}H$), 5.66 (d, J=7, 1H, C_2H), 7.48, 7.63 and 8.08 (2t, 1d, J=8, 5H, OBz). ^{13}C NMR ($CDCl_3$, 62.5 MHz) 9.06 (C_{19}), 12.97 (C_{18}), 17.53 (C_{16}), 21.37 ($CO\underline{CH_3}$), 32.53 (C_{17}), 36.46 (C_6), 42.71 (C_{14}), 43.36 (C_{15}), 45.79 (C_3), 58.46 (C_8), 71.32 (C_7), 72.85 (C_2), 75.69 (C_{10}), 76.17 (C_{20}), 77.40 (C_1), 80.57 (C_4), 84.26 (C_5), 128.49 (OBz), 129.09 (C_1 of OBz), 129.76 (OBz), 133.57 (OBz), 138.57 (C_{12}), 157.57 (C_{11}), 166.20 (CO of 2-OBz), 170.15 (CO at C_4), 199.08 (C_{13}), 208.56 (C_9); FABMS m/z 543 (MH^+).

Reduction of 13-oxo-10-deacetylbaccatin III 5 in acidic medium: In 20 ml of aqueous acetic acid (75%) was added a solution of 13-oxo-10-deacetylbaccatin III **5** (100 mg, 0.18 mmol) in methanol (6 ml) at room temperature. Next, 33 eq. of zinc (400 mg) was added. The mixture was sonicated for 4 hours. After neutralisation with $NaHCO_3$, extraction with methylene chloride, the resulting extract was purified on silica gel (methylene chloride/acetonitrile/methanol : 80/10/10) yielding 11,12-dihydro-10-deacetylbaccatin III **6** (28.5 mg, 29%) and compound **7** (34 mg, 35%).

To a solution of **5** (20 mg) in methanol (6 ml) and acetic acid (0.1 µl) was added 200 mg of Zn/Cu[13]. The mixture was stirred at room temperature for 40 min. The reaction mixture was filtrated and water was added to the filtrate. After extraction with dichloromethane, the combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to dryness. The residue was purified on silica gel (dichloromethane/methanol: 95/5) to give **7** with a yield of 35%.

A solution of **5** (20 mg) in ethyl acetate (0.5 ml) and methanol-acetic acid (50/50, 1ml) was treated with Zn/Ni[14] at room temperature for 3h. The reaction mixture was filtrated and water was added to the filtrate. After extraction with dichloromethane, the combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to dryness. The residue was purified on silica gel (dichloromethane/methanol: 95/5) to give **6** and **8** with a yield of 10% and 11% respectively.

13-oxo-11,12-dihydro-10-deacetylbaccatin III 6: IR ($CHCl_3$) 3690, 3465, 2980, 1725, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.12 (s, 3H, $C_{16}H_3$), 1.25 (d, 3H, J=6 Hz, $C_{18}H_3$), 1.32 (s, 3H, $C_{17}H_3$), 1.68 (s, 3H, $C_{19}H_3$), 1.95 (m, 1H, C_6H), 2.3O (dd, 1H, J=4 and 5, $C_{11}H$), 2.45 (d, 1H, 16 Hz, $C_{14}H$), 2.5 (s, 3H, $COCH_3$), 2.58 (m, 1H, C_6H), 2.72 (d, 1H, J=7 Hz, C_3H), 3.01 (d, 1H, J=16 Hz, $C_{14}H$)), 3.23 (m, 1H, $C_{12}H$), 4.15 (md 1H, J=4, $C_{10}H$), 4.17(m, 1H, C_7H), 4.21 (d, 1H, J=8 Hz, $C_{20}H$), 4.4 (d, 1H, J=8 Hz, $C_{20}H$), 5.02 (m, 1H, C_5H), 5.68 (d, 1H, J=7 Hz, C_2H), 7.5, 7.66 and 8.13 (m, 5H, OBz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 8.94 (C_{19}), 12.04 (C_{18}), 21.97 ($CO\underline{CH_3}$), 23.98(C_{16}), 32.41 (C_{17}), 35.51 (C_6), 41.11 (C_{15}), 41.71 (C_3), 45.03 (C_{12}), 46.05 (C_{14}), 56.37 (C_8), 62.13 (C_{11}), 70.07 (C_7), 70.15 (C_{10}), 73.31 (C_2), 76.65 (C_{20}), 82.20 (C_4), 82.81 (C_1), 84.16 (C_5), 128.90 (OBz *ortho*), 129.13 (OBz C_1), 129.76 (OBz *meta*), 134.07 (OBz *para*), 167.37 ($\underline{CO}$Ph), 170.56 ($\underline{CO}CH_3$), 199.07 (C_{13}), 209.98 (C_9); FABMS m/z 567 (MNa^+)

Compound 7: IR ($CHCl_3$) 3460, 2930, 2560, 1731, 1675, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz) δ 1.14 (s, 6H, $C_{16}H_3$ and $C_{17}H_3$), 1.78 (s, 3H, $C_{19}H_3$), 1.79 (m, 1H, C_6H), 1.8 (s, 3H, $C_{18}H_3$), 2.01 (s, 3H,

COCH3), 2.43 (m, 1H, C6H), 2.83 (d, 1H, J=17 Hz, C14H), 3.01 (d, 1H, J=17 Hz, C14H), 3.45 (d, 1H, J=12 Hz, C3H), 4.27 (d, 1H, J=8 Hz, C20H), 4.5 (m, 1H, C7H), 4.62 (d, 1H, J=8 Hz, C20H), 4.94 (m, 1H, C5H), 5.03 (s, 1H, OH), 5.93 (d, 1H, J=12 Hz, C2H), 6.23 (s, 1H, C11H), 7.40, 7.61 and 7.93 (m, 5H, OBz), 9.56 (s, 1H, C10H); ^{13}C NMR ($CDCl_3$, 75 MHz) 10.21 (C19), 15.02 (C16), 21.92 (COCH3), 25.93 (C18), 26.33 (C17), 36.32 (C6), 40.41 (C3), 42.81 (C15), 47.80 (C8), 52.16 (C14), 68.11 (C7), 73.46 (C2), 74.43 (C20), 79.87 (C4), 83.52 (C1), 85.23 (C5), 95.32 (C9), 129.07 (OBz *ortho*), 129.69 (OBz C1), 130.67 (OBz *meta*), 132.11 (C12), 134.21 (OBz *para*), 157.63 (C11), 165.48 (COPh), 170.57 (COCH3), 194.80 (C10), 196.88 (C13); CIMS m/z 543 (MH^+).

Reduction of 13-oxo-10-deacetylbaccatin III 5 in basic medium: In a solution of 13-oxo-10-deacetylbaccatin III **5** (50 mg, 0.09 mmol) in 2.5 ml of methanol was added 3 ml of NH_3/H_2O containing 1 mole of NH4Cl. The mixture was treated with 50 mg of zinc powder and vigourously stirred at room temperature for 1.5 hours. After filtration, the resulting filtrate was extracted with methylene chloride. The extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a crude mixture which was purified by chromatography (silica gel: methylene chloride/ethyl acetate/methanol 60/38/2) to give 11,12-dihydro-10-deacetylbaccatin III **6** (14 mg), 13-oxo-10-deacetoxybaccatin III **8** (11 mg) and epimers **9** (1.5 mg) and **10** (2 mg).

13-oxo-10-deacetoxybaccatin III 8: IR ($CHCl_3$) 3592, 2938, 1714, 1672, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.15 (s, 3H, C16H3), 1.2 (s, 3H, C17H3), 1.63 (s, 3H, C19H3), 1.86 (s, 3H, C18H3), 1.9 (m, 1H, C6H), 2.1 (s, 3H, COCH3), 2.55 (m, 1H, C6H), 2.7 (d, 1H, J=20 Hz, C14H), 2.98 (d, 1H, J=20 Hz, C14H), 3.62 (d, 1H, J=15Hz, C10H), 4.0 (d, 1H, J=15Hz, C10H), 4.11 (d, 1H, J=8 Hz, C20H), 4.13 (d, 1H, J=6 Hz, C3H), 4.24 (d, 1H, J=8 Hz, C20H), 4.4 (m, 1H, C7H), 4.9 (m, 1H, C5H), 5.72 (d, 1H, J=6 Hz, C2H), 7.52, 7.66, 8.09 (m, 5H, OBz); ^{13}C ($CDCl_3$, 75 MHz) δ 10.71 (C19), 14.39 (C18), 21.89 (C16), 22.79 (COCH3), 33.30 (C17), 38.01 (C6), 44.24 (C14), 45.68 (C15), 46.68 (C3), 48.04 (C10), 62.07 (C8), 71.77 (C7), 74.40 (C2), 77.28 (C20), 78.75 (C4), 81.91 (C1), 85.38 (C5), 129.47 (OBz *ortho*), 130.56 (OBz C1), 130.90 (OBz *méta*), 134.34 (OBz *para*), 136.90 (C12), 158.77 (C11), 167.02 (COPh), 170.90 (COCH3). 199.06 (C13), 207.13 (C9); CIMS m/z 529 (MH^+).

Compound 9: IR ($CHCl_3$) 3444, 2931, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.1 (s, 3H, C16H3), 1.28 (d, 3H, J=6 Hz, C18H3), 1.45 (s, 3H, C17H3), 1.73 (s, 3H, C19H3), 1.9 (m, 1H, C6H), 2.37 (m, 1H, C11H), 2.4 (m, 1H, C6H), 2.5 (d, 1H, J=18 Hz,C14H), 2.6 (s, 3H, OAc), 2.87 (d, 1H, J=9.5 Hz, C3H), 3.11 (d, 1H, J=18 Hz, C14H), 3.22 (m, 1H, C12H), 3.64 (m, 1H, C7H), 4.41 (d, 1H, J=9 Hz, C20H), 4.46 (d, 1H, J=9 Hz, C20H), 4.5 (m, 1H, C10H), 5.02 (m, 1H, C5H), 5.70 (d, 1H, J=9,5 Hz, C2H), 7.53, 7.68, 8.16 (m, 5H, OBz); CIMS m/z 545 (MH^+).

Compound 10: IR ($CHCl_3$) 3550, 2938, 1707, 1672, 1616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.15 (s, 3H,C16H3), 1.28 (s, 3H, C17H3), 1.58 (s, 3H, C19H3), 1.69 (m, 1H, C6H), 1.90 (s, 3H, C18H3), 2.28 (s, 3H, COCH3), 2.3 (m, 1H, C6H), 2.69 (d, 1H, J=20 Hz, C14H), 3.05 (d, 1H, J=20 Hz, C14H), 3.71 (d, 1H, J=15Hz, C10H) and (m, 1H, C7H), 4.3 (d, 1H, J=15Hz, C10H), 4.36 (d, 1H, J=8 Hz, C20H), 4.39 (d, 1H, J=6,5 Hz, C3H), 4.44 (d, 1H, J=8 Hz, C20H), 4.9 (m, 1H, C5H), 5.85 (d, 1H, J=6,5 Hz, C2H), 7.52, 7.67, 8.1 (m, 5H, OBz); CIMS m/z 529 (MH^+)

Preparation of 13-oxo-7-*O*-triethylsilyl-10-deacetylbaccatin III 11: To a solution of 13-oxo-10-deacetylbaccatin III **5** (390 mg, 0.73 mmol) in pyridine (1.5 ml) was added 8 eq. (0.975 ml, 5.8 mmol) of triethylsilyl chloride. The solution was stirred for 22 hours at room temperature. Pyridine was removed *in vacuo* and water was added to the reaction mixture. After extraction with methylene chloride, the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was submitted to chromatography on silica gel using methylenechloride/methanol (96/4) as the eluant to give 330 mg 13-oxo-7-o-triethylsilyl-10-deacetylbaccatin III **11** with a yield of 70%: IR ($CHCl_3$) 3451, 2966, 1721, 1672, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.45 (m, 6H, OSi($\underline{CH_2}CH_3)_3$), 1.00 (t, 9H, OSi($CH_2\underline{CH_3}$)3), 1.21 (s, 3H, $C_{16}H_3$) ,1.28 (s, 3H, $C_{17}H_3$), 1.77 (s, 3H, $C_{19}H_3$), 1.94 (m, 1H, C_6H), 2.15 (s, 3H, $C_{18}H_3$), 2.25 (s, 3H, CO$\underline{CH_3}$), 2.54 (m, 1H, C_6H), 2.6 (d, 1H, J=20 Hz, $C_{14}H$), 3.04 (d, 1H, J=20 Hz, $C_{14}H$), 4.01 (d, 1H, J=7 Hz, C_3H), 4.2 (d, 1H, J=8 Hz, $C_{20}H$), 4.4 (d, 1H, J=8 Hz, $C_{20}H$), 4.42 (m, 1H, C_7H), 4.98 (m, 1H, C_5H), 5.38 (s, 1H, $C_{10}H$), 5.71 (d, 1H, J=7 Hz, C_2H), 7.55, 7.69, 8.03 (m, 5H, OBz); ^{13}C ($CDCl_3$, 75 MHz) δ 5.89 (OSi($\underline{CH_2}CH_3)_3$), 7.40 (OSi($CH_2\underline{CH_3}$)3), 10.27 (C_{19}), 14.25 (C_{18}), 18.27 (C_{16}), 22.42 (CO$\underline{CH_3}$), 33.70 (C_{17}), 37.91 (C_6), 43.27 (C_{14}), 44.15 (C_{15}), 46.69 (C_3), 59.51 (C_8), 73.50 (C_7), 73.65 (C_2), 76.44 (C_{10}), 76.96 (C_{20}), 79.26 (C_4), 81.15 (C_1), 84.69 (C_5), 129.45 (OBz *ortho*), 129.47 (OBz C1), 130.75 (OBz *meta*), 134.77 (OBz *para*), 139.78 (C_{12}), 157.29 (C_{11}), 167.54 ($\underline{CO}$Ph), 170.91 ($\underline{CO}CH_3$), 199.78 (C13), 208.93 (C9); CIMS : m/z 657 (MH^+).

Reduction of 13-oxo-7-*O*-triethylsilyl-10-deacetylbaccatin III 11 in basic medium: 13-oxo-7-*O*-triethylsilyl-10-deacetylbaccatin III **11** (30 mg, 0.046 mmol) was dissolved in a solution of ethyl acetate (3 ml), ethanol (2 ml) and NH_3/H_2O (28.5%) containing 1 mole of NH_4Cl (2.5 ml). Then, zinc (200 mg) was added and the mixture was stirred vigorously at room temperature for 35 min.. Saturated aqueous sodium chloride was added and the aqueous layer was extracted with methylene chloride. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give, after purification on HPLC (reverse phase, 20% water in methanol), compounds **12** (45%), **13** (30%) and **15** (10%). Compound **13** is unstable and gives compound **15**. When the reaction is carried out under argon, compound **12** is obtained with a yield of 85%.

13-oxo-7-*O*-triethylsilyl-11,12-dihydro-10-deacetylbaccatin III 12: IR ($CHCl_3$) 3564, 2966, 1700, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.52 (m, 6H, OSi($\underline{CH_2}CH_3)_3$), 0.90 (m, 9H, OSi($CH_2\underline{CH_3}$)3), 1.11 (s, 3H, $C_{16}H_3$), 1.23 (d, 3H, J=6 Hz, $C_{18}H_3$), 1.40 (s, 3H, $C_{17}H_3$), 1.66 (s, 3H, $C_{19}H_3$), 1.82 (m, 1H, C_6H), 2.33 (m, 1H, $C_{11}H$), 2.46 (d, 1H, J=16 Hz, $C_{14}H$), 2.48 (s, 3H, OAc), 2.50 (m, 1H, C_6H), 2.65 (d, 1H, J=7 Hz, C_3H), 3.01 (d, 1H, J=16 Hz, $C_{14}H$), 3.20 (m, 1H, $C_{12}H$), 3.52 (d, J=7, 1H, C_7-OH), 4.10 (m, 1H, $C_{10}H$), 4.20 (d, 1H, J=8 Hz, $C_{20}H$), 4.28 (m, 1H, C_7H), 4.37 (d, 1H, J=8 Hz, $C_{20}H$), 5.00 (m, 1H,C_5H), 5.64 (d, 1H, J=7 Hz, C_2H), 7.49, 7.62, 8.12 (m, 5H, OBz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 5.42 (OSi($\underline{CH_2}CH_3)_3$), 6.97 (OSi($CH_2\underline{CH_3}$)3), 9.12 (C_{19}), 12.04 (C_{18}), 22.48 (C_{16}), 23.73 (CO$\underline{CH_3}$), 29.93 (C_{17}), 33.08 (C_6), 36.66 (C_3), 41.19 (C_{15}), 45.03 (C_{12}), 46.04 (C14), 57.07 (C_8), 62.73 (C_{11}), 69.47 (C_7), 71.89 (C_2), 73.35 (C_{10}), 77.03 (C_{20}), 79.70 (C_4), 82.09 (C_1), 84.25 (C_5), 128.98 (OBz *ortho*), 129.1 (OBz C_1), 130.37 (OBz *méta*), 134.14 (OBz *para*), 166.37 ($\underline{CO}$Ph), 169.56 ($\underline{CO}CH_3$), 199.67 (C_{13}), 208.93 (C_9); CIMS m/z 659 (MH^+)

Compound 13: IR ($CHCl_3$) 3264, 2964, 1722, 1600 cm^{-1}; U.V (EtOH) λmax (ε) 230 (15435); ^1H NMR ($CDCl_3$, 250 MHz) δ 0.52 (m, 6H, OSi($\underline{CH_2}CH_3)_3$), 0.9 (m, 9H, OSi($CH_2\underline{CH_3}$)3), 1.08 (s, 3H, $C_{16}H_3$), 1.48 (s, 3H, $C_{17}H_3$), 1.75 (s, 3H, $C_{18}H_3$), 1.80 (s, 3H, $C_{19}H_3$), 1.82 (m, 1H, C_6H), 2.47 (m, 1H, C_6H), 2.49 (s, 3H, OAc), 2.53 (d, 1H, J=7,5 Hz, C_3H), 2.60 (m, 1H, $C_{11}H$), 2.90 (d, 1H, J=16 Hz, $C_{14}H$), 3.04 (d,

1H, J=16 Hz, $C_{14}H$), 4.07 (d, J=6 Hz, $C_{10}OH$), 4.2 (m, 1H ,$C_{10}H$), 4.25 (m, 1H, C_7H), 4.26 (d, 1H, J=8 Hz, $C_{20}H$), 4.37 (d, 1H, J=8 Hz, $C_{20}H$), 4.95 (m, 1H, C_5H), 5.69 (d, 1H, J=7,5 Hz, C_2H), 7.5, 7.61, 8.11 (m, 5H, OBz), 8.67 (-OOH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 5.25 (OSi($\underline{CH_2}CH_3)_3$), 6.85 (OSi($CH_2\underline{CH_3})_3$), 9.45 (C_{19}), 17.55 (C_{18}), 22.56 ($\underline{CH_3}CO$), 24.96 (C_{16}), 33.66 (C_{17}), 36.73 (C_6), 40.52 (C_3), 42.35 (C_{15}), 42.72 (C_{14}), 57.09 (C_8), 63.31 (C_{11}), 71.32 or 72.53 (C_7), 72.53 or 71.32 (C_{10}), 73.15 (C_2), 76.95 (C_{20}), 79.80 (C_4), 82.09 (C_1), 84.17 (C_5), 89.39 (C_{12}), 128.86 (OBz *ortho*), 129.27 (OBz C_1), 130.23 (OBz *meta*), 133.97 (OBz *para*), 167.12 ($\underline{CO}$Ph), 170.78 ($\underline{CO}CH_3$), 204.7 (C_{13}), 211.76 (C_9); MS FAB m/z 713 (MNa^+).

Compound 15: IR ($CHCl_3$) 3472, 2917, 1721, 1665, 1595 cm^{-1}; U.V (EtOH) λmax (ε) 230 (4740); ^1H NMR ($CDCl_3$, 250 MHz) δ 0.55 (m, 6H, (OSi($\underline{CH_2}CH_3)_3$)), 0.9 (m, 9H, (OSi($CH_2\underline{CH_3})_3$), 1.10 (s, 3H, $C_{16}H_3$), 1.12 (s, 3H, $C_{17}H_3$), 1.73 (s, 6H, $C_{19}H_3$ and $C_{18}H_3$), 1.75 (m, 1H, C_6H), 2.01 (s, 3H, $CO\underline{CH_3}$), 2.47 (m, 1H, C_6H), 2.81 (d, 1H, J=17 Hz, $C_{14}H$), 2.99 (d, 1H, J=17 Hz, $C_{14}H$), 3.42 (d, 1H, J=12 Hz, C_3H), 4.22 (d, 1H, J=8 Hz, $C_{20}H$), 4.5 (m, 1H, C_7H), 4.6 (d, 1H, J=8 Hz, $C_{20}H$), 4.88 (s, 1H, OH), 4.9 (m, 1H, C_5H), 5.9 (d, 1H, J=12 Hz, C_2H), 6.22 (s, 1H, $C_{11}H$), 7.47, 7.6, 7.91 (m, 5H, OBz), 9.45 (s, 1H, $C_{10}H$); CIMS m/z 657 (MH^+).

$NaBH_4$ Reduction of 13-oxo-7-*O*-triethylsilyl-11,12-dihydro-10-deacetylbaccatin III 12. To a solution of compound **12** (188 mg, 0.29 mmol) in methanol (35 ml) was added $NaBH_4$ (130 mg). The reaction was stirred for 2 hours at 50°C under argon. The solution was then neutralized with 0.01N HCl and extracted with methylene chloride. The organic layers were washed with brine, dried over $MgSO_4$, and the solvent removed *in vacuo*. The extract was purified (methylene chloride/methanol 96/4) to give compound **16** (130 mg). IR ($CHCl_3$) 3564, 1725, 1706 cm^{-1}; U.V (EtOH) λmax (ε) 230 (16434); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.55 (m, 6H, (OSi($\underline{CH_2}CH_3)_3$), 0.94 (m, 9H, (OSi($CH_2\underline{CH_3})_3$), 1.03 (s, 3H, $C_{16}H_3$), 1.13 (s, 3H, $C_{17}H_3$), 1.24 (d, 3H, J=6 Hz, $C_{18}H_3$), 1.7 (s, 3H, $C_{19}H_3$), 1.75 (m, 1H, $C_{11}H$), 1.77 (d, 1H, J=16 Hz, $C_{14}H$), 1.85 (m, 1H, C_6H), 2.22 (1H, OH_{13}), 2.26 (s, 3H, OAc), 2.38 (m, 1H, $C_{12}H$), 2.44 (d, 1H, J=16 Hz, $C_{14}H$), 2.49 (m, 1H, C_6H), 3.35 (1H, J=8,5Hz, OH at C-10), 4.02 (m, 1H, $C_{13}H$), 4.27 (d, 1H, J=8 Hz, $C_{20}H$), 4.32 (d, 1H, J=8 Hz, $C_{20}H$), 4.35 (m, 1H, C_7H), 4.38 (d, 1H, J=8 Hz, C_3H), 4.98 (dd, J=5,6 et 8,5 Hz, $C_{10}H$), 5.11 (m, 1H, C_5H), 5.61 (d, 1H, J=8 Hz, C_2H), 7.5, 7.61, 8.18 (m, 5H, OBz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 5.79 (OSi($\underline{CH_2}CH_3)_3$), 6.08 (OSi($CH_2\underline{CH_3})_3$), 10.06 (C_{19}), 16.57 (C_{18}), 23.27 ($CO\underline{CH_3}$), 26.52 (C_{16}), 33.40 (C_{17}), 33.44 (C_{12}), 36.39(C_6), 37.32 (C_{14}), 41.24 (C_{15}), 41.50 (C_3), 57.33 (C_8), 61.49 (C_{11}), 70.37 (C_{10}), 71.76 (C_{13}), 72.50 (C_7), 74.30 (C_2), 77.12 (C_{20}), 80.69 and 81.05 (C_1 and C_4), 84.75 (C_5), 129.40 (OBz *ortho*), 130.68 (OBz C_1), 131.04 (OBz *meta*), 134.29 (OBz *para*), 168.58 ($\underline{CO}$Ph), 170.90 ($\underline{CO}CH_3$), 216 (C_9); FABMS m/z 683 (MNa^+).

11, 12-dihydro-10-deacetylbaccatin III 17 A solution of **16** (30 mg, 0.045 mmol) in 2 ml of a 0.5% hydrochloric acid/ethanol solution was stirred at 0°C for 1 hour. The mixture was diluted with methylene chloride and washed with aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The extract was purified on silica gel (ethyl acetate/cyclohexane/methanol 80/20/2) to give 15 mg of compound **17.** IR ($CHCl_3$) 3493, 1712, 1606 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 3H, $C_{16}H_3$), 1.07 (s, 3H, $C_{17}H_3$), 1.17 (d, 3H, J=6 Hz, $C_{18}H_3$), 1.64 (s, 3H, $C_{19}H_3$), 1.68 (m, 1H, $C_{11}H$), 1.70 (m, 1H, C_6H), 1.76 (d, 1H, J=16 Hz, $C_{14}H$), 2.19 (s, 3H, OAc), 2.27 (m, 1H, $C_{12}H$), 2.41 (d, 1H, J=16 Hz, $C_{14}H$),

2.53 (m, 1H, C_6H), 3.97 (m, 1H, $C_{13}H$), 4.08 (m, 1H, C_7H), 4.20 (d, 1H, J=8 Hz, $C_{20}H$), 4.27 (d, 1H, J=8 Hz, $C_{20}H$), 4.38 (d, 1H, J=8 Hz, C_3H), 5.04 (m, 1H, $C_{10}H$), 5.05 (m, 1H, C_5H), 5.56 (d, 1H, J=8 Hz, C_2H), 7.41, 7.53, 8.09 (m, 5H, OBz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.80 (C_{19}), 16.49 (C_{18}), 23.05 (C_{16}), 26.53 ($CO\underline{C}H_3$), 33.05 (C_{17}), 33.33 (C_{12}), 35.88 (C_6), 36.26 (C_{14}), 41.04 (C_{15}), 41.04 (C_3), 57.43 (C_8), 60.92 (C_{11}), 70.85 (C_{10}), 71.07 (C_{13}), 71.54 (C_7), 74.07 (C_2), 76.99 (C_{20}), 80.66 and 80.99 (C_1 and C_4), 84.54 (C_5), 129.25 (OBz *ortho*), 130.44 (OBz C_1), 130.83 (OBz *meta*), 134.21 (OBz *para*), 168.34 ($\underline{C}OPh$), 170.80 ($\underline{C}OCH_3$), 214.74 (C_9); FABMS m/z 547 (MH^+).

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