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New Skeletal Rearrangements of C and D Rings of a 13-Oxobaccatin III Derivative

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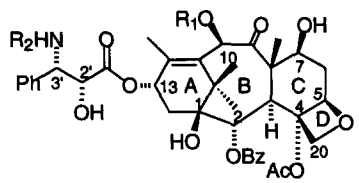
Abstract

13-Oxobaccatin III (**4**) was oxidized to 7,13-dioxo D-secobaccatin III (**5**). This compound, when treated with base or cyanide ion, underwent rearrangements involving the rupture of the C-7,C-8 bond, the migration of the benzoyl and acetyl groups and intramolecular formation of new rings. Four new compounds were isolated and fully characterized.

Paclitaxel (Taxol®)[1] **1a** and docetaxel **1b** (Taxotère®)[2], are the most important compounds of the taxoid series, new leads for the treatment of cancer.



Paclitaxel (Taxol®) **1a** R_1=Ac, R_2=Bz

Docetaxel (Taxotere®) **1b** R_1=H, R_2=Boc

The discovery of paclitaxel's unique antimitotic mechanism[3] and the clinical importance of such compounds have led to increased interest in understanding the structure-activity relationships (S.A.R.)[4]. Many efforts have been made to synthesize more active analogues. In the course of these works, it has been observed that these polyoxygenated diterpenoids have a propensity to undergo complex rearrangements on the taxane core[5-15]. We wish to report herein new skeletal rearrangements that occur on the C and D rings when we tried to modify the oxetan D-ring[16,17].

Kingston et al.[18] have described the formation of compound **2** bearing an α,ß-unsaturated ketone on ring C. This derivative resulted from the oxidation of the C-7 hydroxyl group of paclitaxel followed by the base catalyzed oxetan ring opening.

Dedicated to Professor A.I. Scott on the occasion of his seventieth birthday.

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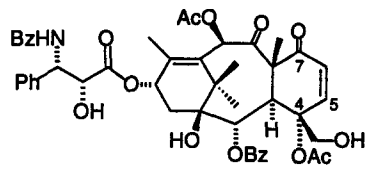
Compound **2** seemed to be a good synthon to introduce new D-rings by Michael addition. In order to avoid side reaction on the side chain at C-13, the derivative of 13-oxo baccatin III **3** was chosen as starting material.



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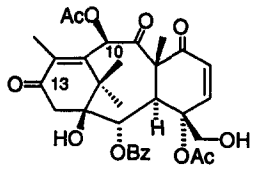
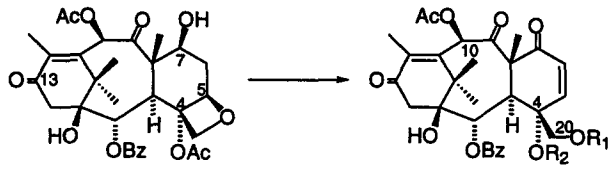


3

Unlike the Jones' oxidation realized by Kingston[18], 13-oxobaccatin III **4**[19] was oxidized by an excess of PCC in pyridine at 80°C. Under these conditions, the base catalyzed opening of the oxetan ring occurred in the reaction medium[20] (scheme 1).



4

3 $R_1 = H$, $R_2 = Ac$
5 $R_1 = Ac$, $R_2 = H$

Reagents : PCC (8 equiv.)/pyridine, 80°C, 4h, **5** (70%)

Scheme 1

Further unsuccessful attempts to functionalize the C-20 position of the oxidation product led us to suspect a wrong interpretation in the expected structure **3**. To determine unambiguously the structure of the isolated product, X-rays diffraction analysis was used.

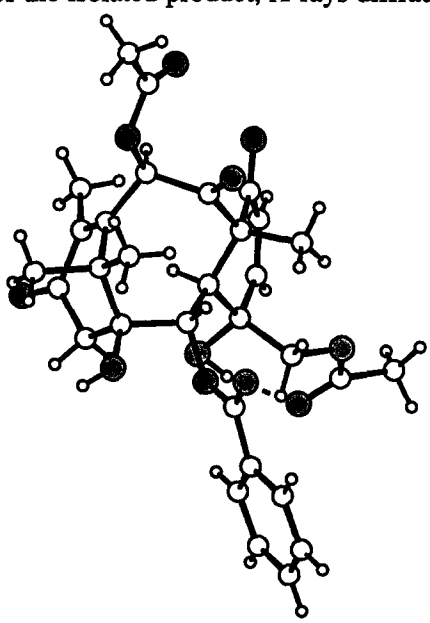
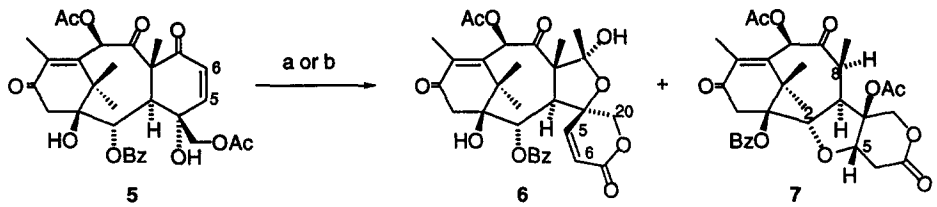


Figure 1 : X-ray crystallographic structure of compound **5**

The oxidation product of 13-oxobaccatin III **4** was thus shown to correspond to structure **5** (figure 1) in which the acetyl groups were present on positions 10 and 20 and not on positions 10 and 4 as described by Kingston for compound **2**. Attempts to deacylate position 20 in the presence of alcohol led only to migration of the benzoyl group from the C-2 to C-20 position as it was already observed in this series of opened D-ring compounds when the alcohol at C-20 is free[20,21].

Michael additions were tried on compound **5** with malonyl carbanion under different conditions. None of the two major products **6** and **7** was the desired compound but both of them showed important skeletal rearrangements. It rapidly appeared that these rearrangements were due to the basicity of the reaction medium and the same derivatives were obtained in the presence of a base only (scheme 2).



Reagents : (a) NaH (excess)/ THF, r.t., 1h45, **6** (50%) and **7** (8%); (b) K_2CO_3 aq. 0.1N/THF, r.t., 1h50, **6** (20%) and **7** (40%)

Scheme 2

The mass spectra (FAB+) of each compound showed a molecular ion [MNa^+] at *m/z* 605 corresponding to that of compound **5**. The infrared spectra of **6** and **7** exhibited carbonyl absorption bands at 1720 and 1728 cm^{-1} respectively, consistent with the presence of a ∂ lactone.

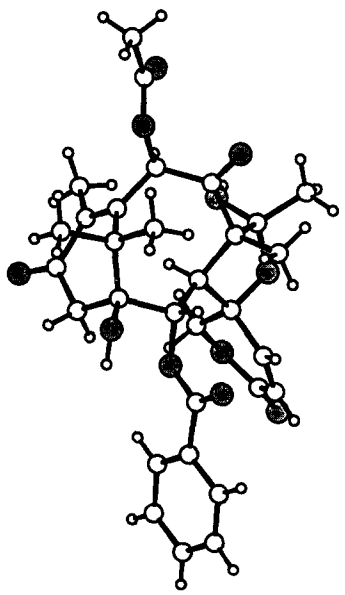


Figure 2 : X-ray crystallographic structure of compound **6**

In comparison to the ^{1}H and ^{13}C NMR spectra of compound **5**, those of compound **6** showed the disappearance of two carbonyl signals, attributed by HMBC to C-7 and CO of the C-20 acetyl group, and the appearance of two signals of quaternary carbons at 162.3 and 107.9 ppm. These observations suggested the presence of a lactone and a hemiacetal. Our hypothetic structure of **6** was confirmed by its single crystal X ray analysis (figure 2).
The ^{1}H NMR data of compound **7** indicated the loss of the C-5,C-6 double bond, the appearance of an ABX system (H-6, H-6, H-5) and the presence of a proton at 2.93 ppm located at C-8 because of its coupling with the C-3 proton and the C-19 methyl group. The upfield shift of the C-2 proton from 5.64 to 4.90 ppm and downfield shift of the C-1 carbon from 77.9 to 88.2 ppm suggested the migration of the benzoyl group from C-2 to C-1. As for compound **6**, the C-7 carbonyl group was shifted from 196.8 to 162.3 ppm, indicating the formation of a lactone, and showed a three-bond ^{1}H ^{13}C correlation with the C-20 protons. The chemical shifts of both carbon (76.1 ppm) and proton (4.17 ppm) at C-5 indicated the presence of an oxygen in that position. Finally, the NOESY spectrum allowed the attribution of the configuration at carbons 5 and 8 (figure 3).

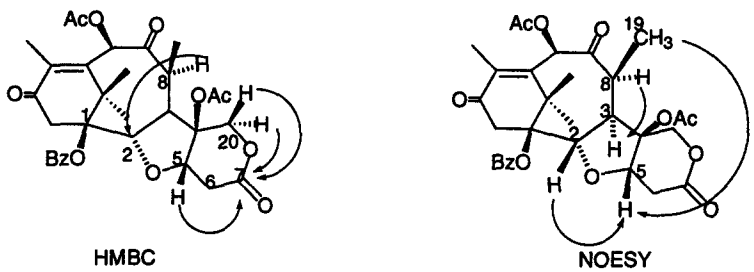
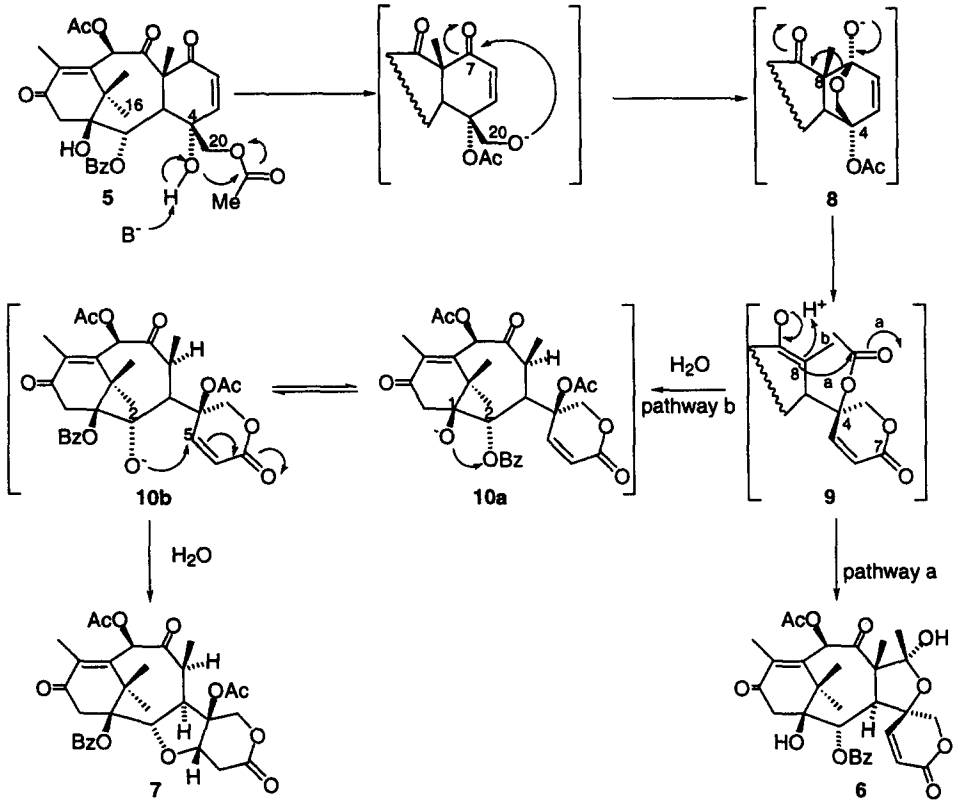


Figure 3 : Key HMBC and NOESY correlations of compound **7**

The formation of compounds **6** and **7** can be explained by the mechanism depicted on scheme 3: compound **5** first undergoes a transacetylation between positions 20 and 4; then, the C-20 alkoxide so formed attacks the C-7 carbonyl leading to the lactol **8** that can undergo a retro-aldol reaction; then a new aldol condensation can occur between the C-8 enol group and the electrophilic C-4 acetyl carbonyl carbon (pathway a), leading to the spiro α-ß unsaturated lactone **6**. The facile formation of a five-membered C-ring in this taxoid series has already been reported[13]. Moreover, the observed stereochemistry of the final aldol **6** is in perfect agreement with the mechanism of that condensation. In fact, molecular modeling studies (Macromodel and Mopac) proposed an intermediate **9** of lowest energy which shows orbital overlapping between the HOMO of the enol and the LUMO of the carbonyl; this is the best situation leading to the aldol condensation with the observed stereochemistry[22]. When water is present in the reaction medium, the enolate **9** can be more easily protonated (pathway b). Then, under basic conditions an equilibrium might exist between the anions **10a** and **10b**, as already reported by Chaudary et al.[23]. Though the anion **10b** would not be actually thermodynamically favored, this equilibrium can be displaced by the nucleophilic attack of the C-2 alkoxide on the C-5,C-6 double bond in a Michael reaction way, leading to compound **7**. The enhancement of the ratio of compound **7** versus compound **6** when aqueous carbonate was used as a base greatly supports the hypothesis of the protonation of the enolate (pathway b) before transbenzoylation and cyclisation.

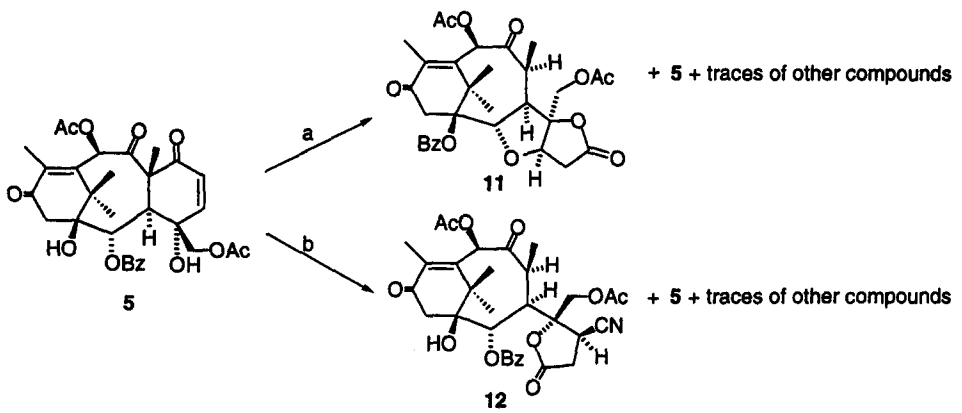
Molecular modeling studies of the intermediates **9** and **10b** showed that protonation of the C-8 enol can only occur on the α face of the B-ring because of the presence of the C-16 methyl group and, as well, that the only way for C-2 alkoxide to attack at C-5 is trans to the acetyl group.



Scheme 3

Michael additions were also realized in the presence of cyanide ions, either with Et_2AlCN in THF[24] or with KCN in DMF in the presence of ammonium chloride[25] (scheme 4). Both reactions led to many compounds and only the major ones were isolated. None of the isolated compounds were the expected adduct though compound **12** showed by CI mass spectrometry a molecular ion [MH+] at *m/z* 610, consistent with the addition of a nitrile. The mass spectrum of compound **11** showed a FAB+ molecular ion [MNa+] at *m/z* 605 as the starting compound **5**. The infrared spectra of **11** and **12** exhibited carbonyl absorption bands at respectively 1793 and 1812 cm^{-1}, consistent with the presence of a γ-lactone. For both compounds, the ^1H and ^{13}C NMR spectra showed an ABX system (H-6,H-6,H-5) indicating an addition at C-5 to the double bond. As for compound **7**, a proton at C-8 was coupled with the C-3 proton and the C-19 methyl group, and the C-7 carbon was shifted from 196.8 to 173.1 ppm due to the formation of the lactone. NMR data of compound **11** were very close to those of compound **7** but the C-20 protons showed a three-bond ^1H ^{13}C correlation with the carbonyl carbon of one acetyl group and not of the lactone. These observations indicate that the C-20 methylene group possesses an acetoxyl group not involved in the lactone ring. As well, the NOESY spectrum revealed that the C-5 and C-8 protons are on the same face as the C-3 proton and one of the C-20 protons also showed a

correlation with the C-8 proton assessing a *cis* stereochemistry for the C-D bicycle junction (figure 4). As for compound **7** molecular modeling studies support this stereochemistry.



Reagents : (a)Et_2AlCN in THF, 50°C, 24h, **12** (32%) and **5** (10%); (b) KCN, NH_4Cl in DMF, 60°C, 4h, **11** (20%) and **5** (17%)

Scheme 4

The NMR data of compound **12** showed that no transesterification occurred between C-1 and C-2. In comparison to the ^{13}C NMR spectrum of **5**, an additional carbon at 116.7 ppm indicated the presence of a nitrile. The following three-bond ^1H ^{13}C correlations were observed in the HMBC experiment : the C-6 protons with the nitrile carbon, the C-5 proton with the carbonyl carbon of the lactone, and the C-20 protons with the carbonyl carbon of one acetyl group. These observations indicated that the nitrile was located at C-5, the acetoxyl group at C-20 and led us to propose that structure for **12**. The absolute configuration at C-5 was difficult to assess, but, from the NOESY spectrum, no correlation was found between the C-5 and C-20 protons, while one proton at C-6 correlated with those at C-20 and the other with the C-5 proton. This suggested that the nitrile was *cis* to the C-20 acetoxymethyl group what was in agreement with the coupling constants between the C-5 and C-6 protons. Thus, the S configuration was proposed for C-5.(figure 4)

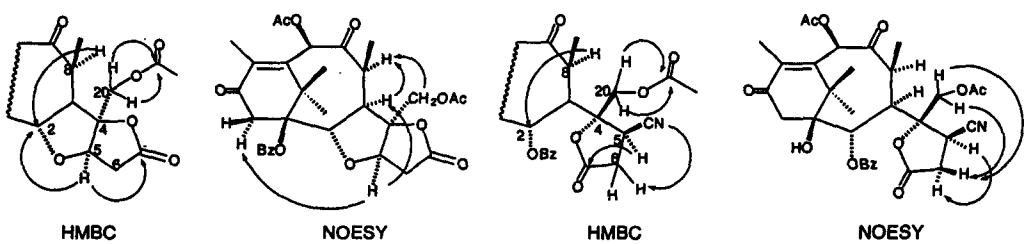
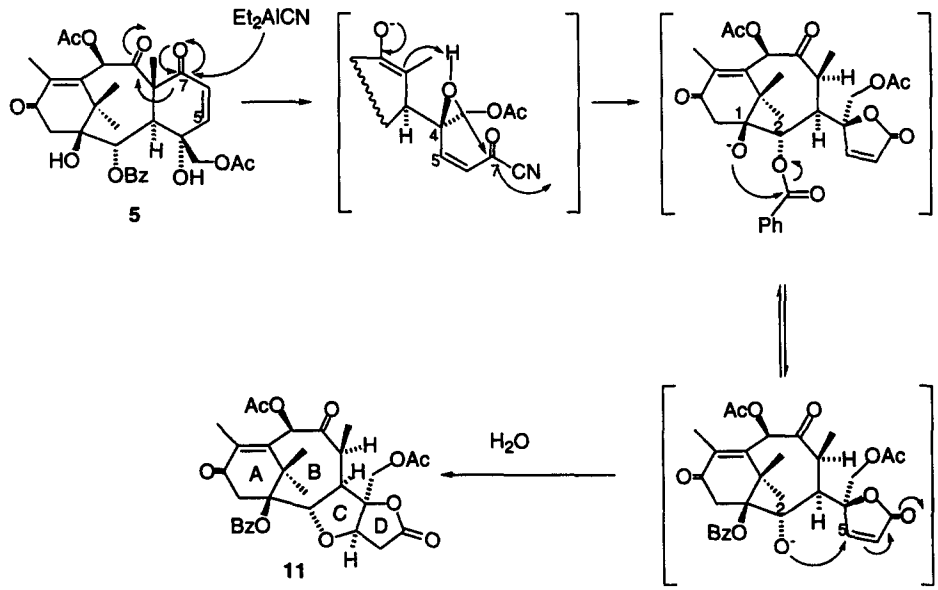


Figure 4 : Key HMBC and NOESY correlations of compound **11** and **12**

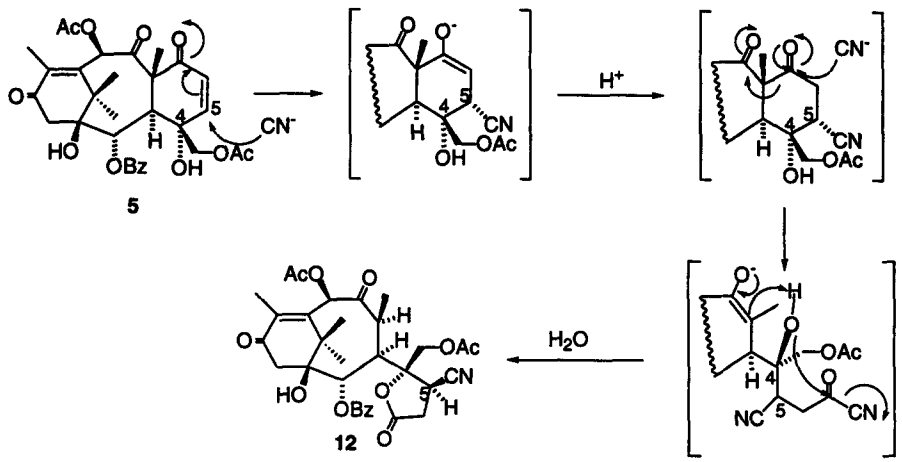
The mechanisms of formation of compounds **11** and **12** were based on that of the hydrocyanation of α,ß-unsaturated ketones that have been extensively studied. When diethylaluminium cyanide is used, leading in our case to compound **11**, Nagata et al[24] have

shown that 1,2 addition occurred overwhelmingly in the initial stage of the reaction but, in the absence of a proton, this reaction proceeded reversibly giving ultimately the thermodynamic 1,4 adduct. On the starting compound **5**, the addition of a cyanide ion at C-7 leads to the opening of the C-7,C-8 bond which is facilitated by the presence of the ketone at C-9. The α,ß-unsaturated lactone is formed by the attack of the C-4 alkoxide at C-7. Then, as for the formation of compound **7**, the transbenzoylation from C-2 to C-1 allows thereafter the Michael addition of the C-2 alkoxide at C-5 (scheme 5). Unlike the ∂ lactones (scheme 3), no derivative resulting from the attack of the C-8, C-9 enolate on the acetyl carbonyl group was detected. The stereochemistry of the nucleophilic attack of the C-2 alkoxide is governed by the C-4 absolute configuration, leading, as for compound **7**, to a *cis* junction of the C-D bicycle.



Scheme 5

Finally, only the use of KCN in the presence of ammonium chloride in DMF afforded the 1,4 adduct (compound **12**). This reagent is known to effect either 1,2- or 1,4-addition on α,ß-unsaturated ketones[24]. On compound **5** the cyanide ion is supposed to add first at C-5 by a 1,4-Michael addition followed by an 1,2-addition at C-7 leading to the C-7,C-8 bond cleavage and lactonisation (scheme 6). In the taxoid series, the sensitivity of the C-7-C-9 ß-diketone towards nucleophiles has already been noticed by Magri and Kingston[18]. The absence among the reaction products of compound **11** that would result from the addition at C-5 of the C-2 alkoxide, greatly suggests that this position is not free any more because of primary cyanide addition. Thus Michael addition of the cyanide ion is supposed to be the very first event in this reaction. As expected from the literature[26], hydrocyanation takes place in a stereoelectronic controlled manner, i.e. axial addition on the less hindered α face.



Scheme 6

All the rearrangements shown here involve a great degree of reorganization of the carbon skeleton, especially at the C and D rings. The cleavage of the C-7, C-8 bond followed by the formation of a lactone was always observed. It appeared that the ß-diketonic C-7, C-9 system is very sensitive to nucleophiles, especially when there is no double bond conjugated with one of the ketones. It is worth noting that the formation of ∂-lactones occurred with only intramolecular attack of alkoxide whereas γ-lactones were formed when an external nucleophile attacks either at C-7 carbonyl group (1,2 addition) or on the double bond at C-5 (1,4 addition). The increasing number of rearranged taxoids published in the literature clearly indicates that we still have to learn about the chemistry of taxoids. Though these highly functionalized molecules have been extensively studied for the past twelve years, original or unexpected reactions are still to be discovered and can lead to new interesting compounds.

EXPERIMENTAL

General experimental procedures. All non-aqueous reactions were performed in oven-dried glassware. THF was distilled from Na/benzophenone. Dichloromethane was distilled from CaH_2 and DMF from molecular sieves 4 Å under reduced pressure. Thin and thick layer chromatographies were performed on precoated silica gel plates (Merck 60F, 0.25 or 2 mm thick). Infrared spectra were recorded on a Nicolet 205 spectrophotometer. ^1H, ^{13}C and 2D NMR spectra were recorded on Bruker AC200, AC250, AM300 and AM400 spectrometers using tetramethylsilane as internal standard. Chemical shifts are expressed in part per million (ppm). Coupling constants (J) are given in Hertz; s, bs, t, d, dd, q and m indicate singlet, broad singlet, triplet, doublet, doublet of doublet, quadruplet and multiplet. Mass spectra were measured on a Kratos MS80 (FAB) and on an AEI MS9 (CI). X-Rays analysis were performed by measuring intensity data on a Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Cu Kα radiation and the (θ-2θ) scan technique up to θ = 66° for compound **5** and θ = 65° for compound **6**. Computer-programs: *SHELXS86*[27], *SHELXL93*[28] (lists of atomic cooordinates, bond distances, bond angles, torsional angles has been deposited at the Cambridge Crystallographic Data Center). 13-oxo baccatin III **4** was prepared as previously described[20,29] from 10-deacetylbaccatin III,

isolated from the leaves of *Taxus baccata*[30]. The phrase "worked up under standard methods" refers to diluting the reaction mixture with an excess of solvent (CH_2Cl_2 or EtOAc), successive washing with H_2O and brine, drying over Na_2SO_4 and evaporating the solvent *in vacuo* unless otherwise specified.

13-Oxo-D-seco-5,6-dehydrobaccatin III (5). 13-Oxobaccatin III **4** (100 mg, 0.022 mmol) was dissolved in pyridine (10 mL). To this solution PCC (28 mg, 0.13 mmol) was added and the mixture stirred at 80°C for 4 hours. After removal of pyridine *in vacuo* the residue was diluted with dichloromethane and the solution was worked up under standard methods. The crude product was purified by preparative TLC (heptane/EtOAc/MeOH 60/40/2) affording compound **5** (70 mg, 70% yield). Compound **5** was recrystallized in $MeOH/CH_2Cl_2$ for X-ray analysis. IR ($CHCl_3$) 3582, 1755-1735, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) ∂ 1.23 (s, 3H, C-17H_3), 1.28 (s, 3H, C-16H_3), 1.62 (s, 3H, C-19H_3), 1.87 (s, 3H, OAc), 1.96 (s, 3H, C-18H_3), 2.27 (s, 3H, OAc), 2.69 (d, 1H, J = 19, C-14H), 3.74 (d, 1H, J = 19, C-14H), 4.03 (d, 1H, J = 6, C-3H), 4.25 (d, 1H, J = 12, C-20H), 4.44 (d, 1H, J = 12, C-20H), 5.64 (d, 1H, J = 6, C-2H), 5.97 (d, 1H, J = 10, C-6H), 6.40 (s, 1H, C-10H), 6.45 (d, 1H, J = 10, C-5H), 7.52-7.65-8.09 (m, 5H, OBz); ^{13}C NMR ($CDCl_3$, 75 MHz) ∂ 13.3 (C-18), 17.6 (C-19), 17.9 (C-16), 20.1 (AcO), 20.7 (AcO), 32.2 (C-17), 43.2 (C-15), 43.3 (C-14), 53.0 (V-3), 63.4 (C-8), 68.8 (C-20), 74.0 (C-4), 74.4 (C-2), 77.6 (C-10), 77.9 (C-1), 123.4 (C-6), 128.7-128.9-130.1-133.8 (Bz), 140.5 (C-12), 150.1 (C-11), 153.5 (C-5), 166.4 (CO-Bz), 168.8 (CO-OAc), 172.1 (CO-OAc), 196.8-197.4-199.5 (C-7, C-9, C-13); CIMS : *m/z* 582 [MH^+], 565 [$M-H_2O + H^+$]

Crystal structure of 5

Crystal data : C_{31} H_{34} O_{11}, H_2O, M_w = 600.6, orthorhombic, space group P 2_1 2_1 2_1, Z=4, a = 9.579(6), b = 11.471(9), c = 26.505(14) Å, V = 2912(3) $Å^3$, d_{calc} = 1.37 g cm^{-3}, λ (Cu Kα) = 1.5418 Å, μ = 0.89 mm^{-1}.

3419 collected reflexions, 2890 unique (R_{int} = 0.20) of which 2541 were considered as observed having I ≥ 2 σ(I). Hydrogen atoms fitted at theoretical positions except those of the water molecule, not located. Refinement minimizing the function $\sum w(Fo^2-|Fc|^2)^2$, R1 (Fo) = 0.076 and wR_2 = 0.197, goodness of fit = 1.04. The residual electron density in the final difference map was located between -0.47 and 0.44 e $Å^{-3}$. Intramolecular hydrogen bond: C4-O4-H...O38 (2.940 Å). Intermolecular hydrogen bonds: C1-O1-H.. O13-C13 (x-1/2, 1/2-y, 2-z, 2.893 Å). The water molecule links two molecules: C7-O7...H-OH(3.182 Å) and C9-O9... H-OH (3.202 Å) where the H atom is probably disordered and HO-H.. O38 (x, y -1, z, 2.842 Å).

Action of a base on 13-oxo-D-seco-5,6-dehydrobaccatin III (5). *Method A (NaH/THF).* 13-Oxo-D-seco-5,6-dehydrobaccatin III **5** (24 mg, 0.041 mmol) was dissolved in dry THF (1.5 mL). To this solution was added NaH (5 mg, 0.21 mmol) and the mixture was stirred at room temperature for 1.5 hours. The reaction was stopped by addition of a saturated solution of NH_4Cl. The solvent was removed *in vacuo* and the residue was diluted with EtOAc. The solution was worked up under standard methods and the residue was purified by preparative TLC (CH_2Cl_2/MeOH 94/6) affording compound **6** (12 mg, 50% yield) and compound **7** (2 mg, 8% yield). Compound **6** was recrystallized in $MeOH/CH_2Cl_2$ for X-ray analysis.

Method B (K_2CO_3/THF). 13-Oxo-D-seco-5,6-dehydrobaccatin III **5** (30 mg, 0.051 mmol) was dissolved in THF (1 mL). To this solution was added K_2CO_3 0.1N (0.5 mL, 0.05 mmol) and the mixture was stirred at room temperature for 3 hours. The reaction was stopped by addition of HCl 0.1N. The solvent was removed *in vacuo* and the residue was diluted with CH_2Cl_2. The solution was worked up under standard methods and the residue was purified by preparative TLC (CH_2Cl_2/acetone 98/2) affording compound **6** (6 mg, 20% yield) and compound **7** (12 mg, 40% yield).

Compound 6. IR ($CHCl_3$) 3181, 1733, 1720, 1682, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) ∂ 1.21 (s, 3H, C-17H_3), 1.29 (s, 3H, C-16H_3), 1.35 (s, 3H, CH_3), 1.60 (s, 3H, C-19H_3), 2.08 (s, 3H, C-18H_3), 2.15 (s, 3H, OAc), 2.80 (d, 1H, J = 20.0, C-14H), 3.15 (d, 1H, J = 20.0, C-14H), 4.18 (dd, 1H, J = 11.6, 1.6, C-20H), 4.18 (d, 1H, J = 9.8, C-3H), 4.55 (d, 1H, J = 11.6, C-20H), 4.65 (s, 1H, OH), 5.35 (d, 1H, J = 10.0, C-6H), 5.86 (d, 1H, J = 9.8, C-2H), 6.60 (dd, 1H, J = 10.0, 1.6, C-5H), 6.79 (s, 1H, C-10H), 7.48-7.65-7.75 (m, 5H, OBz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) ∂ 12.9 (C-19), 16.3 (C-18), 18.7 (C-16), 20.8 (CH_3), 21.2 (AcO), 31.9 (C-17), 43.5 (C-14 and C-15), 47.8(C-3), 60.1 (C-8), 73.5 (C-2), 75.8 (C-20), 76.3 (C-4 or C-1), 77.2 (C-10), 80.0 (C-1 or C-4), 107.9 (Cq), 119.9 (C-6), 128.9-129.1-129.6-134.2 (Bz), 140.0 (C-12), 143.9 (C-5), 154.0 (C-11), 162.3 (C-7), 169.7 (CO-Bz), 174.5 (CO-Ac), 198.1 (C-7), 198.8(C-13), 201.0 (C-9); LRFABMS : *m/z* 605 [MNa+]; HRMS (CI) calcd for $C_{31}H_{35}O_{11}$ (MH^+) 583.2179, found 583.2200.

Crystal structure of 6

Crystal data : $C_{31}H_{34}O_{11}$, CH_2Cl_2 M_w = 667.5, orthorhombic, space group P 2_1 2_1 2_1, Z = 4, a = 9.395(6), b = 14.387(9), c = 24.008(14) Å, V = 3245(4) $Å^3$, d_{calc} = 1.37 g cm^{-3}, λ (Cu Kα) = 1.5418 Å, μ = 2.3 mm^{-1}.

3681 collected reflexions, 3562 unique (R_{int} = 0.06) of which 3170 were considered as observed having $I \geq 2\ \sigma(I)$. Hydrogen atoms fitted at theoretical positions. A molecule of CH_2Cl_2 was observed. Refinement minimizing the function $\Sigma w(Fo^2-|Fc|^2)^2$, R1 = 0.072 and wR_2 = 0.194, goodness of fit = 1.04. The residual electron density in the final difference map was located between -0.33 and 0.47 e $Å^{-3}$. Intermolecular hydrogen bonds: C1-O1-H .. O13-C13 (x-1/2, -y-1/2, 2-z, 2909 Å) and C21-O21-H.. O7-C7 (x-1/2, 1/2-y, 2-z, 2.876 Å).

Compound 7. IR ($CHCl_3$) 3551, 1755, 1728, 1682, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) ∂ 1.33 (s, 3H, C-17H_3), 1.40 (s, 3H, C-16H_3), 1.55 (d, 3H, J = 6.8, C-19H_3), 2.05 (s, 3H, C-18H_3), 2.12 (s, 3H, OAc), 2.28 (s, 3H, OAc), 2.81 (dd, 1H, J = 17.5, 3.5, C-6H), 2.93 (qd, 1H, J = 6.8, 2.5, C-8H), 3.11 (dd, 1H, J = 17.5, 6.1, C-6H), 3.28 (dd, 1H, J = 8.5, 2.5, C-3H), 3.52 (d, 1H, J = 19.5, C-14H), 3.80 (d, 1H, J = 19.5, C-14H), 4.01 (d, 1H, J = 11.7, C-20H),4.17 (m, 1H, C-5H), 4.67 (dd, 1H, J = 11.7, 1.5, C-20H), 4.90 (d, 1H, J = 8.5, C-2H), 6.33 (s, 1H, C-10H), 7.47-7.57-7.98 (m, 5H, OBz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) ∂ 13.4 (C-18), 13.8 (C-19), 20.6 (C-16), 20.8 (Ac), 21.4 (Ac), 31.4 (C-17), 33.7 (C-6), 41.5 (C-14), 44.5 (C-15), 44.9(C-8), 45.8 (C-3), 67.8 (C-20), 76.1 (C-5), 77.0 (C-10), 81.5 (C-2), 83.6 (C-4), 88.2 (C-1), 128.7-129.8-131.3-133.3 (Bz), 140.2 (C-12), 151.9 (C-11), 164.6(CO-Bz), 168.5 (C-7), 169.2(CO-Ac), 170.2 (CO-Ac), 197.0(C-13), 201.2 (C-9); LRFABMS : *m/z* 605 [MNa+]; HRMS (CI) calcd for $C_{24}H_{29}O_9$ (MH^+- $PhCO_2H$) 461.1811, found 461.1804.

Action of cyanide ion on 13-oxo-D-seco-5,6-dehydrobaccatin III (5). *Method A (Et2AlCN/THF).* 13-Oxo-D-seco-5,6-dehydrobaccatin III **5** (31.5 mg, 0.054 mmol) was dissolved in dry THF (2 mL). To this solution was added Et_2AlCN 1M in THF (54 µL, 0.054 mmol) and the mixture was stirred at room temperature for 24 hours. Then Et_2AlCN 1M in THF (220 µL, 0.22 mmol) was added again and the mixture was stirred at 50 °C for 24 hours. The reaction was stopped by addition of a saturated solution of $NaHCO_3$. The solution was worked up under standard methods and the residue was purified by preparative TLC (CH_2Cl_2/MeOH 95/5) affording compound **11** (10 mg, 32% yield), starting compound **5** (3 mg, 10% yield) and other non-isolable compounds.
Method B (KCN, NH4Cl/DMF). 13-Oxo-D-seco-5,6-dehydrobaccatin III **5** (30 mg, 0.051 mmol) was dissolved in DMF (1.5 mL). To this solution were added KCN (7.0 mg, 0.11 mmol) and NH_4Cl (4.0 mg, 0.075 mmol) in H_2O (0.1 mL) and the mixture was stirred at 60°C for 4 hours. NH_4Cl (1.4 mg, 0.025 mmol) was then added to the reaction mixture, DMF was removed *in vacuo* and the residue was diluted with CH_2Cl_2. The solution was worked up under standard methods and the residue was purified by preparative TLC (c-hexane/EtOAc/MeOH 50/50/2) affording compound **12** (6.5 mg, 20% yield), starting compound **5** (5 mg, 17% yield) and other non-isolable compounds.

Compound 11. IR ($CHCl_3$) 1793, 1756, 1716, 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) ∂ 1.30 (s, 3H, C-16H_3), 1.37 (s, 3H, C-17H_3), 1.61 (d, 3H, J = 6.8, C-19H_3), 2.05 (s, 3H, C-18H_3), 2.09 (s, 3H, OAc), 2.28 (s, 3H, OAc), 2.73 (m, 2H, C-6H_2), 2.98 (qd, 1H, J = 6.8, 2.5, C-8H), 3.64 (d, 1H, J = 20.0, C-14H), 3.68 (d, 1H, J = 8.5, 2.5, C-3H), 3.82 (d, 1H, J = 20.0, C-14H), 3.88 (d, 1H, J = 12.0, C-20H), 4.33 (d, 1H, J = 12.0, C-20H), 4.58 (dd, 1H, J = 4.2, 1.5, C-5H), 4.93 (d, 1H, J = 8.5, C-2H), 6.35 (s, 1H, C-10H), 7.46-7.58-7.95 (m, 5H, OBz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) ∂ 13.4 (C-18), 13.5 (C-19), 20.2 (C-16), 20.7 (Ac), 20.8 (Ac), 32.9 (C-17), 36.1 (C-6), 41.3 (C-14), 43.9 (C-8), 44.4 (C-15), 45.5 (C-3), 61.8 (C-20), 76.9 (C-10), 79.9 (C-5), 84.0 (C-2), 89.5 (C-4), 93.5 (C-1), 128.7-129.8-133.3 (Bz), 139.6 (C-12), 153.4 (C-11), 165.1 (CO-Bz), 169.4 (CO-Ac), 169.9 (CO-Ac), 173.1 (C-7), 197.0(C-13), 201.3 (C-9); LRFABMS : *m/z* 605 [MNa^+]; HRMS (CI) calcd for $C_{31}H_{H35}O_{11}$ (MH^+) 583.2179, found 583.2163.

Compound 12. IR ($CHCl_3$) 1812, 1755, 1716, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) ∂ 1.20 (s, 3H, C-16H_3), 1.35 (s, 3H, C-17H_3), 1.55 (d, 3H, J = 6.5, C-19H_3), 2.12 (s, 3H, C-18H_3), 2.14 (s, 3H, OAc), 2.29 (s, 3H, OAc), 2.57 (dd, 1H, J = 17.5, 10.0, C-6H), 2.80 (dd, 1H, J = 17.5, 9.8, C-6H), 2.87 (qd, 1H, J = 6.5, 1.5, C-8H), 3.02 (d, 1H, J = 20.5, C-14H), 3.28 (d, 1H, J = 20.5, C-14H), 3.78 (dd, 1H, J = 6.5, 1.5, C-3H), 4.02 (bt, 1H, J = 10.0, 9.8, C-5H), 4.23 (d, 1H, J = 12.0, C-20H), 4.30 (d, 1H, J = 12.0, C-20H), 5.90 (d, 1H, J = 6.5, C-2H), 6.38 (s, 1H, C-10H), 7.50-7.63-7.92 (m, 5H, OBz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) ∂ 10.9 (C-19), 13.7 (C-18), 19.3 (C-16), 20.8 (2 x Ac), 32.1 (C-6), 32.3 (C-5), 33.6 (C-17), 43.3 (C-14), 43.5 (C-15), 44.7 (C-8), 47.1 (C-3), 66.4 (C-20), 73.0 (C-2), 76.6 (C-10), 79.3 (C-1), 84.7 (C-4), 116.2 (CN), 129.1-129.7-134.4 (Bz), 140.8 (C-12), 153.0 (C-11), 166 (CO-Bz), 169.2 (CO-Ac), 169.3(CO-Ac), 170.0 (C-7), 197.0(C-13), 199.7(C-9); LRFABMS : *m/z* 632 [$M+Na^+$], 614 [$M-H_2O+Na^+$]; HRMS (CI) calcd for $C_{32}H_{36}NO_{11}$ (MH^+) 610.2288, found 610.2242.

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