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Semi-synthesis of Some 7-Deoxypaclitaxel Analogs from Taxine B


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Taxine B (3), isolated from the dried needles of Taxus baccata, was converted into six novel 7-deoxypaclitaxel analogs, 20, 21a,b, and 23-25, that have structural changes at C1, C2, and C4. A method for the introduction of the benzoyl function at C2, via a benzylidene acetal at C1-C2, will be revealed. All compounds were obtained very low or no measurable cytotoxic activity against some well-characterized human tumor cell lines, probably due to the nonacylated hydroxyl group at C4.

The diterpenoid paclitaxel (1) (Chart 1), first isolated by Wani and co-workers from the bark of the western yew Taxus brevifolia, is a new and very promising antitumor agent. The structural complexity of (1), and its unique mechanism of action, has stimulated extensive research toward the synthesis of paclitaxel as well as the synthesis of new analogs. Until recently, the synthesis of paclitaxel has been achieved both by semisynthesis, starting from 10-deacetylbaccatin III (2) (Chart 1), and by total synthesis.

The synthesis of analogs for structure-activity relationship (SAR) studies have mostly been accomplished by structurally modifying paclitaxel itself. In several cases, precursors, such as baccatin III, have been used. The introduction of the 7-hydroxyl group, in particular, was of paclitaxel or for the synthesis of its analogs. To our knowledge, only one investigation to date has been carried out using taxine B as a starting material. This synthesis, however, did not lead to analogs that possessed the necessary /3-amino acid side chain. A retrosynthetic analysis showed that the synthesis of paclitaxel itself from taxine B would require more than 20 steps. This introduction of the 7-hydroxy group, in particular, was expected to be difficult. We concentrated our efforts on the synthesis of 7-deoxypaclitaxel analogs, when in vitro assays showed that the 7-hydroxy group had practically no effect on activity.

From SAR studies it is known that the oxetane ring, the paclitaxel side chain, and the hydroxyl group at C4 are important structural features for antitumor activity. The synthesis of analogs for structure-activity relationship (SAR) studies have mostly been accomplished by structurally modifying paclitaxel itself. In several cases, precursors, such as baccatin III, have been used. The introduction of the 7-hydroxyl group, in particular, was of paclitaxel or for the synthesis of its analogs. To our knowledge, only one investigation to date has been carried out using taxine B as a starting material. This synthesis, however, did not lead to analogs that possessed the necessary /3-amino acid side chain. A retrosynthetic analysis showed that the synthesis of paclitaxel itself from taxine B would require more than 20 steps. This introduction of the 7-hydroxy group, in particular, was expected to be difficult. We concentrated our efforts on the synthesis of 7-deoxypaclitaxel analogs, when in vitro assays showed that the 7-hydroxy group had practically no effect on activity.

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<Diagram> Chart 1</Diagram>
C2' are important for cytotoxic activity and the functional groups at the upper side of paclitaxel, positions C7, C9, and C10, are of less importance for cytotoxic activity. The bottom side of paclitaxel, positions C1, C2, and C4, was a black box at the start of our research. In this paper, we present the synthesis of some 7-deoxypaclitaxel analogs (20, 21a,b, and 23–25) with structural changes at C1, C2, and C4. At positions C9 and C10, all the analogs have either free hydroxyl groups or hydroxyl groups protected by an isopropylidene functionality. The introduction of the C2-benzoate functionality was not possible by earlier described methods. Therefore, a method has been developed to introduce the benzoate group via oxidation of the benzylidene acetal.

Results

Crude taxine B can easily be isolated, without chromatographic steps, from the needles of the European yew, Taxus baccata L., in yields of 12 g per kg of dried leaves, by an extraction method based on procedures described by Lucas and Graf. The yield of 10-deacetylbebacatin III, the precursor used in the synthesis of paclitaxel, from these needles is at least five times less.

Crude taxine B, therefore, seemed to be an excellent precursor for the synthesis of some functional groups at the upper side of paclitaxel, positions C2' are important for cytotoxic activity and that the 7-deoxypaclitaxel analogs (20, 21a,b, and 23–25) with structural changes at C1, C2, and C4, was a black box at the start of our research. In this paper, we present the synthesis of some 7-deoxypaclitaxel analogs (20, 21a,b, and 23–25) with structural changes at C1, C2, and C4. At positions C9 and C10, all the analogs have either free hydroxyl groups or hydroxyl groups protected by an isopropylidene functionality. The introduction of the C2-benzoate functionality was not possible by earlier described methods. Therefore, a method has been developed to introduce the benzoate group via oxidation of the benzylidene acetal.

A closer investigation of isolated crude taxine B showed that it was a mixture of several compounds, 40% of which had a taxane skeleton (4a–f). No further purification was necessary, however, because the compounds with the taxane skeleton were easily separated from the other compounds by crystallization as am­monium salts after reaction with methyl iodide. The complete conversions of the crude taxine B mixture 4a–f into the protected 7-deoxypaclitaxel derivatives 15a–c are presented in Scheme 1. The preparation of the intermediates 14 was carried out analogously to an approach of Ettouati et al., although we have made some modifications to the synthetic route. After these ammonium salts were collected by filtration, trimethylammonium iodide was eliminated by K2CO3 to give a mixture of 5a–f. In the next step, the acetyl groups were removed with 1.2 equiv of sodium methoxide to give a mixture of 6a,b. Selective introduction of the acetonide bridge at 6a,b using acetone and CuSO4 yielded a mixture of 7a,b. At this stage the first purification by chromatography was carried out. Separation of 7a and 7b was unsuccessful, however. The yield of 7a,b was 55% starting from 6a–f. Treatment of the mixture of 7a,b with dihydro­pyran, acetone, or the dimethyl acetal of benzaldehyde, respectively, yielded 8a, 8b, and 8c, respectively, mixed with 7b. At this stage it was possible to separate compound 7b (14%), which itself is an interesting precursor for the synthesis of 1-deoxypac­litaxel analogs, from compounds 8a,b,c (82, 73, and 85%) by chromatography. In order to discriminate between the OH groups at C1, C2, C9, and C10, the tetra­hydro­pyranyl-protected compound 8a was prepared. We expected that the tetrahydro­pyranyl groups could be re­moved independently from the isopropylidene functionality as well as from each other. The benzylidene functionality (8c) was selected because it is possible to convert it into a benzoyl group by oxidation. Since all the hydroxyl groups were protected as acetics, it was possible to remove the cinnamoyl side chain with 20 N NaOH, yielding compounds 9a,b,c (95, 93, and 76%). Conversion of the allylic alcohol function into an oxetane ring was achieved by established methods. Dihydroxylation with osmium tetroxide gave 10a,b,c (75, 87, and 55%). Protection of the primary alcohol with tert-butyl­dimethylsilyl chloride and mesylation of the secondary alcohol gave 11a,b,c (85, 81, and 77%). From compound 11a we followed two routes to compound 14a. The first route (11a via 12a to 14a) had already been worked out by Ettouati et al., in the preparation of compound 14f from 11b. Removal of the tert-butyl­dimethylsilyl group with Bu3NF, followed by ring closure with Bu3N+ OAc, yielded 12a (75%). Reduction of the carbonyl at C13 with DIBALH gave the α-isomer 14a (37% from 11a; the β-isomer was isolated in 11% yield). In order to find a more selective reduction of the carbonyl group at C13 by a different route (11a via 13a to 14a) this carbonyl of 11a was first reduced by DIBALH. Use of models and calculations indicated that the mesyl functionality at C5 is able to shield the back side of the compound.
carbonyl at C13. The attack of a hydride, therefore, can only take place from the front side. Indeed, only the α-isomer, 13a, was formed; the β-isomer was not detected. Unfortunately, 13a was isolated in only 45% yield. From the remaining 55%, about 30% was lost as a result of column chromatography. The other 25% consisted of several products that were not further identified. The reduction was not studied further at this stage although it may be optimized by using other (leaving) groups instead of the mesyl functionality.

(24) mm"-calculations were carried out with the computer program and CS Chem3D Pro (version 3.2).
Bu₄N⁺“OAC yielded 14a (36% from 11a). The yield of 14a, therefore, was about the same for both routes, although purification by column chromatography after each step appeared to be much more difficult for route 2, probably due to the early reduction step that yielded too many side products. For this reason, compounds 14b (24%) and 14c (29%) were synthesized from 11b and 11c, respectively, by the first route. Coupling of compounds 14a,b,c with the oxazinone side chain, according to the protocol described by Holton, gave the protected analogs of 7-deoxypaclitaxel, 15a,b,c (89%, 66%, and 70%).

Protected analog 19 was synthesized as depicted in Scheme 2. Starting from compound 12a, the hydroxyl groups at C1 and C2 were first deprotected, after which the benzoate group was introduced at C2. It appeared, however, not to be possible to hydrolyze both THP groups. Only the THP group at C1 was hydrolyzed, yielding 16 (89%), as became clear after the free hydroxyl group was benzoylated with benzoyl chloride in pyridine, yielding 17 (96%). The 400 MHz 1H-NMR spectrum of compound 17 showed no downfield shift of the proton at C2 as would be expected if the benzoate group is attached to C2 (4.14 ppm in 16 and 4.15 ppm in 17). In order to achieve selective reduction of the C13 carbonyl and avoid reduction of the benzoyl group, we tried several reducing agents including BH₃–THF, NaBH₄, LiBH₄, and K-selectride. The best results were obtained after reduction with BH₃–THF, although in this case concomitant reduction of the C11–C12 double bond could not be avoided. The obtained yield of 18, therefore, was only 21%. Coupling of 18 with the paclitaxel side chain by the method described above yielded 19 (80%).

Deprotection of the 7-deoxypaclitaxel analogs 15a–c and 19 was performed by acid hydrolysis. Treatment of 15a with a 2/2/1 mixture of H₂O/HOAc/THF provided 20 (76%), as shown in Scheme 3. Using a 2/4/1 mixture at 40 °C, the isopropylidene functionality at C9,C10 of 15a and 15b, respectively, was also hydrolyzed, yielding 21a (63%) and 21b (66%). Unfortunately, it was not possible to remove the THP group at C2 of compound 21a or to remove the isopropylidene functionality at C1,C2 of compound 21b without destruction of other parts of the molecule. Recently, analogous problems with the hydrolysis of the isopropylidene functionality of a related taxane compound have been reported by Nicolaou et al. Compound 23 was isolated in 68% yield after deprotection of compound 15c with a 2/4/1 mixture of H₂O/HOAc/THF at 40 °C, as shown in Scheme 4. Deprotection of compound 15c with a 2/2/1 mixture of H₂O/HOAc/THF at room temperature gave 22 in 73% yield.

Due to the surprising acid stability of an acetal protecting functionality at C2, it is not possible to introduce the necessary benzoate group at C2 via benzoylation of an OH group at the C2 position. Taking this into account, we rationalized that the benzoate group may be selectively introduced at C2 via oxidation of a benzylidene acetal at C1,C2. For the oxidation of the benzylidene functionality to a benzoyl group we tried several methods. Best results were obtained when the benzylidene functionality at C1,C2 of 22 was oxidized by r-BuOOH in the presence of a catalytic amount of Pd(OAc)₂ to yield compound 24 (28%), with a 55% recovery of compound 22.
Acid hydrolysis of compound 19 to give 25 (Scheme 5) appeared to be rather difficult. In a 4/2/1 mixture of AcOH/H$_2$O/THF at 50 °C, the isopropylidene functionality was not hydrolyzed. It was necessary to use a 12/2/1 mixture of AcOH/H$_2$O/THF at 50 °C. Under these conditions the paclitaxel side chain was split off for 32%. Nevertheless, we were able to isolate 25 in 61% yield.

**Structure Determination of Compound 23**

The structure of 23 is presumed to be as drawn in Scheme 4. The configurations at C4, C5, C13, and C4' (for numbering see 23, Scheme 4) were confirmed by NOE difference experiments. The following NOE contacts were found: H(2)-H(9); H(2)-CH$_3$(17); H(2)-CH$_2$(19); H(2)-H(4'); H(9)-CH$_3$(19); H(13)-H(14/β; H(13)-CH$_2$(16); H(14/β)-CH$_3$(16), and CH$_3$(19)-H(20/β). The configuration at C13 must be the S-configuration, as no NOE contact is possible between H(13) and CH$_3$(16) in the case of the R-configuration. The configuration at C4' must also be the S-configuration because of the NOE contact between CH$_3$(19) and H(20/β). In the R-configuration these protons are in the trans-position; such a NOE contact, therefore, is not possible. The S-configuration was assigned at C4 and the R-configuration at C5 because of the NOE contact between CH$_3$(19) and H(20/β).

**Biological Evaluation**

All the compounds 20, 21a,b, and 23–25 showed no or very slight in vitro cytotoxicity against seven well-characterized human tumor cell lines. This lack of activity was first attributed to the missing benzoate group at C2, an assumption in agreement with SAR studies in which it was shown that the benzoate functionality at C2 is necessary for activity.

In compounds 21a and 23 we hoped that the THP group and the benzylidene acetal functionality could be a substitute for the benzoate group at C2, due to the two acetal oxygens, which are in about the same position as the two oxygens of the benzoate group. Compound 25 could demonstrate that a benzyol group at this position does not have the same important influence on the activity as this functionality has on C2. Also, no cytotoxicity was found for compound 24, which has a benzoate group at C2.

Recent SAR studies on paclitaxel analogs with substituent variations at C4 have shown that the substituent at C4 is very important for cytotoxic activity. We suppose, therefore, that the lack of activity seen in the compounds presented here is probably due to the missing acetate group at C4.

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(28) (a) The determination of the cytotoxicity was carried out by H. J. Kolker, J. Verweij, G. Stoter, and J. H. M. Schellens, from the laboratory of Experimental Chemotherapy and Pharmacology, Department of Medical Oncology, Rotterdam Cancer Institute (Dr. Daniel den Hoed Kliniek). (b) For details of the in vitro assay, see: Keiper, Y. P.; Pizao, P. J.; Peters, O. J.; Van Ark-Otte, J.; Winograd, B.; Pinedo, H. M. Eur. J. Cancer 1991, 27, 897–900. (c) The seven human tumor cell lines used for the cytotoxicity tests were as follows: MCF7, breast cancer; EVSA-T, breast cancer; WIDR, colon cancer; IGROV, ovarian cancer; M19 MEL, melanoma; A498, renal cancer; H226, nonsmall cell lung cancer.

Our future synthetic program is directed toward 7-deoxypaclitaxel analogs that possess a benzoate group at C2 as well as an acetate group at C4. Furthermore, the conversion of 7b into 1,7-deoxypaclitaxel analogs is now in progress.10

Experimental Section

Chemical shift values are reported as δ-values relative to TMS as internal standard; deuteriochloroform was used as solvent. Mass spectra were obtained with a double-focusing spectrometer. Melting points are uncorrected.

Compounds 8b–14b were prepared as reported by Ettouati et al.11 The 1H-NMR spectra of 8b–14b were in agreement with those reported in the literature.11

Extraction Procedure for Crude Taxine B. Dried leaves (17 kg) of *Taxus baccata* were macerated in an aqueous solution of H$_2$SO$_4$ (100 L, 0.5% v/v) for 3 days. The sulfuric acid solution was separated from the leaves and (in portions of 20 L) with diethyl ether (3 L) in a continuous extraction apparatus for 1 d, in order to remove the major part of the undesirable neutral organic compounds. The sulfuric acid solution was brought to pH 9 by addition of aqueous ammonia. This solution was extracted twice with diethyl ether in an atmosphere. After addition of 5a–f (9.50 g, 17.7 mmol), the mixture was stirred at reflux temperature for 16 h. After cooling the mixture, methanol (550 mL) was cooled to 0 °C under an argon atmosphere. After addition of p-toluenesulfonic acid (150 mg), the reaction mixture was stirred at reflux temperature for 2 d. The reaction mixture was subsequently diluted with water (50 mL) and extracted twice with CH$_2$Cl$_2$ (150 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 2:5) giving 7b$_2$ (0.68 g, 1.3 mmol, 14%) and 8a (5.4 g, 7.7 mmol, 82%): mp 66 °C; *H-NMR (400 MHz, CDCl$_3$): δ 7.73 (m, 2H), 7.41 (m, 3H), 7.61 (d, J = 15.9 Hz, 1H), 6.33 (d, J = 15.9 Hz, 1H), 5.58 (bs, 1H), 5.33 (s, 1H), 5.27 (bs, 1H), 4.91 (m, 1H), 4.90 (d, J = 9.2 Hz, 1H), 4.83 (m, 1H), 4.38 (d, J = 9.2 Hz, 1H), 3.75 (m, 1H), 3.49 (m, 1H), 3.39 (m, 1H), 3.09 (d, J = 5.6 Hz, 1H), 2.67 (s, 2H), 2.12 (s, 3H), 1.59 (s, 3H), 1.50 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.30 (1H, s), FAB-MS 705 [M + H$^+$]. Anal. Calcd for C$_{33}$H$_{46}$O$_{8}$: C, 71.57; H, 8.01. Found: C, 71.91; H, 7.95.

1,2-O-Benzylidene-9,10-(O-propene-2,2-diyi)-5c-cinnamoyltaxicin-I (8c). The same procedure was followed for as 8a. Instead of dihydroxypropan, the dimethyl acetal of benzaldehyde (2.8 mL, 18.6 mmol) was added. Compound 8c was isolated in 85% yield (4.98 g, 7.98 mmol, 85%): mp 108–110 °C; FAB-MS 670 [M + Na$^+$]. Anal. Calcd for C$_{36}$H$_{48}$O$_{8}$: C, 74.98; H, 7.10. Found: C, 74.63; H, 7.23.

Hydrolysis of 8a to 9a. To a solution of 8a (5.4 g, 7.7 mmol) in dry THF (60 mL) was added 20 N NaOH (aq) (25 mL). The reaction mixture was stirred at reflux temperature for 2 d. The reaction mixture was subsequently diluted with water (50 mL) and extracted twice with CH$_2$Cl$_2$ (150 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 1:1), yielding 9a (4.20 g, 7.32 mmol, 96%): mp 66–69 °C; *H-NMR (400 MHz, CDCl$_3$): δ 5.47 (bs, 1H), 5.00 (bs, 1H), 4.91 (d, J = 9.2 Hz, 1H), 4.89 (m, 1H), 3.75 (m, 1H), 3.47 (m, 1H), 3.40 (m, 1H), 3.23 (d, J = 5.4 Hz, 1H), 2.60 (bs, 2H), 2.06 (s, 3H), 1.56 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.32 (s, 3H), 1.05 (s, 3H); CIMS, 574 [M$^+$]. Anal. Calcd for C$_{33}$H$_{46}$O$_{7}$: C, 69.85; H, 8.79. Found: C, 69.17; H, 8.63.

Hydrolysis of 8c to 9c. The same procedure was followed as for 8a, using 8c (4.98 g, 7.98 mmol). Compound 9c was isolated in 76% yield (3.00 g, 6.07 mmol): mp 180 °C; FAB-MS 496 [M + H$^+$]. Anal. Calcd for C$_{32}$H$_{46}$O$_{6}$: C, 72.85; H, 6.74. Found: C, 72.51; H, 6.00.

Dihydroxypropan to 10a. To a solution of 9a (4.20 g, 7.32 mmol) in THF/H$_2$O (50/40 mL) were added N-methylmorpholine-N-oxide monohydrate (900 mg, 6.70 mmol) and a solution of OsO$_4$ (2.5% in t-BuOH, 6.4 mL). The reaction mixture rapidly turned red. After 20 h, Florisil (2.0 g), water (26 mL), and Na$_2$SO$_4$ (256 mg) were added. The mixture was stirred for an additional 10 min and then filtered. The filtrate was diluted with a saturated solution of NH$_4$Cl in water (100 mL) and extracted twice with EtOAc (150 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 1:1) giving 10a (1510 mg, 56%): mp 72 °C; *H-NMR (400 MHz, CDCl$_3$): δ 4.97 (m, 1H), 4.81 (d, J = 9.3 Hz, 1H), 4.55 (m, 1H), 4.15 (d, J = 9.3 Hz, 1H), 4.09 (d, J = 4.9 Hz, 1H), 4.04 (bs, 1H), 3.87 (m, 1H), 3.82 (bs, 1H), 3.77 (m, 1H), 3.59 (bs, 1H), 3.50 (m, 1H), 3.42 (m, 1H), 3.23 (d, J = 19.3 Hz, 1H), 2.65 (d, J = 4.9 Hz, 1H), 2.62 (d, J = 19.3 Hz, 1H), 2.03 (s, 3H), 1.56 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.08 (s, 3H); FAB-MS 524 [M + THP + H$^+$]. Anal. Calcd for C$_{37}$H$_{54}$O$_{8}$: C, 65.11; H, 8.61. Found: C, 64.72; H, 8.28.

Dihydroxypropan of 9e to 10e. The same procedure was followed as for 10a, using 9e (3.00 g, 6.07 mmol). Compound 10e was isolated in 55% yield (1.77 g, 3.35 mmol): mp 133 °C; FAB-MS 551 [M + Na$^+$]. Anal. Calcd for C$_{34}$H$_{48}$O$_{6}$: C, 65.90; H, 7.75. Found: C, 66.26; H, 7.57.

Silylation and Mesylation of 10a to 11a. A solution of imidazole (5.10 g, 74.8 mmol) and TBDMSI (4.46 g, 30.9 mmol) in DMF (30 mL) was stirred for 15 min. Compound 10a (3.33 g, 5.48 mmol) was subsequently added. After 3 h the reaction mixture was diluted with a solution of 10% citric acid in water (200 mL) and extracted twice with EtOAc (100 mL). The combined organic layers were washed with brine,
dried over NaSO\textsubscript{4} and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 2/5), yielding the silylated compound (3.78 g, 5.23 mmol, 95%); mp 52 °C; FAB-MS 746 [M + Na]\textsuperscript{+}. Anal. Calcd for C\textsubscript{48}H\textsubscript{56}O\textsubscript{10}SiS: C, 61.64; H, 7.83; S, 4.45. Found: C, 61.35; H, 7.98; S, 4.46.

### Construction of the Oxetane Ring: 11c to 12c (Route 1)

To a solution of 11a (3.70 g, 4.63 mmol) in THF (75 mL) was added tetrabutylammonium fluoride (1.8 g, 6.9 mmol). The reaction mixture was stirred for 1 h at rt, after which time EtOAc (150 mL) was added. The organic layer was washed with saturated NaHCO\textsubscript{3} solution, dried over NaSO\textsubscript{4}, and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 7/3), yielding 12a (2.04 g, 3.46 mmol, 77%); mp 126 °C; FAB-MS 655 [M + Na]\textsuperscript{+}. Anal. Calcd for C\textsubscript{48}H\textsubscript{56}O\textsubscript{10}SiS: C, 61.64; H, 7.58; S, 4.46. Found: C, 61.35; H, 7.64; S, 4.63.

To a solution of the desilylated compound (3.10 g, 4.52 mmol) in butane (75 mL) was added tetrabutylammonium acetate (12.0, 39.9 mmol). The reaction mixture was stirred at reflux temperature for 17 h. The mixture was diluted with EtOAc (100 mL) and washed with a saturated solution of NH\textsubscript{4}Cl in water. The organic layer was dried over NaSO\textsubscript{4} and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 3/7), yielding 13a (2.04 g, 3.46 mmol, 77%); mp 65 °C; FAB-MS 665 [M + Na]\textsuperscript{+}; 679 [M + Na]\textsuperscript{+}. Anal. Calcd for C\textsubscript{48}H\textsubscript{56}O\textsubscript{10}SiS: C, 61.64; H, 7.83; S, 4.46. Found: C, 61.35; H, 7.98; S, 4.46.  

### 2-Debenzoyl-1,2-(dithydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-O-(propane-2,2-diyl)-9(\textit{R})-dihydrobaccatin III (14a) (Route 1)

The same procedure was followed as for 13a (route 2), using 12a (2.04 g, 3.46 mmol). Compound 14a was isolated in 94% yield (1.54 g, 2.65 mmol). To a solution of 14a (3.70 g, 4.63 mmol) in THF (75 mL) was added tetrabutylammonium fluoride (1.8 g, 6.9 mmol). The reaction mixture was stirred for 1 h at rt, after which time EtOAc (150 mL) was added. The organic layer was washed with saturated NaHCO\textsubscript{3} solution, dried over NaSO\textsubscript{4}, and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 1/1), yielding the desilylated compound (3.10 g, 4.52 mmol, 98%); mp 89 °C; FAB-MS 687 [M + Na]\textsuperscript{+}. Anal. Calcd for C\textsubscript{48}H\textsubscript{56}O\textsubscript{10}SiS: C, 61.64; H, 7.83; S, 4.46. Found: C, 61.35; H, 7.98; S, 4.46.  

To a solution of the desilylated compound (3.10 g, 4.52 mmol) in butane (75 mL) was added tetrabutylammonium acetate (12.0, 39.9 mmol). The reaction mixture was stirred at reflux temperature for 17 h. The mixture was diluted with EtOAc (100 mL) and washed with a saturated solution of NH\textsubscript{4}Cl in water. The organic layer was dried over NaSO\textsubscript{4} and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 2/5), yielding 12a (2.04 g, 3.46 mmol, 77%); mp 126 °C; FAB-MS 655 [M + Na]\textsuperscript{+}. Anal. Calcd for C\textsubscript{48}H\textsubscript{56}O\textsubscript{10}SiS: C, 61.64; H, 7.58; S, 4.46. Found: C, 61.35; H, 7.64; S, 4.63.

**Conclusion:** This compound was not obtained completely pure and was used as such in the next step.  

### 2-Debenzoyl-1,2-(dithydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-O-(propane-2,2-diyl)-2'(ethoxyethyl)-(9'R)-dihydrobaccatin III (14a) (Route 1)

The same procedure was followed as for 13a (route 2), using 12c (0.85 g, 1.7 mmol). Compound 14c was isolated in 46% yield (0.40 g, 0.78 mmol) mp 105–108 °C; FAB-MS 535 [M + Na]\textsuperscript{+}. Anal. Calcd for C\textsubscript{48}H\textsubscript{56}O\textsubscript{10}SiS: C, 64.89; H, 8.91. Found: C, 65.26; H, 8.63.  

**Conclusion:** This compound was not obtained completely pure and was used as such in the next step.  

### 2-Debenzoyl-1,2-(dithydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-O-(propane-2,2-diyl)-2'(ethoxyethyl)-(9'R)-dihydrobaccatin III (14a) (Route 1)

The same procedure was followed as for 13a (route 2), using 13a (0.47, 0.59 mmol). The desilylated compound was not further purified. Compound 14a was isolated in 79% yield (0.28 g, 0.47 mmol); mp 49 °C; FAB-MS 745 [M + Na]\textsuperscript{+}. Anal. Calcd for C\textsubscript{48}H\textsubscript{56}O\textsubscript{10}SiS: C, 61.64; H, 7.83; S, 4.46. Found: C, 61.35; H, 7.98; S, 4.46.  

**Conclusion:** This compound was not obtained completely pure and was used as such in the next step.  

### 2-Debenzoyl-1,2-(dithydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-O-(propane-2,2-diyl)-2'(ethoxyethyl)-(9'R)-dihydrobaccatin III (14a) (Route 1)

The same procedure was followed as for 13a (route 2), using 12c (0.85 g, 1.7 mmol). Compound 14c was isolated in 46% yield (0.40 g, 0.78 mmol) mp 105–108 °C; FAB-MS 535 [M + Na]\textsuperscript{+}. Anal. Calcd for C\textsubscript{48}H\textsubscript{56}O\textsubscript{10}SiS: C, 64.89; H, 8.91. Found: C, 65.26; H, 8.63.  

**Conclusion:** This compound was not obtained completely pure and was used as such in the next step.  

### 2-Debenzoyl-1,2-(dithydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-O-(propane-2,2-diyl)-2'(ethoxyethyl)-(9'R)-dihydrobaccatin III (14a) (Route 1)

The same procedure was followed as for 13a (route 2), using 13a (0.47, 0.59 mmol). The desilylated compound was not further purified. Compound 14a was isolated in 79% yield (0.28 g, 0.47 mmol); mp 49 °C; FAB-MS 745 [M + Na]\textsuperscript{+}. Anal. Calcd for C\textsubscript{48}H\textsubscript{56}O\textsubscript{10}SiS: C, 61.64; H, 7.83; S, 4.46. Found: C, 61.35; H, 7.98; S, 4.46.  

**Conclusion:** This compound was not obtained completely pure and was used as such in the next step.
NO₃·H₂O; C, 67.20; H, 7.74; N, 1.70. Found: C, 67.53; H, 7.70; N, 1.98.

2-Debenzoyl-1,2-0-benzylidene-4-deacetyl-7-deoxy-10-deacetyl-9,10-O-(propane-2,2-diyl)-2'-ethoxyethyl-9(R)-dihydrolaptaclatex (15c).

The same procedure was followed as for 15a, using 14c (0.40 g, 0.78 mmol). Compound 15c was isolated in 70% yield (0.47 g, 0.55 mmol): mp 73 °C; FAB-MS 617 [M + Na]⁺. Anal. Calcd for C₆₅H₆₈NO₁₃: C, 68.83; H, 6.92; N, 1.90. Found: C, 68.94; H, 6.92; N, 1.90.

Hydrolysis of 12a to 16.

Compound 12a (1.00 g, 1.69 mmol) was dissolved in a mixture of H₂O/H₂O/THF (89/10/17 mL). After being stirred for 24 h at rt, the mixture was diluted with EtOAc (10 mL). The organic layer was washed with saturated NaHCO₃ solution (75 mL) and with brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 1/1), yielding 16 (770 mg, 1.52 mmol, 89%): mp 66 °C; H-NMR (400 MHz, CDCl₃) δ 4.94 (t, J = 5.4 Hz, 1H), 3.26 (s, J = 8.2 Hz, 1H), 3.05 (d, J = 19.2 Hz, 1H), 2.90 (s, 3H), 1.33 (s, 3H); FAB-MS 629 [M + Na]⁺. Anal. Calcd for C₆₅H₆₈NO₁₃: C, 66.63; H, 7.31; N, 1.61. Found: C, 66.84; H, 6.92; N, 1.90.

Benzylation of 16 to 17.

To a solution of 16 (0.77 g, 1.5 mmol) in EtOAc (10 mL) were added triethylamine (0.62 mL, 4.4 mmol) and benzyl chloride (0.32 mL, 2.8 mmol). After the mixture was stirred for 24 h at rt, EtOAc (50 mL) was added. The mixture was washed with a 10% citric acid solution in water (50 mL) and with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 2/3), yielding 17 (891 mg, 1.46 mmol, 96%): mp 184 °C; H-NMR (400 MHz, CDCl₃) δ 5.04 (dd, J = 5.2, 1.8 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.04 (m, 1H), 4.27 (m, 1H), 4.07 (m, 1H), 3.92 (m, 1H), 3.67 (m, 1H), 3.39 (m, 1H), 1.94 (m, 2H), 1.85 (m, 1H); FAB-MS 774 [M + H⁺], 796 [M + Na⁺]. Anal. Calcd for C₆₅H₆₈NO₁₃·H₂O: C, 66.32; H, 7.35; N, 1.66. Found: C, 65.89; H, 7.34; N, 1.80.
Calcd for C_{46}H_{63}N_{10}O_{12}H_{2}O: C, 67.14; H, 6.80; N, 1.85. Found: C, 67.81; H, 6.57; N, 2.15.

4-Deacetyl-7-deoxy-10-deacetyl-9,10-O-(propane-2,2-diyl)-9(R)-dihydropaclitaxel (24). To a solution of 22 (0.10 g, 0.13 mmol) in toluene (5 mL) were added a solution of t-BuOOH in decane (26 μL, 5.0–6.0 M) and Pd(OAc)\_2 (2.4 mg, 0.011 mmol). The reaction mixture was stirred at 50 °C for 24 h. The reaction mixture was diluted with EtOAc (20 mL) and filtered over Hyflo. The filtrate was washed with water and brine. The organic layer was dried over NaSO\_4 and concentrated in vacuo. The residue was purified by chromatography (EtOAc/hexane 1/1), yielding 24 (29 mg, 0.036 mmol, 28%): mp 125–128 °C; \textsuperscript{1}H-NMR (400 MHz, CDCl\_3) \( \delta \) 8.23 (d, \( J = 7.5 \) Hz, 2H), 7.78 (d, \( J = 7.3 \) Hz, 2H), 7.60 (d, \( J = 7.4 \) Hz, 2H), 7.42 (m, 9H), 7.07 (d, \( J = 9.6 \) Hz, 1H), 6.16 (d, \( J = 9.5 \) Hz, 1H), 6.01 (m, 1H), 5.87 (d, \( J = 5.2 \) Hz, 1H), 4.89 (dd, \( J = 6.7, 1.8 \) Hz, 1H), 4.70 (d, \( J = 9.5 \) Hz, 1H), 4.67 (bs, 1H), 4.40 (d, \( J = 9.6 \) Hz, 1H), 4.34 (d, \( J = 7.9 \) Hz, 1H), 4.19 (d, \( J = 7.9 \) Hz, 1H), 3.41 (bs, 1H), 2.91 (dd, \( J = 15.7, 3.6 \) Hz, 1H), 2.55 (d, \( J = 5.2 \) Hz, 1H), 2.30 (dd, \( J = 15.7, 6.4 \) Hz, 1H), 2.05 (m, 4H), 1.90 (s, 1H), 1.85 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H), 1.46 (s, 3H), 1.49 (s, 3H), 1.19 (s, 3H); FAB-MS 796 [M + H]+, 818 [M + Na]+. Anal. Calcd for C\textsubscript{46}H\textsubscript{63}N\textsubscript{10}O\textsubscript{12}: C, 67.08; H, 6.85; N, 1.78. Found: C, 67.88; H, 6.85; N, 1.67. 

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Supporting Information Available: 400 MHz \textsuperscript{1}H-NMR spectral data for compounds 8b,c, 9b,c, 10b,c, 11b,c, 12b,c, 14b,c, 15b,c, 21b, and 23. All analytical data of 2-TMS-[7b] (4 pages). This material is contained in libraries on microfiche; it immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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