Semisynthesis of Some 7-Deoxypaclitaxel Analogs from Taxine B

Peter H. G. Wiegerinck, Lizette Fluks, Jeannet B. Hammink, Suzanne J. E. Mulders, Franciscus M. H. de Groot, Hendrik L. M. van Rozendaal, and Hans W. Scheeren*

Department of Organic Chemistry, University of Nijmegen, NSR-Center, Toernooiveld, 6525 ED Nijmegen, The Netherlands

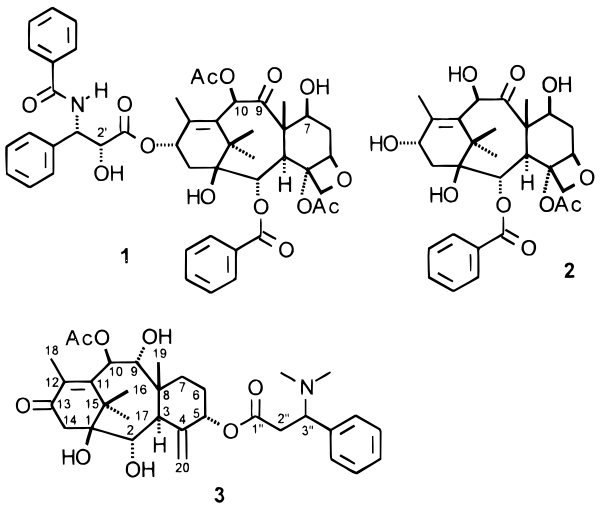
Received March 4, 1996[⊗]

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 showed very little 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 Wall[1] from the bark of the western yew *Taxus brevifolia*, is a new and very promising antitumor compound.[2] The structural complexity of (**1**), and its unique mechanism of action,[3] have 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,[4] starting from 10-deacetylbaccatin III (**2**) (Chart 1), and by total synthesis.[5]

The synthesis of analogs for structure−activity relationship (SAR) studies have mostly been accomplished by structurally modifying paclitaxel itself.[6] In several cases, precursors, such as baccatin III,[7] brevifoliol,[8] 13-acetyl-9-dihydrobacatin III,[9] and 14-β-hydroxy-10-desacetylbaccatin,[10] isolated from the needles of different *Taxus* species, were used.

Chart 1



Taxine B (**3**), the most abundant precursor present in the needles of *Taxus baccata* L. (Chart 1), has had little attention paid to it as a precursor for either the synthesis of paclitaxel or for the synthesis of its analogs. To our knowledge, only one investigation[11] 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 β-amino acid side chain. A retrosynthetic analysis showed that the synthesis of paclitaxel itself from taxine B would require more than 20 steps. The introduction of the 7-hydroxyl group, in particular, was expected to be difficult. We concentrated our efforts on the synthesis of 7-deoxypaclitaxel analogs, when in *in vitro* assays it was shown that the 7-hydroxyl group had practically no effect on activity.[12]

From SAR studies it is known that the oxetane ring,[13] the paclitaxel side chain,[14] and the hydroxyl group[15] at

* To whom correspondence should be addressed. Phone: 31-24-3652331. Fax: 31-243652929. E-mail: JSCH@SCI.KUN.NL.

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1996.

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S0022-3263(96)00438-0 CCC: $12.00

C2′ are important for cytotoxic activity and that the functional groups at the upper side of paclitaxel, positions C7,[12] C9,[9,16] and C10,[9,12b,16] 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.[17] The yield of 10-deacetylbaccatin III, the precursor used in the synthesis of paclitaxel, from these needles is at least five times less.[18] Crude taxine B, therefore, seemed to be an excellent precursor for the synthesis of 7-deoxypaclitaxel analogs.

A closer investigation of isolated crude taxine B showed[19] 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.[11] for **14b**, although we have made some modifications to the synthetic route. After these ammonium salts were collected by filtration, trimethylammonium iodide was eliminated by K_2CO_3 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 $CuSO_4$ 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 **5a**−**f**. Treatment of the mixture of **7a,b** with dihydropyran, acetone, or the dimethyl acetal of benzaldehyde, respectively, yielded **8a**, **8b**,[20] 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,[21] 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.[22]

Since all the hydroxyl groups were protected as acetals, it was possible to remove the cinnamoyl side chain[11] 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.[11,23] Dihydroxylation with osmium tetraoxide 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.[11] in the preparation of compound **14b** from **11b**. Removal of the *tert*-butyldimethylsilyl group with $Bu_4N^+\ ^-F$, followed by ring closure with $Bu_4N^+\ ^-OAc$, 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[24] indicated that the mesyl functionality at C5 is able to shield the back side of the

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(18) (a) Crude taxine B, which is isolated in 12 g per kg of dried leaves, contains about 40% (5 g) of the compounds **4a**−**f**. Denis et al. claim to isolate 10-deacetylbaccatin III, the precursor applied in the synthesis of paclitaxel, in yields of ca. 1 g per kg of fresh leaves.[4] Mostly, much lower yields, however, are reported in the literature.[18b] Furthermore, the isolation of the taxines is much less labor intensive and also less expensive. No organic solvents are required in the initial extraction procedure and no chromatographic steps are needed for the purification. (b) ElSohly, H. N.; Croom, E. M.; Kopycki, W. J.; Joshi, A. S.; ElSohli, M. A.; McChesney, J. D. *Phytochem. An.* **1995**, *6*, 149−156.

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(21) (a) Compound **7b** was difficult to purify. Therefore, the C2-OH of **7b** was protected with trimethylsilyl chloride. This silylated compound was then fully characterized; see also the supporting information. (b) In a similar way as described for **8a**−**c** in this paper, compound **7b** can be converted into 1,7-dideoxypaclitaxel analogs (to be published).

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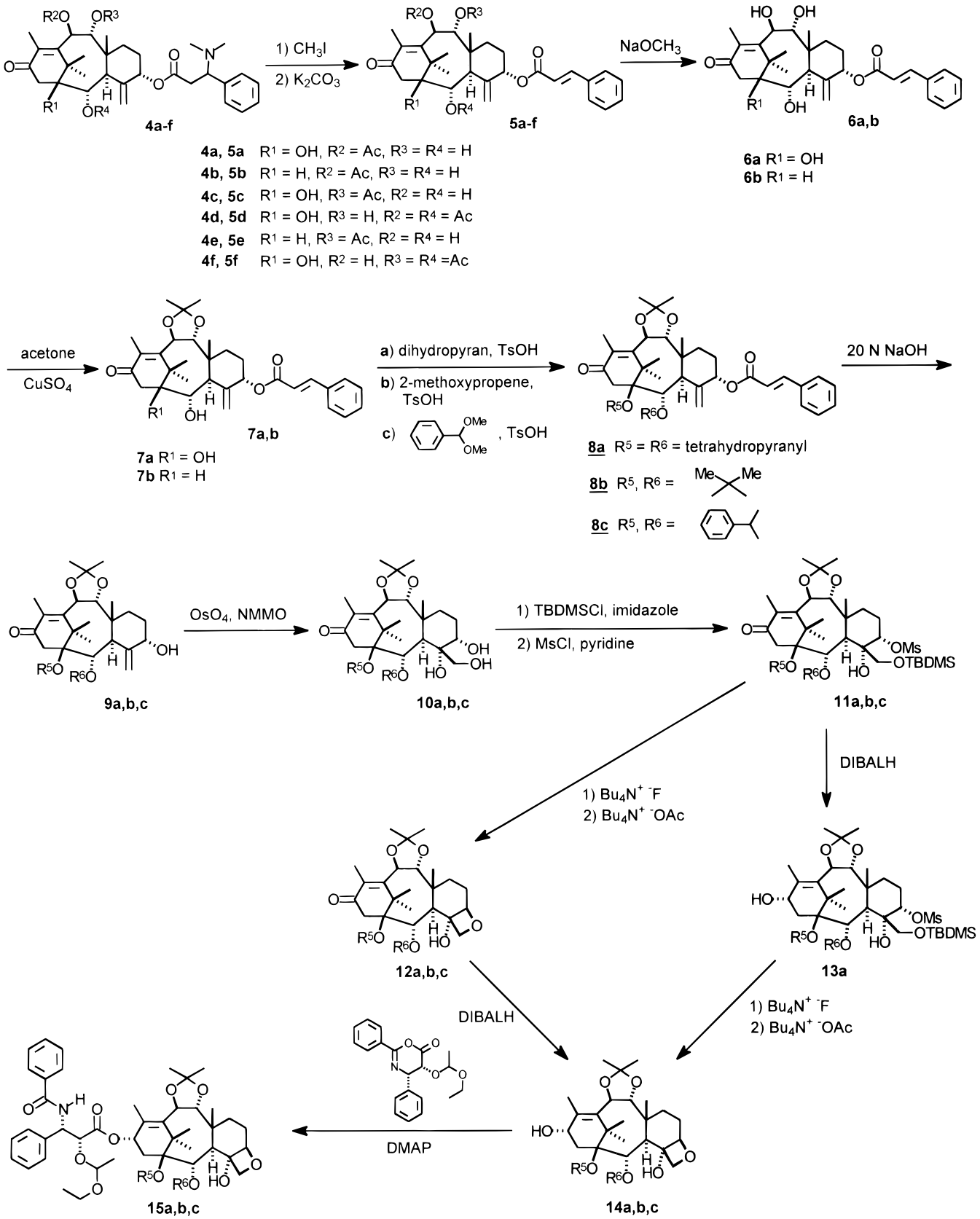
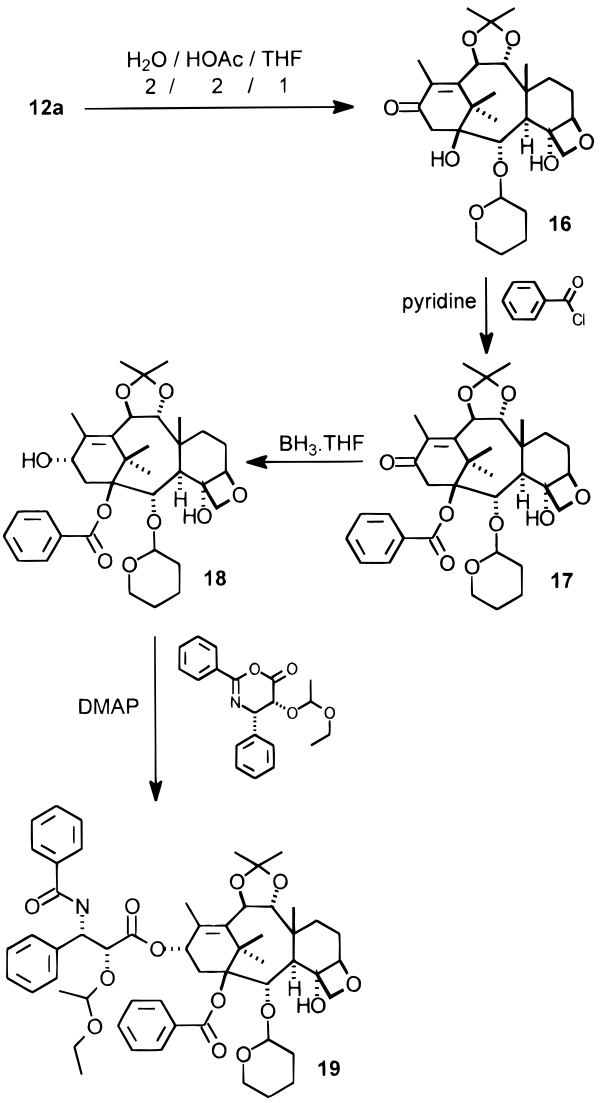
Scheme 1



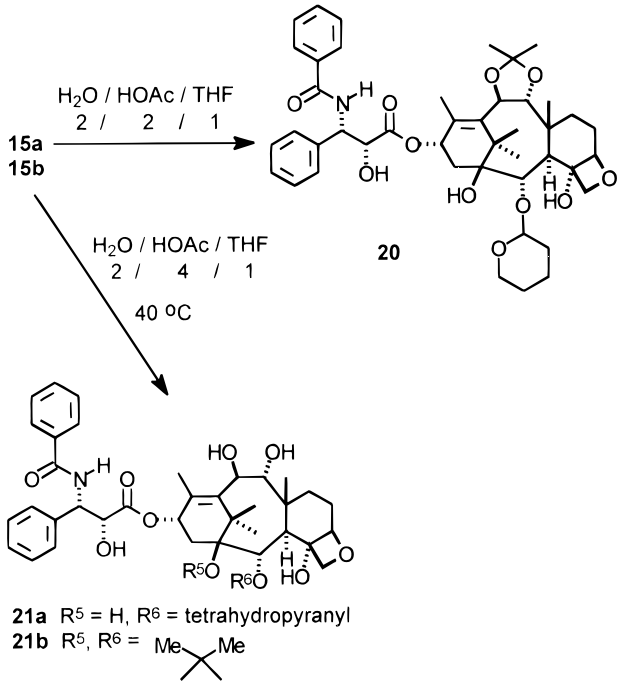
carbonyl at C13. The attack of a hydride, therefore, can only take place from the front side. Indeed, only the α-isomer, **13a**, was formed; the *β*-isomer was not detected. Unfortunately, **13a** was isolated in only 45% yield. From the remaining 55%, about 30% was lost as a result of column chromatography. 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. Desilylation with $Bu_4N^+ {}^-F$ followed by treatment with

(24) mm$^+$-calculations were carried out with the computer program and CS Chem3D Pro (version 3.2).

Scheme 2



Scheme 3



$Bu_4N^+ {}^-OAC$ 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,[25] 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 ^{1}H-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 BH_3−THF, $NaBH_4$, $LiBH_4$, and K-selectride. The best results were obtained after reduction with BH_3−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 H_2O/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.[26]

Compound **23** was isolated in 68% yield after deprotection of compound **15c** with a 2/4/1 mixture of H_2O/HOAc/THF at 40 °C, as shown in Scheme 4. Deprotection of compound **15c** with a 2/2/1 mixture of H_2O/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.[22] Best results were obtained when the benzylidene functionality at C1,C2 of **22** was oxidized by *t*-BuOOH in the presence of a catalytic amount of $Pd(OAc)_2$ to yield compound **24** (28%), with a 55% recovery of compound **22**.

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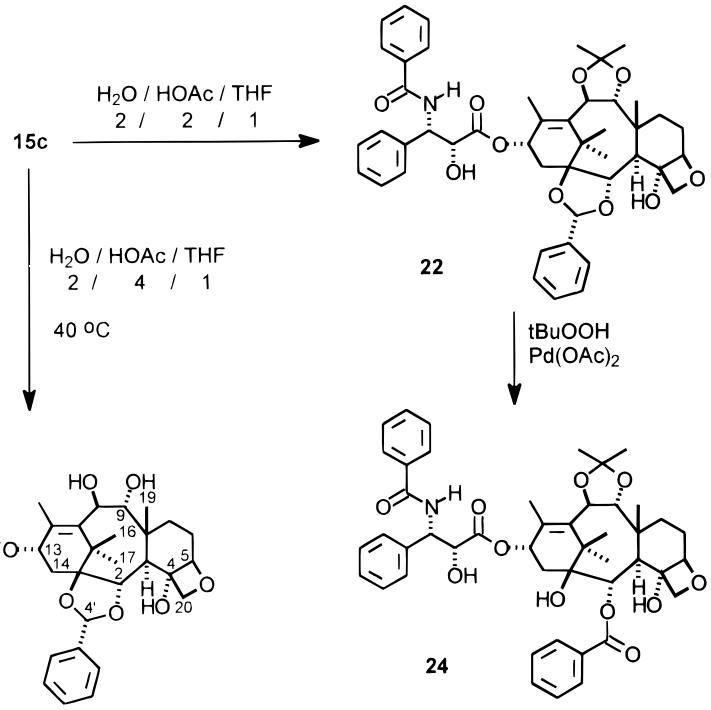
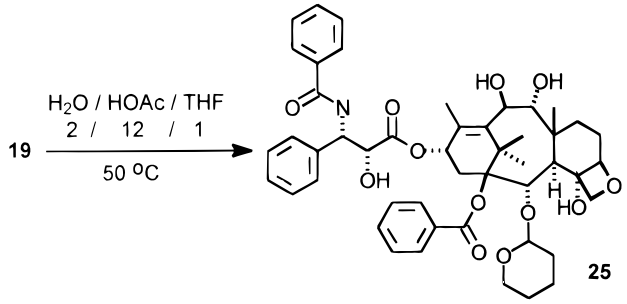
Scheme 4



Scheme 5



Acid hydrolysis of compound **19** to give **25** (Scheme 5) appeared to be rather difficult. In a 4/2/1 mixture of AcOH/H_2O/THF at 50 °C, the isopropylidene functionality was not hydrolyzed. It was necessary to use a 12/2/1 mixture of AcOH/H_2O/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_3(19); H(2)−H(4′); H(9)−CH_3(19); H(13)−H(14β); H(13)−CH_3-(16); H(14β)−CH_3(16), and CH_3(19)−H(20β). 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.[27] The configuration at C4′ must also be the *S*-configuration because of the NOE contact between H(4′) and H(2). 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(20β).

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.[28] This lack of activity was first attributed to the missing benzoate group at C2, an assumption in agreement with SAR studies[6c,7a,b,29] 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 benzoyl 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.[9b,13c,30] 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: Kepers, Y. P.; Pizao, P. E.; Peters, G. 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 cytotoxity 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.

(29) (a) Chaudhary, A. G.; Gharpure, M. M.; Rimoldi, J. M.; Chordia, M. D.; Gunatilaka, A. A. L.; Kingston, D. G. I.; Grover, S.; Lin, C. M.; Hamel, E. *J. Am. Chem. Soc.* **1994**, *116*, 4097−4098. (b) Nicolaou, K. C.; Renaud, J.; Nantermet, P. G.; Couladouros, E. A.; Guy, E. A.; Wrasidlo, W. *J. Am. Chem. Soc.* **1995**, *117*, 2409−2420.

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 compound **7b** into 1,7-dideoxypaclitaxel analogs is now in progress.[21b]

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 ^{1}H-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 *T. baccata* were soaked in an aqueous solution of H_2SO_4 (100 L, 0.5% v/v) for 3 days. The sulfuric acid solution was separated from the leaves and extracted (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 (3 L) in a continuous extraction apparatus for 1 d. The combined ether layers were dried over Na_2SO_4 and concentrated *in vacuo*, yielding crude taxine (150−200 g from 17 kg, depending on the quality of the leaves) as a light yellow amorphous powder.

Preparation of the Mixture of 5a−f. To a solution of crude taxine B (containing 40% of **4a**−**f**) (25.0 g, 42.9 mmol) in ether (150 mL) was added methyl iodide (12.5 mL). After 1 d the pale yellow amorphous iodide salt of **4a**−**f** was collected, washed with ether, and dried (13.4 g, 18.3 mmol). A solution of this salt (13.4 g) in ethanol (50 mL) was added to a solution of K_2CO_3 (15.0 g) in water (750 mL). The reaction mixture was stirred for 2 h. The precipitated mixture of **5a**−**f** was collected, washed with water, and dried (9.50 g, 17.7 mmol).

Preparation of the Mixture of 5α-Cinnamoyltaxicin-I (6a) and 5α-Cinnamoyltaxicin-II (6b). A solution of sodium methoxide prepared from 0.49 g of sodium (0.021 mol), in methanol (550 mL) was cooled to 0 °C under an argon atmosphere. After addition of **5a**−**f** (9.50 g, 17.7 mmol), the mixture was stirred for 16 h at 0 °C. The reaction mixture was subsequently acidified with glacial acetic acid and concentrated, and water (500 mL) was added. This solution was extracted twice with ether (200 mL). The combined ether layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo*, yielding a mixture of **6a,b** (7.45 g, 15.0 mmol, 85%).

Preparation of the Mixture of 9,10-*O*-(Propane-2,2-diyl)-5α-cinnamoyltaxicin-I (7a) and 9,10-*O*-(Propane-2,2-diyl)-5α-cinnamoyltaxicin-II (7b). To a suspension of anhydrous $CuSO_4$ (35 g, 0.22 mol) in dry acetone (750 mL) was added the mixture of 6a,b (7.45 g, 15.0 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After 2 d at rt the solution was filtered. The filtrate was concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 2/5) to give a mixture of 7a and 7b (5.23 g, 9.80 mmol, 65%).

1,2-Di(tetrahydropyran-2-yl)-9,10-*O*-(propane-2,2-diyl)-5α-cinnamoyltaxicin-I (8a). To a solution of **7a,b** (5.0 g, 9.4 mmol) and *p*-toluenesulfonic acid (10 mg, 0.05 mmol) in CH_2Cl_2 (75 mL) was slowly added dihydropyran (2.3 g, 27 mmol) in CH_2Cl_2 (10 mL) at rt. After 1 d the reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 2/5), yielding **7b**[21] (0.68 g, 1.3 mmol, 14%) and **8a** (5.4 g, 7.7 mmol, 82%): mp 66 °C; ^{1}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), 4.56 (m, 1H), 4.26 (d, J = 9.2 Hz, 1H), 4.14 (d, J = 5.6 Hz, 1H), 3.85 (m, 1H), 3.73 (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), 1.10 (s, 3H); FAB-MS 705 $[M + H]^+$. Anal. Calcd for $C_{42}H_{56}O_9$: C, 71.57; H, 8.01. Found: C, 71.91; H, 7.95.

1,2-*O*-Benzylidene-9,10-*O*-(propane-2,2-diyl)-5α-cinnamoyltaxicin-I (8c). The same procedure was followed as for **8a**. Instead of dihydropyran, 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 625 $[M + H]^+$, 647 $[M + Na]^+$. Anal. Calcd for $C_{39}H_{44}O_7$: 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_2Cl_2 (150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 1/1), yielding **9a** (4.20 g, 7.32 mmol, 95%): mp 66−69 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.47 (bs, 1H), 5.09 (bs, 1H), 4.91 (d, J = 9.2 Hz, 1H), 4.89 (m, 1H), 4.58, (m, 1H), 4.22 (d, J = 9.2 Hz, 1H), 4.17 (bs, 1H), 4.10 (d, J = 5.4 Hz, 1H), 3.87 (m, 1H), 3.74 (m, 1H), 3.50 (m, 1H), 3.40 (m, 1H), 3.23 (d, J = 5.4 Hz, 1H), 2.60 (bs, 2H), 2.06 (s, 3H), 1.58 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.32 (s, 3H), 1.05 (s, 3H); CIMS, 574 $[M]^+$. Anal. Calcd for $C_{33}H_{50}O_8$: C, 68.95; H, 8.79. Found: C, 69.17; H, 8.63.

Hydrolysis of 8c to 9c. The same procedure was followed as for **9a**, 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 495 $[M + H]^+$. Anal. Calcd for $C_{30}H_{38}O_6$: C, 72.85; H, 7.74. Found: C, 72.51; H, 8.00.

Dihydroxylation of 9a to 10a. To a solution of **9a** (4.20 g, 7.32 mmol) in THF/H_2O (80/40 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 $Na_2O_4S_2$ (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_4Cl in water (100 mL) and extracted twice with EtOAc (150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc), yielding **10a** (3.33 g, 5.48 mmol, 75%): mp 72 °C; ^{1}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 $C_{33}H_{52}O_{10}$: C, 65.11; H, 8.61. Found: C, 64.72; H, 8.28.

Dihydroxylation of 9c to 10c. The same procedure was followed as for **10a**, using **9c** (3.00 g, 6.07 mmol). Compound **10c** was isolated in 55% yield (1.77 g, 3.35 mmol): mp 133 °C; FAB-MS 551 $[M + Na]^+$. Anal. Calcd for $C_{30}H_{40}O_8 \cdot H_2O$: 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 TBDMSCl (4.64 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,

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dried over Na_2SO_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 $[M + Na]^+$. Anal. Calcd for $C_{39}H_{66}O_{10}Si \cdot H_2O$: C, 63.20; H, 9.27. Found: C, 63.56; H, 8.95.

To a solution of the silylated compound (3.78 g, 5.23 mmol) in pyridine (50 mL) at 0 °C was added MsCl (2.5 mL). The reaction mixture was stirred for 20 h at rt, after which time CH_2Cl_2 (150 mL) was added. The mixture was washed with a solution of 10% citric acid in water (75 mL) and with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 2/5), yielding **11a** (3.70 g, 4.63 mmol, 89%): mp 57 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.94 (m, 1H), 4.86 (bs, 1H), 4.80 (d, J = 9.3 Hz, 1H), 4.57 (m, 1H), 4.18 (d, J = 9.3 Hz, 1H), 4.12 (d, J = 10.4 Hz, 1H), 4.02 (d, J = 4.1 Hz, 1H), 3.86 (m, 1H), 3.74 (m, 1H), 3.66 (d, J = 10.4 Hz, 1H), 3.51 (m, 1H), 3.47 (d, J = 19.4 Hz, 1H), 3.38 (m, 1H), 2.94 (s, 3H), 2.56 (d, J = 19.4 Hz, 1H), 2.51 (d, J = 4.1 Hz, 1H), 2.07 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.08 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); FAB-MS 823 $[M + Na]^+$. Anal. Calcd for $C_{40}H_{68}O_{12}SiS$: C, 59.97; H, 8.56; S, 4.00. Found: C, 60.14; H, 8.47; S, 2.69.[31]

Silylation and Mesylation of 10c to 11c. The same procedure was followed as for **11a**, using **10c** (1.77 g, 3.35 mmol). The silylated compound was isolated in 93% (2.03 g, 3.16 mmol) yield: mp 61 °C; FAB-MS, 665 $[M + Na]^+$. Anal. Calcd for $C_{36}H_{54}O_8Si$: C, 67.26; H, 8.47. Found: C, 67.07; H, 8.83.

Compound **11c** was isolated in 83% yield (1.91 g, 2.65 mmol): mp 199 °C; FAB-MS 743 $[M + Na]^+$. Anal. Calcd for $C_{37}H_{56}O_{10}SiS$: C, 61.64; H, 7.83; S, 4.45. Found: C, 61.35; H, 8.09; S, 4.47.

Construction of the Oxetane Ring: 11a to 12a (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 $NaHCO_3$ solution, dried over Na_2SO_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 $[M + H]^+$, 709 $[M + Na]^+$. Anal. Calcd for $C_{34}H_{54}O_{12}S$: C, 59.46; H, 7.92; S, 4.67. Found: C, 59.35; H, 7.88; S, 3.31.[31]

To a solution of the desilylated compound (3.10 g, 4.52 mmol) in butanone (75 mL) was added tetrabutylammonium acetate (12.0 g, 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_4Cl in water. The organic layer was dried over Na_2SO_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 65 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.94 (m, 1H), 4.86 (bs, 1H), 4.80 (d, J = 9.3 Hz, 1H), 4.57 (m, 1H), 4.18 (d, J = 9.3 Hz, 1H), 4.12 (d, J = 10.4 Hz, 1H), 4.02 (d, J = 4.1 Hz, 1H), 3.86 (m, 1H), 3.74 (m, 1H), 3.66 (d, J = 10.4 Hz, 1H), 3.51 (m, 1H), 3.47 (d, J = 19.4 Hz, 1H), 3.38 (m, 1H), 2.94 (s, 3H), 2.56 (d, J = 19.4 Hz, 1H), 2.51 (d, J = 4.1 Hz, 1H), 2.07 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.08 (s, 3H); FAB-MS 591 $[M + H]^+$, 613 $[M + Na]^+$. Anal. Calcd for $C_{33}H_{50}O_9$: C, 67.09; H, 8.53. Found: C, 67.04; H, 8.47.

Construction of the Oxetane Ring: 11c to 12c (Route 1). The same procedure was followed as for **12a**, using **11c** (1.91 g, 2.65 mmol). The desilylated compound was isolated in 98% yield (1.60 g, 2.64 mmol): mp 116−120 °C; FAB-MS 629 $[M + Na]^+$. Anal. Calcd for $C_{31}H_{42}O_{10}S$: C, 61.37; H, 6.98; S, 5.28. Found: C, 61.06; H, 7.08; S, 4.63.[31]

Compound **12c** was isolated in 64% yield (0.85 g, 1.7 mmol): mp 109 °C; FAB-MS 533 $[M + Na]^+$. Anal. Calcd for $C_{30}H_{38}O_7 \cdot H_2O$: C, 68.15; H, 7.64. Found: C, 67.80; H, 7.59.

Reduction of 11a to 13a (route 2). To a solution of **11a** (1.00 g, 1.25 mmol) in CH_2Cl_2 (10 mL) at −10 °C was added a solution of DIBALH in CH_2Cl_2 (2.0 mL, 1 M, 2.0 mmol) was added. The reaction mixture was stirred at 0 °C for 3 h, after which time a solution of 10% citric acid in water (20 mL) was carefully added. The water layer was extracted twice with CH_2Cl_2 (50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution and with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 2/5), yielding **13a** (0.47 g, 0.59 mmol, 45%): mp 49 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.88 (m, 2H), 4.74 (d, J = 9.4 Hz, 1H), 4.58 (m, 1H), 4.43 (m, 1H), 4.26 (d, J = 10.5 Hz, 1H), 4.02 (d, J = 9.4 Hz, 1H), 3.86 (m, 2H), 3.74 (m, 1H), 3.63 (d, J = 10.5 Hz, 1H), 3.51 (m, 1H), 3.47 (s, 1H), 3.39 (m, 1H), 3.06 (s, 3H), 2.69 (d, J = 4.0 Hz, 1H), 2.41 (bd, J = 6.3 Hz, 2H), 2.06 (s, 3H), 1.59 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.06 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); FAB-MS: 825 $[M + Na]^+$. Anal. Calcd for $C_{40}H_{70}O_{12}SiS$: C, 59.82; H, 8.53; S, 3.99. Found: C, 59.74; H, 8.78; S, 3.56.

2-Debenzoyl-1,2-(ditetrahydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-9(*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 49% yield (1.02 g, 1.72 mmol): mp 50 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.91 (m, 1H), 4.79 (dd, J = 8.0, 3.6 Hz, 1H), 4.65 (d, J = 8.9 Hz, 1H), 4.62 (d, J = 8.0 Hz, 1H), 4.54 (m, 1H), 4.49 (d, J = 8.0 Hz, 1H), 4.41 (m, 1H), 4.10 (d, J = 8.9 Hz, 1H), 3.98 (d, J = 4.4 Hz, 1H), 3.91 (m, 1H), 3.79 (m, 1H), 3.73 (s, 1H), 3.50 (m, 1H), 3.41 (m, 1H), 2.43 (dd, J = 16.0, 9.8 Hz, 1H), 2.16 (m, 2H), 2.00 (m, 2H), 1.93 (s, 3H), 1.63 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H), 1.13 (s, 3H); FAB-MS 615 $[M + Na]^+$. Anal. Calcd for $C_{33}H_{52}O_9 \cdot H_2O$: C, 64.89; H, 8.91. Found: C, 65.25; H, 8.83.

2-Debenzoyl-1,2-(ditetrahydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-9(*R*)-dihydrobaccatin III (14a) (Route 2). The same procedure was followed as for **12a** (route 1), using **13a** (0.47 g, 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; ^{1}H-NMR (400 MHz, $CDCl_3$) was the same as for **14a** in route 1.

2-Debenzoyl-1,2-*O*-benzylidene-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-9(*R*)-dihydrobaccatin III (14c) (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 $[M + Na]^+$. Anal. Calcd for $C_{30}H_{40}O_7$: C, 70.29; H, 7.86. Found: C, 70.27; H, 8.00.

2-Debenzoyl-1,2-(ditetrahydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-2′-(ethoxyethyl)-9(*R*)-dihydropaclitaxel (15a). To a solution of **14a** (1.02 g, 1.72 mmol) in toluene (50 mL) were added DMAP (210 mg, 1.72 mmol), pyridine (1 mL) and modified paclitaxel sidechain[25] (2.75 g, 7.99 mmol). The reaction mixture was stirred for 12 h at rt, after which time the reaction mixture was diluted with EtOAc (200 mL). This mixture was washed with a solution of 10% $CuSO_4$ in water (50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 2/5), yielding **15a** (1.41 g, 1.51 mmol, 89%): mp 63 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.48 (m, 5H), 7.33 (m, 3H), 7.08 (d, J = 10.3 Hz, 1H), 6.12 (d, J = 10.3 Hz, 1H), 5.88 (m, 1H), 4.95 (m, 1H), 4.79 (m, 1H), 4.61 (m, 3H), 4.47 (m, 3H), 4.18 (m, 2H), 3.94 (bs, 1H), 3.78 (m, 1H), 3.63 (m, 1H), 3.47 (m, 1H), 3.28 (m, 2H), 3.08−2.95 (dq, J = 7.03 Hz, 1H), 2.24 (m, 3H), 2.06 (m, 3H), 1.86 (s, 3H), 1.63 (s, 3H), 1.52 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H), 1.26 (d, J = 4.2 Hz, 3H), 1.19 (s, 3H), 0.92−0.85 (dt, J = 7.03 Hz, 3H); FAB-MS, 955 $[M + Na]^+$. Anal. Calcd for $C_{53}H_{73}NO_{13} \cdot 0.5H_2O$: C, 67.62; H, 7.94; N, 1.49. Found: C, 67.47; H, 7.58; N, 1.90.

2-Debenzoyl-1,2-acetonide-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-2′-(ethoxyethyl)-9(*R*)-dihydropaclitaxel (15b). The same procedure was followed as for **15a**, using **14b** (0.49 g, 1.1 mmol). Compound **15b** was isolated in 66% yield (0.58 g, 0.72 mmol): mp 65 °C; FAB-MS 804 $[M + H]^+$, 826 $[M + Na]^+$. Anal. Calcd for $C_{46}H_{61}$-

(31) This compound was not obtained completely pure and was used as such in the next step.

NO_{11}·H_2O: C, 67.20; H, 7.74; N, 1.70. Found: C, 67.53; H, 7.70; N, 1.98.

2-Debenzoyl-1,2-*O*-benzylidene-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-2′-(ethoxyethyl)-9(*R*)-dihydropaclitaxel (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 874 $[M + Na]^+$. Anal. Calcd for $C_{50}H_{61}N\ O_{11}$·H_2O: C, 69.01; H, 7.31; N, 1.61. 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 HOAc/H_2O/THF (68/34/17 mL). After being stirred for 24 h at rt, the mixture was diluted with EtOAc (100 mL). The organic layer was washed with saturated $NaHCO_3$ solution (75 mL) and with brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 1/1), yielding **16** (770 mg, 1.52 mmol, 89%); mp 67 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.94 (t, J = 5.1 Hz, 1H), 4.96 (dd, J = 8.5, 2.2 Hz, 1H), 4.67 (d, J = 9.4 Hz, 1H), 4.61 (d, J = 8.1 Hz, 1H), 4.37 (d, J = 8.1 Hz, 1H), 4.26 (d, J = 9.4 Hz, 1H), 4.14 (d, J = 5.4 Hz, 1H), 3.67 (m, 2), 3.07 (s, 1H), 3.05 (d, J = 19.2 Hz, 1H), 2.59 (d, J = 19.2 Hz, 1H), 2.02 (m, 3H), 1.93 (s, 3H), 1.81 (d, J = 5.3 Hz, 1H), 1.62 (s, 3H), 1.58 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H); FAB-MS 529 $[M + Na]^+$. Anal. Calcd for $C_{28}H_{42}O_8$: C, 66.38; H, 8.36. Found: C, 66.79; H, 8.46.

Benzoylation 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), DMAP (1.16 g, 9.51 mmol), and benzoyl 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 Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 2/5), yielding **17** (891 mg, 1.46 mmol, 96%): mp 184 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 7.4, 1.2 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 4.97 (t, J = 5.1 Hz, 1H), 4.78 (dd, J = 8.4, 2.1 Hz, 1H), 4.67 (d, J = 9.4 Hz, 1H), 4.58 (d, J = 8.1 Hz, 1H), 4.34 (m, 3H), 4.25 (d, J = 9.4 Hz, 1H), 4.14 (d, J = 5.4 Hz, 1H), 3.05 (d, J = 19.2 Hz, 1H), 2.90 (s, 1H), 2.60 (d, J = 19.2 Hz, 1H), 2.02 (m, 3H), 1.93 (s, 3H), 1.82 (d, J = 5.5 Hz, 1H), 1.58 (s, 3H), 1.55 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H); FAB-MS 611 $[M + H]^+$, 633 $[M + Na]^+$. Anal. Calcd for $C_{35}H_{46}O_9$: C, 68.83; H, 7.59. Found: C, 69.01; H, 7.26.

1-Benzoyl-2-debenzoyl-2-(tetrahydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-9(*R*)-dihydrobaccatin III (18). To a solution of **17** (0.89 g, 1.5 mmol) in dry THF (20 mL) was added BH_3·THF (20 mL, 1 M in THF, 20 mmol). After 3 h at rt, EtOAc (50 mL) was added. The mixture was washed with a 10% citric acid solution in water (50 mL) and with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 1/1), yielding **18** (192 mg, 0.314 mmol, 21%): mp 127 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 4.91 (t, J = 5.1 Hz, 1H), 4.80 (dd, J = 10.0, 5.1 Hz, 1H), 4.62 (d, J = 9.4 Hz, 1H), 4.61 (d, J = 8.1 Hz, 1H), 4.36 (m, 4H), 4.09 (d, J = 9.4 Hz, 1H), 3.98 (d, J = 5.4 Hz, 1H), 3.26 (s, 1H), 2.44 (d, J = 16.0 Hz, 1H), 2.14 (m, 2H), 2.03 (m, 3H), 1.93 (s, 3H), 1.49 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.13 (s, 3H); FAB-MS 635 $[M + Na]^+$. Anal. Calcd for $C_{35}H_{48}O_9$·H_2O: C, 66.63; H, 8.01. Found: C, 66.31; H, 7.96.

1-Benzoyl-2-debenzoyl-2-(tetrahydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-2′-(ethoxyethyl)-9(*R*)-dihydropaclitaxel (19). The same procedure was followed as for **15a**, using **18** (0.19 g, 0.31 mmol). Compound **19** was isolated in 80% yield (240 mg, 0.252 mmol): mp 141 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.7 Hz, 2H), 7.83 (d, J = 7.2 Hz, 2H), 7.75 (m, 2H), 7.40 (m, 9H), 7.07 (d, J = 9.6 Hz, 1H), 6.13 (d, J = 9.7 Hz, 1H), 5.85 (m, 1H), 4.94 (bd, J = 5.5 Hz, 1H), 4.81 (m, 1H5), 4.65 (d, J = 9.5 Hz, 1H), 4.59 (d, J = 7.9 Hz, 1H), 4.48 (m, 2H), 4.19 (m, 4H), 3.96 (d, J = 5.3 Hz, 1H), 3.25−2.98 (m, 2H), 2.25 (m, 2H), 2.05 (m, 4H), 1.88 (s, 3H), 1.52 (s, 3H), 1.47 (s, 3H), 1.44 (s, 3H), 1.37 (dd, J = 5.5 Hz, 3H), 1.26 (s, 3H), 1.19 (s, 3H), 0.92 (dt, J = 7.0 Hz, 3H); FAB-MS, 974 $[M + Na]^+$. Anal. Calcd for $C_{55}H_{69}NO_{13}$·H_2O: C, 68.08; H, 7.39; N, 1.44. Found: C, 67.83; H, 7.13; N, 1.44.

2-Debenzoyl-2-(tetrahydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-9(*R*)-dihydropaclitaxel (20). Compound **15a** (0.25 g, 0.27 mmol) was dissolved in HOAc/THF/H_2O (8/4/8 mL). After 20 h at rt the reaction mixture was diluted with EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ solution (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 1/1), yielding **20** (159 mg, 0.205 mmol, 76%): mp 115 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.4 Hz, 2H), 7.58 (d, J = 7.5 Hz, 2H), 7.40 (m, 6H), 7.03 (d, J = 9.5 Hz, 1H), 5.98 (bd, J = 10.0 Hz, 1H), 5.95 (m, 1H), 4.92 (bd, J = 7.4 Hz, 1H); 4.86 (t, J = 4.7 Hz, 1H), 4.60 (m, 3H), 4.49 (d, J = 8.0 Hz, 1H), 4.25 (s, 1H), 4.15 (d, J = 9.5 Hz, 1H), 3.98 (d, J = 5.3 Hz, 1H), 3.59 (bs, 1H), 3.53 (t, J = 5.5 Hz, 2H), 2.39 (dd, J = 15.9, 3.7 Hz, 1H), 2.23 (m, 2H), 2.07 (d, J = 5.3 Hz, 1H), 2.00 (m, 3H), 1.73 (s, 3H), 1.55 (s, 3H), 1.53 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H), 1.46 (s, 3H); FAB-MS 776 $[M + H]^+$, 798 $[M + Na]^+$. Anal. Calcd for $C_{44}H_{57}NO_{11}$·H_2O: C, 66.55; H, 7.49; N, 1.76. Found: C, 66.51; H, 7.40; N, 1.73.

2-Debenzoyl-2-(tetrahydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9(*R*)-dihydropaclitaxel (21a). Compound **15a** (0.20 g, 0.21 mmol) was dissolved in HOAc/THF/H_2O (12/3/6 mL). The reaction mixture was stirred for 24 h at 40 °C. The reaction mixture was diluted with EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ solution (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 7/3), yielding **21a** (97 mg, 0.13 mmol, 63%): mp 198 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.3 Hz, 2H), 7.56 (d, J = 7.6 Hz, 2H), 7.40 (m, 6H), 7.09 (d, J = 9.5 Hz, 1H), 5.97 (bd, J = 9.4 Hz, 1H), 5.89 (m, 1H), 4.91 (dd, J = 8.8, 2.1 Hz, 1H), 4.86 (t, J = 5.3 Hz, 1H), 4.62 (m, 3H), 4.48 (d, J = 8.0 Hz, 1H), 4.15 (bs, 1H), 3.97 (d, J = 9.5 Hz, 1H), 3.93 (d, J = 5.4 Hz, 1H), 3.70 (bs, 1H), 3.54 (t, J = 5.5 Hz, 2), 2.75 (bs, 1H), 2.50 (bs, 1H), 2.36 (dd, J = 15.8, 3.5 Hz, 1H), 2.27 (d, J = 5.3 Hz, 1H), 2.22 (dd, J = 15.7, 6.3 Hz, 1H), 2.00 (m, 5H), 1.67 (s, 3H), 1.55 (s, 3H), 1.48 (s, 3H), 1.16 (s, 3H); FAB-MS 736 $[M + H]^+$, 758 $[M + Na]^+$. Anal. Calcd for $C_{41}H_{53}NO_{11}$·H_2O: C, 65.32; H, 7.35; N, 1.86. Found: C, 65.02; H, 7.40; N, 1.80.

2-Debenzoyl-1,2-acetonide-4-deacetyl-7-deoxy-9-dihydro-10-deacetylpaclitaxel (21b). The same procedure was followed as for **21a**, using **15b** (0.20 g, 0.25 mmol). Compound **21b** was isolated in 66% yield (114 mg, 0.165 mmol): mp 150 °C; FAB-MS 692 $[M + H]^+$, 714 $[M + Na]^+$. Anal. Calcd for $C_{39}H_{49}NO_{10}$·$1.5H_2O$: C, 65.15; H, 7.31; N, 1.95. Found: C, 65.29; H, 7.22; N, 1.92.

2-Debenzoyl-1,2-*O*-benzylidene-4-deacetyl-7-deoxy-10-deacetyl-9,10-*O*-(propane-2,2-diyl)-9(*R*)-dihydropaclitaxel (22). Compound **15c** (0.20 g, 0.24 mmol) was dissolved in HOAc/THF/H_2O (8/4/8 mL). After 2 h at rt the reaction mixture was diluted with EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ solution (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 1/1), yielding **22** (136 mg, 0.175 mmol, 73%): mp 99 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.71−7.15 (m, 15H), 7.10 (d, J = 7.9 Hz, 1H), 5.95 (bd, J = 9.2 Hz, 1H), 5.90 (m, 1H), 5.74 (s, 1H), 4.90 (dd, J = 6.7 Hz, J = 1.8 Hz, 1H), 4.67 (d, J = 8.1 Hz, 1H), 4.62 (bs, 1H), 4.59 (d, J = 9.5 Hz, 1H), 4.44 (d, J = 8.2 Hz, 1H), 4.25 (d, J = 5.2 Hz, 1H), 4.21 (d, J = 9.5 Hz, 1H), 3.91 (s, 1H), 3.75 (bs, 1H), 2.45 (m, 2H), 2.24 (m, 2H), 2.20 (d, J =5.2 Hz, 1H), 1.67 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H), 1.49 (s, 3H), 1.43 (s, 3H), 1.23 (s, 3H); FAB-MS 802 $[M + Na]^+$. Anal. Calcd for $C_{46}H_{53}N\ O_{10}$·$0.5H_2O$: C, 70.03; H, 6.89; N, 1.78. Found: C, 69.93; H, 6.54; N, 2.13.

2-Debenzoyl-1,2-*O*-benzylidene)-4-deacetyl-7-deoxy-10-deacetyl-9(*R*)-dihydropaclitaxel (23). The same procedure was followed as for **21a**, using **15c** (0.10 g, 0.12 mmol). Compound **23** was isolated in 68% yield (60 mg, 0.081 mmol): mp 144 °C; FAB-MS 740 $[M + H]^+$, 762 $[M + Na]^+$. Anal.

Calcd for $C_{43}H_{49}N\ O_{10}\cdot H_2O$: C, 68.14; 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, 5.0−6.0M) 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 Na_2SO_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; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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), 1.43 (s, 3H16), 1.19 (s, 3H); FAB-MS 796 $[M + H]^+$, 818 $[M + Na]^+$. Anal. Calcd for $C_{46}H_{53}NO_{11}\cdot 1.5H_2O$: C, 67.08; H, 6.85; N, 1.78. Found: C, 66.77; H, 6.67; N, 2.00.

1-Benzoyl-2-debenzoyl-2-(tetrahydropyran-2-yl)-4-deacetyl-7-deoxy-10-deacetyl-9(*R*)-dihydropaclitaxel (25). Compound **19** (0.10 g, 0.12 mmol) was dissolved in HOAc/THF/H_2O (36/3/6 mL). After 24 h at 50 °C, the reaction mixture was diluted with EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ solution (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (EtOAc/hexane 1/1), yielding **25** (61 mg, 0.073 mmol, 61%): mp 122 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 7.8, 1.4 Hz, 2H), 7.73 (dd, J = 7.8, 1.6 Hz, 2H), 7.55 (m, 3H), 7.37 (m, 8H), 7.05 (d, J = 9.5 Hz, 1H), 6.02 (bd, J = 9.5 Hz, 1H), 5.88 (m, 1H), 4.91 (dd, J = 8.9, 2.3 Hz, 1H), 4.86 (t, J = 5.6 Hz, 1H), 4.62 (m, 3H), 4.44 (d, J = 7.9 Hz, 1H), 4.24 (m, 2H), 4.09 (s, 1H), 3.98 (d, J = 9.4 Hz, 1H), 3.93 (d, J = 5.5 Hz, 1H), 3.70 (bs, 1H), 2.66 (bs, 1H), 2.35−1.99 (m, 8H), 1.68 (s, 3H), 1.58 (s, 3H), 1.48 (s, 3H), 1.16 (s, 3H); FAB-MS, 840 $[M + H]^+$, 862 $[M + Na]^+$. Anal. Calcd for $C_{48}H_{57}NO_{12}$: C, 68.62; H, 6.85; N, 1.67. Found: C, 68.38; H, 7.05; N, 1.41.

Acknowledgment. We would like to thank Pharmachemie BV and the Dutch Cancer Foundation, Nederlandse Kankerbestrijding Koningin Wilhelmina Fonds, for their financial support.

Supporting Information Available: 400 MHz ^{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.

JO960438A