Pergamon

Tetrahedron 55 (1999) 6567–6576

TETRAHEDRON

Synthesis of Paclitaxel (Docetaxel) / 2-Deacetoxytaxinine J Dimers[1]

Giovanni Appendino,[a]* Emanuela Belloro,[a] Sven Jakupovic[a], Bruno Danieli,[b]* Jasmin Jakupovic[c] and Ezio Bombardelli[d]

[a]: Dipartimento di Scienza e Tecnologia del Farmaco Via Giuria 9, 10125 Torino, Italy

[b]: Dipartimento di Chimica Organica e Industriale, Via Venezian 21, 20133 Milano, Italy

[c]: Institut für Organische Chemie, Technische Universität, Straße des 17. Juni 135, 10623 Berlin, Germany

[d]: Indena S.p.A., Viale Ortles 12, 20141 Milano, Italy

Received 4 January 1999; revised 8 March 1999; accepted 25 March 1999

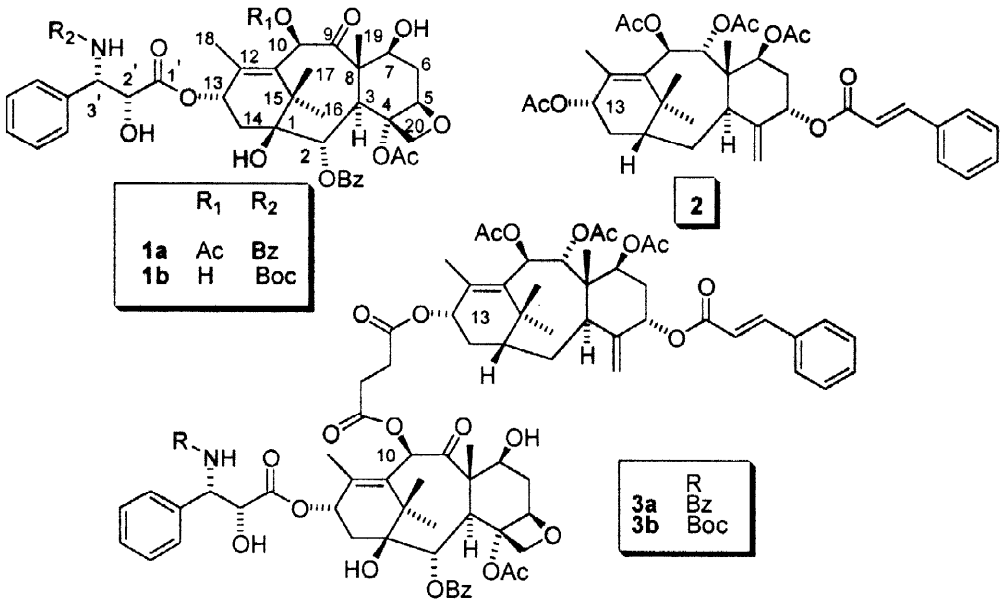
Abstract: Starting from taxanes available in multigram amounts from widespread ornamental yews (10-deacetylbaccatin III (**4**) and 2'-deacetoxyaustrospicatine (**5**)), two dimeric taxoids (**3a**, **3b**) with potential dual target specificity (β-tubulin and P-gp) were synthesised. Both compounds lacked significant cytotoxicity, though **3b** retained a strong activity in the tubulin depolimerisation assay.

Keywords: Taxoids; Dimers; Antitumour compounds

The occurrence of drug-resistance is a major obstacle in the treatment of cancer with chemotherapy, and the emergence of cancerous cells resistant to both the original antineoplastic agent and to structurally and mechanistically unrelated agents has been named multidrug resistance (MDR).[2] MDR has been related to the increased expression of two proteins belonging to the ABC superfamily of transport proteins (P-gp[3] and MRP[4]), which extrude hydrophobic anticancer compounds and maintain their intracellular concentration below a cytotoxic level. Though several "chemosensitisers" are known, no specific agent effective in reversing this resistance is currently available for clinical use.[5]

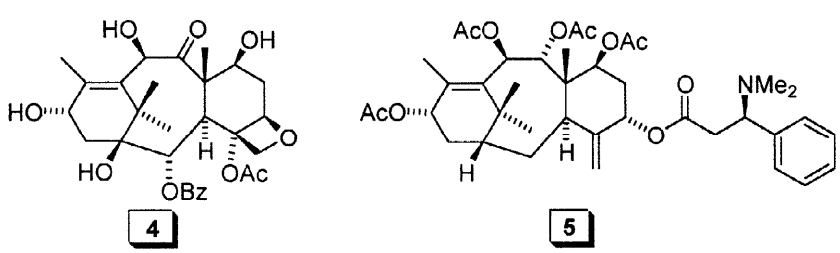
The taxoids paclitaxel (Taxol®, **1a**)[6] and docetaxel (Taxotere®, **1b**)[7] have proved successful anticancer drugs for the treatment of a variety of malignancies. Both compounds are substrates for P-gp, and increased expression of this protein is one of the major factors underlying resistance to taxoids.[8] Interestingly, certain natural and semisynthetic taxoids devoid of cytotoxicity and tubulin affinity are powerful inhibitors of P-gp activity, acting as efficient reversing agents and allowing accumulation of paclitaxel in MDR-cancer cells.[9] Among the natural taxoids, 2-deacetoxytaxinine J (**2**)[10] emerged as the most active member of the class, with a potency higher than that of verapamil.[9a] Unlike other cinnamates related to taxine, **2** does not show cardiac toxicity,[11] and might thus serve as an important starting material for the synthesis of new reversal agents. Twin drugs combining two structural components into a single molecule have been reported in numerous domains of medicinal chemistry,[12] and we explored the possibility of circumventing P-gp-mediated resistance with dual acting dimeric compounds, carrying recognition sites for both the target of taxoid anticancer activity (β-tubulin) and the protein transporter responsible for resistance to their activity (P-gp). The outstanding anticancer activity of the etherodimeric alkaloids vincristine and vinblastine provided additional motivation to the synthesis of paclitaxel-taxinine binary taxoids.

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00290-2



Pivotal to our design of dimeric taxanes were the observations that binding to tubulin is generally insensitive to changes in the Northern hemisphere,[13] that substituents at C-10 can dramatically increase the activity of paclitaxel derivatives against MDR-cells,[14] and that modifications on ring A do not seem critical for the chemosensitising activity of taxinine derivatives.[9a] With these observations in mind, we planned the synthesis of the dimeric compound **3a**, where the acetate at C-10 of paclitaxel (**1a**) and the one at C-13 of 2-deacetoxytaxinine J (**2**) are merged into a succinate tether that holds the two taxoid moieties together. This operation is formally equivalent to an oxidative dimerisation, and a similar line of thinking would generate **3b** from 10-acetyldocetaxel and 2-deacetoxytaxinine J.

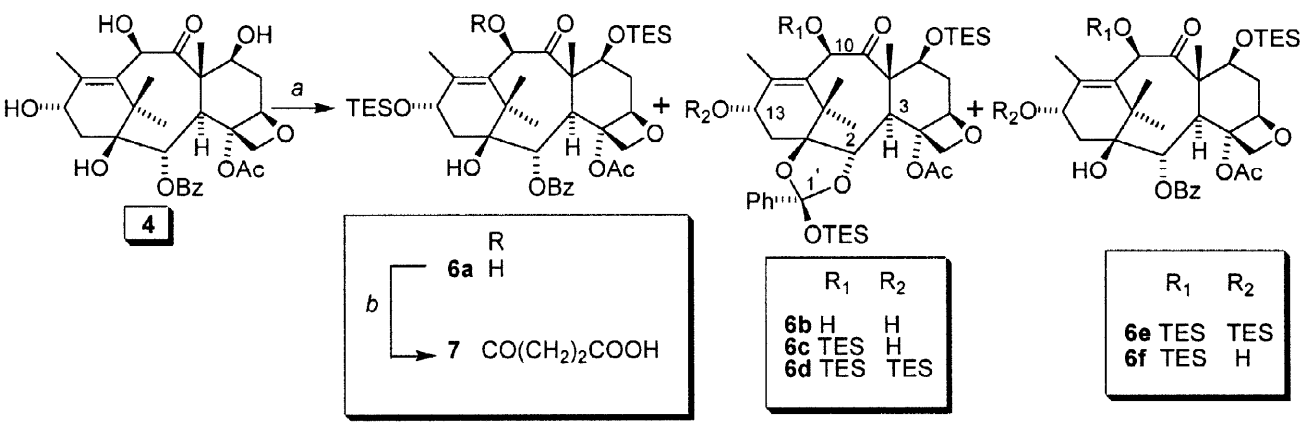
10-Deacetylbaccatin III (**4**) and 2'-deacetoxyaustrospicatin (**5**) are available in multigram amounts from widespread ornamental yews,[15] and were employed as starting materials.[16] Compound **4** has been extensively used for the synthesis of analogues of paclitaxel,[13] and the Winterstein ester **5** can be readily converted into 2'-deacetoxytaxinine J (**2**).[15b] Our synthetic plan to the dimeric taxoids capitalises on the esterification of the 13-deacetylderivative of **2** with a 7,13-diprotected 10-hemisuccinate of **4**. The alternative coupling requires the succinylation of the 13-deacetyl derivative of **2**, and did not seem a good strategy. The hindered nature of the 13-hydroxyl of taxoids requires forced conditions of acylation, feasible with acids but unattainable with succinic anhydride.[17]



The synthesis of the 7,13-diTES (= triethylsilyl)-10-hemisuccinate **7** from **4** was plagued by the formation of several by-products in the silylation step. The silylation of tetraol **4** required three equivalents of TES-Cl to proceed beyond the monosilylation stage. In addition to the 7,13-diTES derivative **6a** (49%), the silylated semi-orthoesters **6b** - **6d** (3, 5, and 5%, respectively), the 7,10-diTES-derivative **6f** (14%), and the 7,10,13-triTES-derivative **6e**[18] (8%) were also obtained (Scheme 1). The smooth formation of a silylated orthoester from the monoester of a vicinal diol is, to the best of our knowledge, unprecedented. Even more surprising was, however, the isolation of silylated orthoesters bearing free hydroxyl(s) at C-13 (**6c**), and at C-10 and C-13 (**6b**),

showing that formation of the silylated orthoester was competing with the silylation of these hydroxyls. The most pre-eminent spectroscopic feature of **6b-6d** was the replacement of the benzoate carbonyl resonance at δ *ca* 168 with an orthoester signal at δ *ca* 116. A corresponding upfield shift of the aromatic protons in the ^{1}H NMR spectrum was also observed. Compounds **6b** and **6c** were obtained as single diastereomers, while **6d** was a *ca* 2:1 mixture of two epimers, differing for the configuration at C-1'. NOE-difference experiments (correlation between the 4-acetate methyl and the *ortho*-protons of the phenyl) established that in **6b**, **6c**, and in the major isomer of **6d** the phenyl on the orthoester carbon is *cis* to H-3 and *trans* to H-2. A similar diastereoselectivity was observed in the reaction of taxine B-related compounds with benzaldehyde dimethylacetal.[19] In our case, however, the presence of a free hydroxyl at C-13 seems necessary to obtain the silylated orthoester in a diastereomerically pure form, suggesting the involvement of subtle factors in orthoester formation and/or silylation. The orthoesters **6b-d** could withstand column chromatography, but were turned into their corresponding benzoates by overnight stirring with wet silica gel.

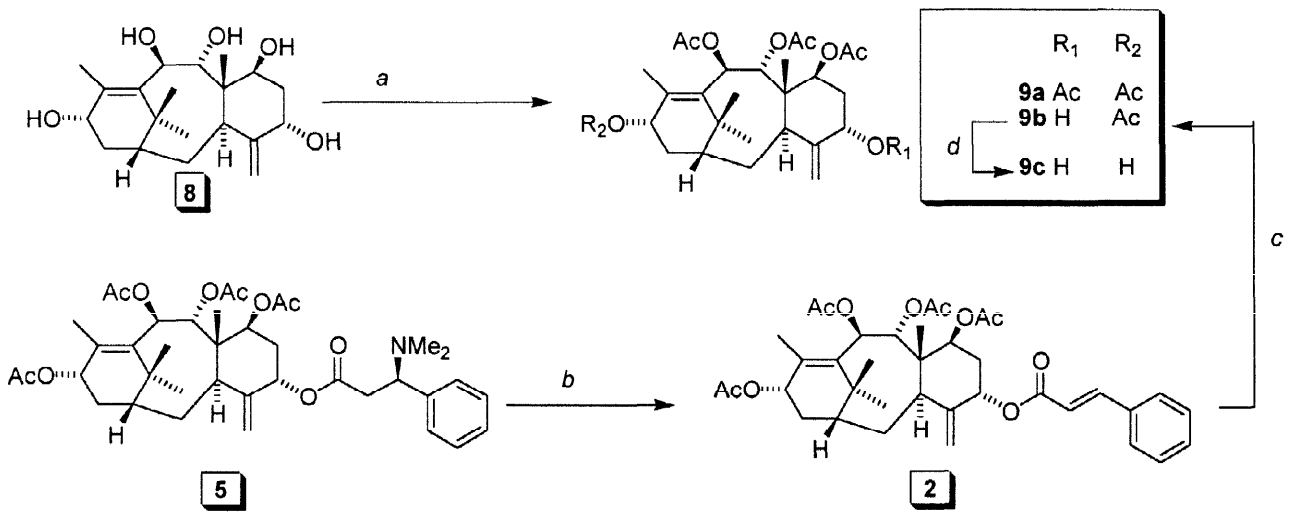
Given the smooth formation of the 7-TES derivative of **4** with near stoichiometric amounts of TES-Cl,[20] the formation of the 7,13-diTES derivative **6a** as the major reaction product when four equivalents are employed shows that the reactivity order of the three secondary hydroxyls toward silylation is 7>>13>10. No parallel exists therefore with acylation reactions, where the reactivity order is instead 7>10>>13.[21] These seemingly contradictory results are presumably the result of the higher acidity of the 10-hydroxyl, which might be substantially deprotonated, and therefore more reactive, under the acylation conditions. Since silylation of an alcohol involves instead attack on silicon by the non-ionised hydroxyl oxygen,[22] differences in acidity are not expected to dramatically affect the order of reactivity with silylating reagents. An alternative way to prepare **6a** by deacetylation of 7,13-diTES-baccatin III failed. No reaction occurred with the three published protocols to deacetylate baccatin III at C-10 ($ZnBr_2$;[23a] hydrazine;[23b] $NaHCO_3$-H_2O_2[23c]), while basic conditions (K_2CO_3, LiOH, NH_3, NaOH) gave mixtures of products. Despite the modest yield (49%) and the chromatographic purification required to remove the by-products, no alternative synthesis of **6a** could be achieved. The succinylation step was however uneventful, affording the stable succinate **7** as the only reaction product.



Scheme 1. Synthesis of the diprotected hemisuccinate 7. *a*: TES-Cl (3 mol. equiv.), imidazole (3 mol. equiv), DMF, room temp., 48 h; 49% **6a**, 3% **6b**, 5% **6c**, 5% **6d**, 8% **6e**, 14% **6f**. *b*: succinic anhydride (30 mol. equiv.), DMAP, DMF, 85°, 48 h, 72%.

The synthesis of the taxinine partner complementary to **7** requires the selective hydrolysis of the allylic 13-acetate of 2'-deacetoxyaustrospicatine (**5**) or its corresponding cinnamate **2**, a reaction which gave complex mixtures of products under a variety of reaction conditions. An alternative strategy to obtain the 13-deacetylderivative of **2** by stepwise esterification of the known pentaol **8**[24] also failed, but provided a hint which eventually paved the way to the synthesis of the target (Scheme 2). Thus, treatment of **8** with a moderate excess (7 molar equivalents) of Ac_2O in pyridine afforded, in modest yield (40%), a 4:1 mixture of the penta-acetate **9a**[24] and the tetra-acetate **9b**.[25] The latter was partly deacetylated during column chromatography to the diol **9c**[26], a reaction which could be achieved in practically quantitative yield with a variety of bases (see *infra*).

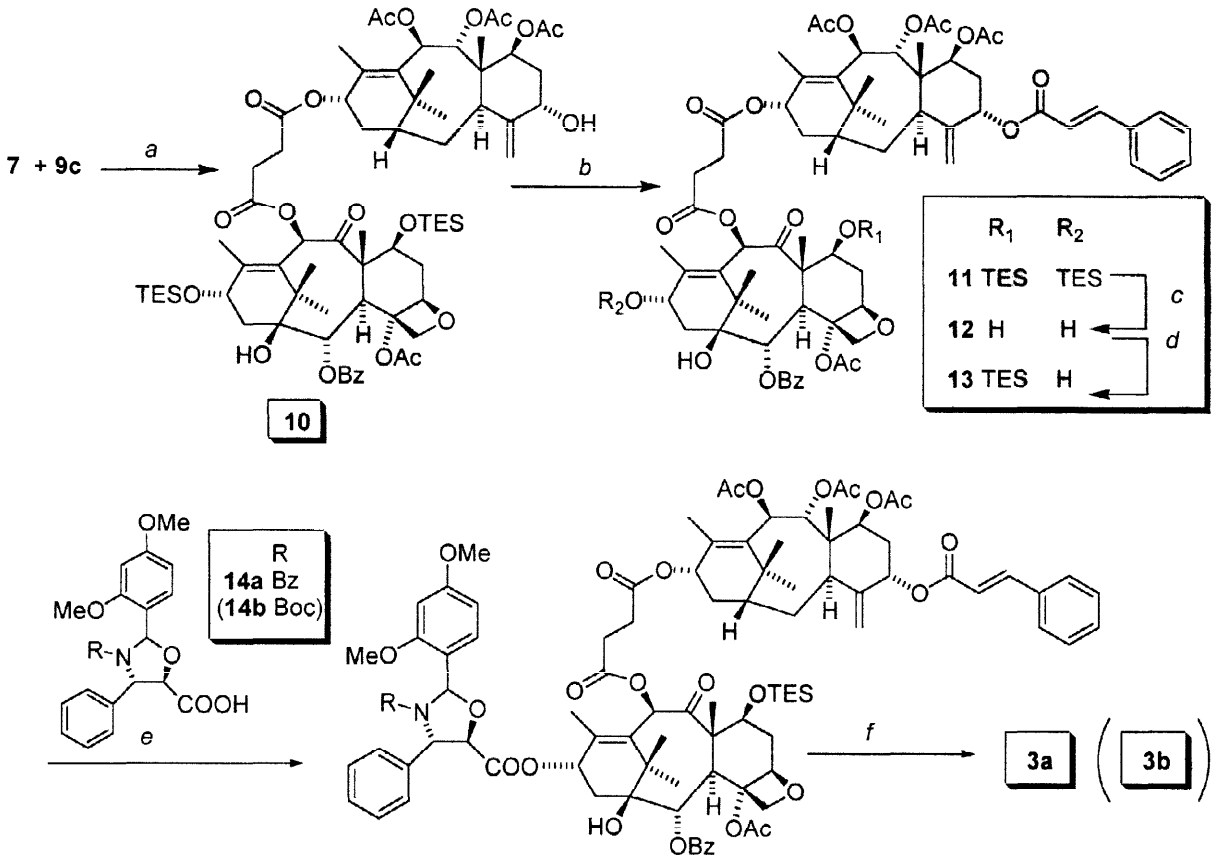
Hydrolysis of the 13-hydroxyl was thus dramatically accelerated by the presence of a free 5-hydroxyl, which presumably helps the delivery of nucleophiles to the carbonyl of the 13-acetate. Owing to the convex shape of the taxane skeleton, the oxygens at C-5α and C-13α are spatially close, and proximity effects of this type are well documented in the chemistry of these compounds.[27] Capitalising on this observation, an efficient synthesis of the triacetate **9c** could eventually be achieved. Thus, after transformation of the Winterstein ester **5** into its corresponding cinnamate **2** by *N*-oxide formation and Cope elimination,[15b] the 5-cinnamoyl group was selectively removed with hydroxylamine,[28] affording the tetraacetate **9b**, then deacetylated at C-13 with LiOH. In this way, the 5,13-diol **9c** was eventually obtained in an overall 54% yield from **5**. An example related to this sequence is the direct formation of **9c** from the Zemplén methanolysis of 2'-deacetylaustrospicatine.[26] Owing to the high hydrolytic reactivity of α-hydroxyesters, the order of events is presumably the same observed in the conversion of **5** to **9c**.



Scheme 2. Synthesis of the diol 9c. *a*: Ac_2O (7 mol. equiv.), TEA (7 mol. equiv.), CH_2Cl_2, RT; *b*: MCPBA, THF; *c*: NH_2OH, EtOH, Δ; *d*: LiOH, water-methanol 1:1 (54% from **5**).

Protecting manoeuvres were not required for the sequential esterification of the two secondary allylic hydroxyls of **9c**, since treatment of this diol with the diprotected baccatin hemisuccinate **7** afforded the dimeric 13-succinate **10** as the only reaction product (Scheme 3). The selective esterification of the 13-hydroxyl of the taxinine domain is in accordance with the results obtained in the acetylation of the pentaol **8**, and was indicated by the marked downfield shift for H-13 of the this moiety (Δδ + 1.43), and by the detection of a HMBC correlation between one of the succinate carbonyls (δ 171.2) and H-13 of the taxinine moiety (δ 5.79). The cinnamoyl group could then be reintroduced at C-5 of the taxinine sector under forced reaction conditions, and the dimeric cinnamoyltaxane obtained in this way was desilylated at C-7 and C-13 by fluoridolysis with TBAF.[29] Selectively resilylation at C-7 was then required to direct coupling with the side chain synthon **11a**[23b,30] at the 13-hydroxyl. This coupling and the removal of the protecting groups were uneventful, eventually affording **3a** as a crystalline powder. Esterification with the protected synthon of the docetaxel side chain **11b**[23b,30] afforded, after deprotection, **3b** in similar yield. Despite their complexity, the ^1H NMR spectra of **3a** and **3b** could be completely assigned by a combination of 1D- and 2D techniques (COSY, NOE-difference spectroscopy).

Compared to paclitaxel, the dimeric taxane **3a** showed a marked decrease of tubulin affinity, whereas **3b** retained one third of the activity of the natural product (Table 1). The higher potency of **3b** in tubulin binding is in accordance with the observation that in this assay paclitaxel analogues of the *N*-BOC series are generally more active than those of the *N*-benzoyl series.[13] Both **3a** and **3b**, however, lacked significant cytotoxicity toward normal- and MDR-human breast-tumour cells (Table 1). The apparent inconsistency between tubulin polymerisation activity and cytotoxicity may be indicative of an impaired cellular penetration for **3b**.[31]



Scheme 3. Coupling of the monomers 7 and 9c and introduction of the cinnamoyl and aminoacyl moieties. *a*: EDC, CH_2Cl_2 (66%); *b*: cinnamic acid, DCC, DMAP, toluene, 90°C (70%); *c*: TBAF, THF (50%); *d*: TES-Cl, imidazole, DMF (54%); *e*: **14a** (for **3a**) or **14b** (for **3b**), DCC, DMAP, toluene; *f*: 0.1 N HCl, MeOH (50 % from **13** for **3a**; 60% from **13** for **3b**).

In conclusion, the discovery that non-cytotoxic taxoids can interfere with the development of resistance to paclitaxel provided a strong rationale for the preparation of the dimeric taxoids **3a** and **3b**. The synthesis of these compounds afforded additional information on the reactivity of the biologically important systems of baccatin III and taxinine J, highlighting subtle differences in the reactivity of their hydroxy groups and disclosing a protocol to incorporate taxinine and baccatin moieties into hybrid compounds. Finally, the biological evaluation of **3a** and **3b** showed that a definite limit exists regarding the size of the ester groups which can be accommodated in the northern hemisphere of the taxane core without a detrimental effect on tubulin affinity and/or cellular penetration and cytotoxicity.

Table 1. Tubulin binding (ED_{50} μM) and cytotoxicity (ED_{50} nM) of the twin taxoids **3a** and **3b**[32]

Compound	Microtubule Assembly Assay	MCF-7	MCF-7R
3a	> 20	> 40	> 5,000
3b	0.9	> 40	> 5,000
Paclitaxel	0.3	2	3,300

Acknowledgements. We are grateful to Prof. Richard H. Himes (Dept. of Biochemistry, University of Kansas, U.S.A.) for the biological evaluation of the compounds.

EXPERIMENTAL

General Methods. Anhydrous conditions were achieved by flame-drying flasks and equipments. Reactions were monitored by TLC on Merck 60 F_{254} (0.25 mm) plates, which were visualized by UV inspection and/or staining with 5% H_2SO_4 in methanol and heating. Merck silica gel was used for column- chromatography (CC). Melting points were obtained on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a Bruker AC-400 spectrometer at 25°C. ^{1}H and ^{13}C NMR chemical shifts refer to C*H*Cl_3 at δ 7.26 and *C*DCl_3 at δ 77.0, respectively. HREIMS Spectra were taken on a MAT 95ST Finnigan MAT apparatus (70 eV, EI mode). Commercially available reagents and solvents were used without further purification, unless otherwise noted. CH_2Cl_2 was dried by distillation from P_4O_{10}, THF by distillation from Na-benzophenone, and DMF by distillation from CaH_2. $MgSO_4$ was used for drying organic solutions in all work up procedures.

Silylation of 10-deacetylbaccatin III (4). To a solution of **4** (5.0 g, 9.2 mmol) in dry DMF (50 mL), imidazole (1.87 g, 27.6 mmol, 3.0 mol. equiv.) and TES-Cl (4.61 mL, 4.14 g, 27.6 mmol, 3.0 mol. equiv.) were added. After stirring for 4 days at room temp., the reaction was worked up by pouring into a slurry of Celite (5 g) in water (300 mL) and filtration. The cake was washed with water to remove DMF, and then with EtOAc to recover the reaction products. After drying and evaporation of the solvent, the residue was purified by CC (hexane-EtOAc gradient), to give **6d** (460 mg, 5%), **6e** (652 mg, 8%) (hexane-EtOAc 99:1), **6c** (407 mg, 5%) (hexane-EtOAc 95:5), **6b** (213 mg, 3%), **6a** (3.56 g, 49%), and **6f** (1.02 g, 14%) (hexane-EtOAc 9:1). Compounds **6b-6d** were quantitatively turned into their corresponding benzoates by overnight stirring with a 10-fold weight of silica gel and water (*ca* 5 ml/g of silica gel).

7,13-diTES-10-Deacetylbaccatin III **(6a).** White powder, mp 198-200°C; $[\alpha]_D^{25}$ –35 (*c* 0.7, $CHCl_3$); IR (KBr) 3459, 1724, 1713, 1698, 1267, 1244, 1106, 1095, 741 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.09 (AA'-Bz), 7.59 (C-Bz), 7.47 (BB'-Bz), 5.61 (d, *J* = 7.2 Hz, H-2), 5.17 (br d, *J* = 1 Hz, H-10), 4.96 (m, H-5 + H-13) 4.40 (dd, *J* = 9.0, 4.5 Hz, H-7), 4.31 (d, *J* = 8.3 Hz, H-20a), 4.27 (d, *J* = 1 Hz, 10-OH), 4.17 (d, *J* = 8.3 Hz, H-20b), 3.89 (d, *J* = 7.4 Hz, H-3), 2.30 (s, Ac), 2.05 (s, H-18), 1.73 (s, H-19), 1.09, 1.04 (s, H-16 and H-17), 1.00 (t, *J* = 9.0 Hz, TES), 0.90 (t, *J* = 9.0 Hz, TES), 0.67 (m, TES), 0.54 (m, TES). HRMS (EI): M^+, found 772.4042. $C_{41}H_{64}O_{10}Si_2$ requires 772.4038.

7,1'-diTES 2-Debenzoyl-10-deacetylbaccatin III-1,2-semiorthobenzoate **(6b)**. White powder, m.p. 132-35 °C; $[\alpha]_D^{25}$ –12 (*c* 1.2, $CHCl_3$); IR (KBr) 3517, 1741, 1696, 1115, 1055, 1003, 980, 746 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.61 (m, Ph), *ca* 7.35 (m, Ph), 5.13 (d, *J* = 2 Hz, H-10), 5.04 (d, *J* = 8 Hz, H-5), 4.76 (d, *J* = 8.5 Hz, H-20a), 4.72 (d, *J* = 8.5 Hz, H-20b), 4.68 (m, H-13), 4.47 (dd, *J* = 9.0, 7.5 Hz, H-7), 4.31 (d, *J* = 2 Hz, OH-10), 4.23 (d, *J* = 5.0 Hz, H-2), 3.45 (d, *J* = 5.0 Hz, H-3), 2.56 (m, H-14a), 2.13 (s, Ac), 2.03 (s, H-18), 1.95 (m, H-6b), 1.82 (s, H-19), 1.15, 1.12 (s, H-16, H-17), 0.92 (t, *J* = 7.5 Hz, TES), 0.79 (t, *J* = 7.5 Hz, TES), 0.55 (m, TES), 0.41 (m, TES). HRMS (EI): M^+, found 772.4043. $C_{41}H_{64}O_{10}Si_2$ requires 772.4038.

7,10,1'-triTES 2-Debenzoyl-10-deacetylbaccatin III-1,2-semiorthobenzoate **(6c)**. White powder, m.p. 78-80 °C; $[\alpha]_D^{25}$ –15 (*c* 0.90, $CHCl_3$); IR (KBr disk) 3498, 1740, 1719, 1055, 1013, 968, 746, 731 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.61 (m, Ph), ca 7.35 (m, Ph), 5.16 (s, H-10), 5.08 (d, *J* = 8 Hz, H-5), 4.73 (s, H-20a + H-20b), 4.67 (m, H-13), 4.41 (dd, *J* = 9.0, 7.5 Hz, H-7), 4.27 (d, *J* = 5.0 Hz, H-2), 3.40 (d, *J* = 5.0 Hz, H-3), 2.60 (m, H-14a), 2.11 (s, Ac), 1.98 (s, H-18), 1.87 (m, H-6b), 1.76 (s, H-19), 1.25 (s, H-16), 1.11 (s, H-17), 0.99 (t, J = 7.5 Hz, TES), 0.96 (t, *J* = 7.5 Hz, TES), 0.77 (t, *J* = 7.5 Hz, TES), ca 0.60 (m, 2 x TES), 0.40 (m, TES). ^{13}C-NMR (CDCl3): δ 206.9 (s, C-1), 171.3 (s, OAc), 142.8 (s, C-12), 139.0 (s, Ph), 136.4 (s, C-11), 128.0 (d, Ph), 127.5 (d, Ph), 125.6 (d, Ph), 116.9 (s, C-1'), 87.1 (s, C-1), 84.4 (d, C-5), 80.7 (s, C-4), 78.2 (d, C-2), 77.5 (t, C-20), 77.2 (d, C-10), 72.5 (d, C-7), 67.7 (d, C-13), 60.0 (s, C-8), 44.1 (d, C-3), 41.0 (s, C-15), 38.2 (t, C-6), 38.1 (t, C-14), 26.0 (q, C-17), 22.6 (q, Ac), 19.7 (q, C-16), 15.1 (q, C-18), 10.5 (q, C-19), 6.9, 6.8, 6.6 (q, 3 x TES), 5.8, 5.3, 5.1 (t, 3 x TES). HRMS (EI): M^+, found 886.4910. $C_{47}H_{78}O_{10}Si_3$ requires 886.4903.

7,10,13,1'-tetraTES 2-Debenzoyl-10-deacetylbaccatin III-1,2-semiorthobenzoate **(6d)**. White powder, m.p. 41 °C; $[\alpha]_D^{25}$ –19 (*c* 1.0, $CHCl_3$); IR (KBr) 1738, 1717, 1242, 1078, 1005, 978, 745 cm^{-1}; ^{1}H-NMR ($CDCl_3$): major epimer: δ 7.60 (m, Ph), *ca* 7.37 (m, Ph), 5.13 (s, H-10), 5.01 (d, J = 8 Hz, H-5), 4.74 (m, H-13), 4.71 (s, H-20a + H-20b), 4.38 (dd, J = 9.0, 7.5 Hz, H-7), 4.28 (d, J = 5.0 Hz, H-2), 3.32 (d, J = 5.0 Hz, H-3), 2.60 (m, H-14a),

2.10 (s, Ac), 1.90 (s, H-18), 1.73 (s, H-19), 1.25 (s, H-16), 1.16 (s, H-17), 0.95 – 0.90 (TES), 0.77 (m, TES), *ca* 0.60 (m, 2 x TES), 0.40 (m, TES); minor epimer: 7.37 (m, Ph), 5.11 (s, H-10), 3.78 (d, J = 5.0 Hz, H-2), 3.40 (d, J = 5.0 Hz, H-3), 2.19 (s, Ac), 1.95 (s, H-18), 1.58 (s, H-19), 1.21 (s, H-17). HRMS (EI): M^+, found 1000.5780. $C_{53}H_{92}O_{10}Si_4$ requires 1000.5768.

7,10,13-triTES-10-Deacetylbaccatin III **(6e).** White powder, mp 198-200 °C; $[\alpha]_D^{25}$ –25 (*c* 1.2, $CHCl_3$); IR (KBr) 3400, 1725, 1713, 1269, 1244, 1107, 1076, 740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.09 (AA'-Bz), 7.58 (C-Bz), 7.47 (BB'-Bz), 5.63 (d, J = 7.2 Hz, H-2), 5.20 (s, H-10), 4.95 (m, H-5 + H-13) 4.43 (dd, J = 9.0, 4.5 Hz, H-7), 4.29 (d, J = 8.3 Hz, H-20a), 4.15 (d, J = 8.3 Hz, H-20b), 3.86 (d, J = 7.4 Hz, H-3), 2.51 (m, H-14a), 2.29 (s, Ac), 1.99 (s, H-18), 1.66 (s, H-19), 1.20, 1.14 (s, H-16 and H-17), *ca* 0.95 (m, TES), *ca* 0.65 (m, TES).). HRMS (EI): M+, found 886.4898. $C_{47}H_{78}O_{10}Si_3$ requires 886.4903.

7,10-diTES-10-Deacetylbaccatin III **(6f).** White powder, mp 182-83 °C; $[\alpha]_D^{25}$ –42 (*c* 0.95, $CHCl_3$); IR (KBr) 3484, 1723, 1707, 1273, 1244, 1109, 1003, 976 cm^{-1}; ^{1}H-NMR: see ref. 18. HRMS (EI): M^+, found 772.4029. $C_{41}H_{64}O_{10}Si_2$ requires 772.4038.

Reaction of 7,10-diTES-10-deacetylbaccatin III-with succinic anhydride. To a soln. of **6a** (567 mg, 0.73 mmol) in dry DMF (10 mL), succinic anhydride (2.2 g, 22 mmol, 30 mol. equiv.) and DMAP (150 mg) were added. The solution was heated at 85°C for 48 h, and then worked up by pouring into a slurry of celite (0.6 g) in water (100 mL). After filtration, the cake was washed with water and then with EtOAc. The organic phase was dried and evaporate, and the residue was purified by CC (hexane-EtOAc 3:7) to give 463 mg **7** (72%) as a white powder, m.p. 120 °C; $[\alpha]_D^{25}$ –48 (*c* 0.90, $CHCl_3$); IR (KBr) 3496, 1725, 1269, 1242, 1107, 739 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.09 (AA'-Bz), 7.59 (C-Bz), 7.45 (BB'-Bz), 6.45 (s, H-10), 5.60 (d, J = 7.0 Hz, H-2), 4.90 (m, H-5 + H-13), 4.45 (dd, J = 9.0, 4.5 Hz, H-7), 4.26 (d, J = 8.3 Hz, H-20a), 4.11 (d, J = 8.3 Hz, H-20b), 3.82 (d, J = 7.0 Hz, H-3), 2.44 (br s, succinate), 2.26 (s, Ac), 1.85 (s, H-18), 1.62 (s, H-19), 1.15, 1.09 (s, H-16 + H-17), *ca* 0.95 (m, 2 x TES), *ca* 0.65 (m, 2 x TES). HRMS (EI): M^+, found 872.4153. $C_{45}H_{68}O_{13}Si_2$ requires 872.4198.

Acetylation of pentaol 8. To a suspension of **8** (150 mg) in CH_2Cl_2 (5 mL), Ac_2O (284 μL, 307 mg, 3.0 mmol, 7 mol. equiv.) and TEA (420 μL, 303 mg, 3.0 mmol, 7 mol. equiv.) were added. After stirring at room temperature for 5 h, the reaction was worked up by dilution with water and extraction with EtOAc. After sequential washing with dil. HCl and brine, the organic phase was dried and evaporated. The residue was purified by CC (hexane-EtOAc 7:3) to give 94 mg of a *ca* 4:1 mixture (^{1}H NMR analysis) of **9a** and **9b** (*ca* 40%). Attempts to further separate this mixture by CC gave 50 mg **9a**,[24] 23 mg **9b**[25] and 6 mg **9c**[26].

Synthesis of diol 9c: To a soln. of **5** (5.35 g, 7.7 mmol) in dry THF, MCPBA (85%, 1.87 g, 9.2 mmol, 1.2 mol. equiv.) was added. After stirring at room temp. for 4 h, the reaction was worked up by dilution with EtOAc and washing with water. The organic phase was washed with 3% $Na_2S_2O_3$, 2% NaOH, and brine. After drying and removal of the solvent, crude **2**[10] (5.06 g) was obtained. The latter was dissolved in EtOH (150 mL), and $NH_2OH.HCl$ (4.94 g, 71.6 mmol, 9.3 mol. equiv.) and a solution of NaOAc (9.98 g, 122 mmol, 15.8 mol. equiv.) in water (150 mL) were added. The reaction mixture was refluxed for 24 h, and then worked up by dilution with water (ca 600 mL) and extraction with EtOAc. After washing with brine and drying, evaporation of the solvent left a semi-solid residue, which was dissolved in H_2O-MeOH (1:1, 60 mL). To this solution, $LiOH.H_2O$ (2.10 g, 50 mmol, 6.5 mol. equiv.) was added, and the mixture was stirred at rom temp. for 6.5 h. The reaction was worked up by dilution with water (*ca* 500 mL) and extraction with EtOAc. The organic phase was washed with brine, dried, and evaporated. The residue was purified by CC (CH_2Cl_2-EtOH 98:2) to give 1.99 g **9c**[26] (54% from **5**).

Coupling of hemisuccinate 7 and diol 9c: To a solution of **7** (1.6 g, 1.8 mmol) and **9c** (965 mg, 2.0 mmol, 1.1 mol. equiv.) in dry CH_2Cl_2 (25 mL), EDC (703 mg, 3.6 mmol, 2 mol. equiv.) and DMAP (448 mg, 3.6 mmol, 2 mol. equiv.) were added. After stirring 4 h at room temp., the reaction was worked up by dilution with CH_2Cl_2 and washing with water. After drying and removal of the solvent, the residue was purified by CC (hexane-EtOAc 7:3) to give **10** (1.6 g, 66%) as a white powder. m.p. 158 °C; $[\alpha]_D^{25}$ –7.8 (*c* 0.90, $CHCl_3$); IR (KBr) 3538, 1740, 1372, 1242, 1107, 1026, 988 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (taxinine moiety) 6.27 (d, J = 11 Hz, H-10), 5.82 (d, J = 11 Hz, H-9), 5.79 (t, J = 8.0 Hz, H-13), 5.67 (dd, J = 11, 5.0, H-7), 5.18 (s, H-20a), 4.84 (s, H-20b), 4.30 (s, H-5), 2.28 (br s, H-18), 2.09 (s, 2 x Ac), 2.06 (s, Ac), 2.03 (s, Ac), 1.57 (s, H-16), 1.00 (s, H-17),

0.81 (s, H-19); (baccatin moiety): δ 8.08 (AA'-Bz), 7.58 (C-Bz), 7.45 (BB'-Bz), 6.43 (s, H-10), 5.61 (d, *J* = 7.0 Hz, H-2), 4.95 (d, *J* = 8 Hz, H-5), 4.82 (m, H-13), 4.41 (dd, *J* = 9, 4.5 Hz, H-7), 4.28 (d, *J* = 8 Hz, H-20a), 4.11 (d, *J* = 8 Hz, H-20b), 3.87 (d, *J* = 7.0 Hz, H-3), 2.31 (s, Ac), 2.17 (s, H-18), 1.65 (s, H-19), 1.20, 1.03 (s, H-16 + H-17), 0.95 (m, TES), 0.65 (m, TES); (succinate): 2.70 (m). ^{13}C NMR ($CDCl_3$): δ 201.9 (s), 171.2 (s), 170.3 (s), 169.9 (s), 169.8 (s), 169.8 (s), 169.2 (s), 146.4 (s), 145.2 (s), 137.5 (s), 134.7 (s), 133.5 (d), 131.4 (s), 130.0 (d), 129.1 (d), 128.2 (d), 116.2 (t), 84.2 (d), 80.7 (s), 79.4 (s), 76.5 (t), 75.8 (d), 75.2 (d), 74.7 (d), 72.1 (d), 71.6 (d), 70.7 (d), 70.1 (d), 68.4 (d), 58.3 (d), 46.9 (d), 46.3 (s), 42.9 (s), 40.2 (d), 39.8 (t), 39.4 (s), 37.5 (d), 37.1 (t), 34.5 (t), 31.7 (t), 31.1 (q), 28.8 (t),28.5 (t), 27.3 (q), 27.3 (t), 26.3 (q), 22.3 (q), 21.4 (q), 21.1 (q), 21.0 (q), 20.9 (q), 15.2 (q), 14.8 (q), 13.3 (q), 10.1 (q), 6.9 (q), 6.8 (q), 5.2 (t), 4.8 (t). HRMS (EI): M^+, found 1332.6671. $C_{71}H_{104}O_{10}Si_2$ requires 1332.6660.

Esterification of the dimeric taxoid 10 with cinnamic acid. To a solution of **10** (616 mg, 0.46 mmol) in dry toluene (20 mL), cinnamic acid (340 mg, 2.3 mmol, 5 mol. equiv.), DCC (473 mg, 2.3 mmol, 5 mol. equiv.) and DMAP (280 mg, 2.3 mmol, 5 mol. equiv.) were added. The solution was heated at 90 °C (oil bath) for 5 h, and then worked up by dilution with EtOAc and washing with water and sat. $NaHCO_3$. The organic phase was dried and evaporated. The residue was purified by column chromatography (hexane-EtOAc 2:8) to afford 470 mg (70%) **11** as a colourless powder. m.p. 139-140 °C; $[\alpha]_D^{25}$ –4.5 (*c* 1.2, $CHCl_3$); IR (KBr) 3400, 1738, 1715, 1370, 1250, 1120, 1060, 960 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (taxinine moiety) 7.79 (d, J = 16 Hz, Cinn), 7.60-7.32 (m, Cinn.) 6.57 (d, J = 16 Hz, Cinn), 6.29 (d, J = 10.6 Hz, H-10), 5.88 (d, J = 10.6 Hz, H-9), 5.80 (br t, J = 8.0 Hz, H-13), 5.67 (dd, J = 11.0, 5.0, H-7), 5.58 (br s, H-5), 5.38 (br s, H-20a), 5.00 (br s, H-20b), 2.29 (br s, H-18), 2.09 (s, Ac), 2.07 (s, Ac). 2.00 (s, Ac), 1.57 (s, H-16), 1.00 (s, H-17), 0.81 (s, H-19); (baccatin moiety): δ 8.10 (AA'-Bz), 7.58 (C-Bz), 7.45 (BB'-Bz), 6.37 (s, H-10), 5.61 (d, *J* = 7.0 Hz, H-2), 4.95 (d, J = 8 Hz, H-5), 4.88 (m, H-13), 4.41 (dd, *J* = 9.0, 4.5 Hz, H-7), 4.28 (d, *J* = 8.3 Hz, H-20a), 4.12 (d, *J* = 8.3 Hz, H-20b), 3.89 (d, *J* = 7.0 Hz, H-3), 2.31 (s, -OAc), 2.17 (s, H-18), 1.65 (s, H-19), 1.20, 1.03 (s, H-16 + H-17), *ca* 0.95 (m, TES), *ca* 0.65 (m, TES); (succinate): 2.60 (m). HRMS (EI): M^+, found 1462.7066. $C_{80}H_{110}O_{21}Si_2$ requires 1462.7078.

Fluoridolysis of the dimeric taxoid 11 and chemoselective resilylation to 13. a) To a cooled (0 °C) solution of **11** (774 mg, 0.53 mmol) in dry THF (15 mL), TBAF (1.44 mL of a 1.1 M soln. in THF, 1.59 mmol, 3.0 mol. equiv.) was added dropwise, and the reaction was stirred for 2 h at 0 °C. The cooling bath was then removed, and stirring was continued for 2.5 h. The reaction was worked up by dilution with water and extraction with EtOAc. After drying and evaporation of the solvent, the residue was purified by CC (hexane-EtOAc 1:1) to give 327 mg (50%) **12** as a colorless powder (mp. 118-120 °C). b) To a solution of **12** (196 mg, 0.16 mmol) in dry DMF (10 mL), imidazole (57 mg, 0.83 mmol, 5.2 mol. equiv.) and TES-Cl (139 μL, 125 mg, 0.83 mmol, 5.2 mol. equiv.) were added. After stirring at room temp. for 48 h, the reaction was worked up by pouring into a slurry of Celite (500 mg) in water (20 mL) and filtration. The cake was washed with water, and then with EtOAc to recover the reaction product. After washing with brine, drying, and evaporation, the residue was purified by CC (hexane-EtOAc 1:1) to give 115 mg **13** (54%) as a colourless powder. M.p. 158-160 °C; $[\alpha]_D^{25}$ + 5.3 (*c* 0.90, $CHCl_3$); IR (KBr) 3470, 1740, 1636, 1246, 1159, 1026, 988 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (taxinine moiety) 7.79 (d, *J* = 16 Hz, Cinn), 7.58 (m, Cinn.), 7.36 (m, Cinn.), 6.63 (d, *J* = 16 Hz, Cinn.), 6.27 (d, *J* = 11 Hz, H-10), 5.90 (d, J = 11 Hz, H-9), 5.82 (br t, *J* = 7 Hz, H-13), 5.66 (dd, *J* = 11.0, 6.0 Hz, H-7), 5.44 (s, H-20a), 5.02 (s, H-20b), 2.08 (s, H-18), 2.08 (s, Ac), 2.20 (s, Ac), 1.95 (s, Ac), 1.57 (s, H-16), 0.97 (H-17), 0.85 (s, H-19); (baccatin moiety): δ 8.09 (AA'-Bz), 7.55 (C-Bz), 7.45 (BB'-Bz), 6.35 (s, H-10), 5.59 (d, *J* = 7.0 Hz, H-2), 5.55 (br t, J = 8.0 Hz, H-13), 4.97 (d, J = 8 Hz, H-5), 4.48 (dd, *J* = 9.0, 4.5 Hz, H-7), 4.27 (d, *J* = 8.3 Hz, H-20a), 4.13 (d, *J* = 8.3 Hz, H-20b), 4.00 (d, *J* = 7.0 Hz, H-3), 2.29 (s, -OAc), 2.25 (s, H-18), 1.67 (s, H-19), 1.13, 1.03 (s, H-16 + H-17), *ca* 0.92 (m, TES), *ca* 0.58 (m, TES); (succinate): 2.70 (m). HRMS (EI): M^+, found 1348.6201. $C_{74}H_{96}O_{21}Si$ requires 1348.6213.

Esterification of 13 with side-chain compact synthons (reaction with **14a** as example): to a solution of **13** (80 mg, 0.059 mmol) in dry toluene (5 mL), *N*-benzoyl (4*S*,5*R*)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid (**14a**) (51 mg, 0.11 mmol, 1.9 mol. equiv.), DCC (14.6 mg, 0.071 mmol, 1.2 mol. equiv.) and DMAP (5 mg, 0.04 mmol, 0.7 mol. equiv.) were added. After stirring 14 h at room temp., the

reaction was worked up by filtration on Celite and evaporation. The residue was purified by CC (hexane-EtOAc 1:1) to give 85 mg of residue. The latter was dissolved in a solution of HCl in MeOH (prepared reacting AcCl (140 μL) and MeOH (20 mL)). After stirring at room temperature for *ca* 1h, the solution was diluted with sat. $NaHCO_3$ and extracted with CH_2Cl_2. After drying and removal of the solvent, the residue was purified CC (hexane-EtOAc 4:6) to give 44 mg **3a** (50%).

Dimeric taxoid **3a**: white powder, m.p. 162-165 °C; $[\alpha]_D^{25}$ –12 (*c* 0.90, $CHCl_3$); IR (KBr) 3432, 1748, 1665, 1450, 1329, 1246, 1069, 712 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ (taxinine moiety): 7.79 (d, *J* = 16.0 Hz, Cinn); 7.55 (m, Cinn.), 7.42 (m, Cinn.), 6.57 (d, *J* = 16.0 Hz, Cinn.), 6.30 (d, *J* = 11.0 Hz, H-10), 5.92 (d, *J* = 11.0 Hz, H-9), 5.82 br dd, *J* = 10.0, 7.5 Hz, H-13), 5.68 (dd, *J* = 10.5, 5.0 Hz, H-7), 5.57 (dd, *J* = 4.0, 2.0 Hz, H-5), 5.39 (br s, H-20a), 5.00 (br s, H-20b), 2.95 (br d, *J* = 6.0 Hz, H-3), 2.64 (ddd, *J* = 14.5, 10.0, 10.0 Hz, H-14a), 2.31 (br s, H-18), 2.07 (s, Ac), 2.04 (s, Ac), 1.98 (s, Ac), 2.0-1.70 (m, H-1 + H-2a + H-2b + H-6a + H-6b), 1.61 (s, H-16), 1.08 (s, H-17), 0.94 (dd, *J* = 14.5, 7.0, H-14b), 0.86 (s, H-19); (paclitaxel moiety): 8.13 (AA', 2-Bz), 7.74 (AA', NHBz), 7.61 (C, 2-Bz), 7.55 (C, NHBz), 7.50 (BB', 2-Bz), 7.55-7.32 (m, 3'-Ph), 7.32 (BB', NHBz), 7.03 (d, *J* = 9.0 Hz, NH), 6.19 (br t, *J* = 8.0 Hz, H-13), 6.16 (s, H-10), 5.78 (dd, *J* = 9.0, 3.5 Hz, H-3'), 5.65 (d, *J* =7.0 Hz, H-2), 4.95 (br dd, *J* = 9.5, 2.5 Hz, H-5), 4.79 (d, *J* = 3.5 Hz, H-2'), 4.38 (br dd, *J* = 11.0, 6.5 Hz, H-7), 4.30 (d, *J* = 8.5 Hz, H-20a), 4.19 (dd, *J* = 8.5 Hz, H-20b), 3.76 (d, *J* = 7.0 Hz, H-3), 2.55 (ddd, *J* = 14.0, 9.5, 6.5 Hz, H-6a), 2.47 (br s, 7-OH), 2.38 (s, Ac), 2.35-2.15 (m, H-14a + H-14b), *ca* 1.85 (m, H-6b), 1.77 (br s, H-18), 1.69 (s, H-19), 1.16 (s, H-17), 1.08 (s, H-16); Succinate: 2.35 – 2.15 (m, 4H). HRMS (EI): M^+, found 1501.6228. $C_{84}H_{95}NO_{24}$ requires 1501.6244.

Dimeric taxoid **3b**: white powder, m.p. 125-127 °C; $[\alpha]_D^{25}$ –14 (*c* 1.3, $CHCl_3$); IR (KBr) 3453, 1740, 1718, 1635, 1372, 1248, 1163, 988, 770 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ (taxinine moiety): 7.79 (d, *J* = 16 Hz, Cinn); 7.54 (m, Cinn.), 7.44 (m, Cinn.), 6.57 (d, *J* = 16 Hz, Cinn.), 6.30 (d, *J* = 11 Hz, H-10), 5.93 (d, *J* = 11 Hz, H-9), 5.83 (dd, *J* = 10, 7.5 Hz, H-13), 5.69 (dd, *J* = 10, 5.0 Hz, H-7), 5.58 (dd, J = 4.0, 2.0 Hz, H-5), 5.41 (s, H-20a), 5.02 (s, H-20b), 2.96 (br d, *J* = 6.0 Hz, H-3), 2.65 (m, H-14a), 2.32 (br s, H-18), 2.07 (s, Ac), 2.04 (s, Ac), 1.98 (s, Ac), 1.96 (ddd, J = 14.0, 5.0, 2.2 Hz, H-6a), 1.90 (m, H-6b), 1.86 (m, H-1 + H-2a), 1.76 (m, H-2b), 1.62 (s, H-16), 1.09 (s, H-17), 0.96 (dd, J = 14.5, 7.0, H-14b), 0.88 (s, H-19); (docetaxel moiety): 8.11 (AA', Bz), 7.61 (C, Bz), 7.50 (BB', Bz), 7.40-7.30 (m, 3'-Ph), 6.21 (br t, *J* = 8.0 Hz, H-13), 6.18 (s, H-10), 5.65 (d, J =7.0 Hz, H-2), 5.37 (d, *J* = 9.5 Hz, NH), 5.26 (br d, *J* = 9.0 Hz, H-3'), 4.95 (dd, *J* = 9.5, 2.5 Hz, H-5), 4.63 (br s, H-2'), 4.38 (br dd, *J* = 11, 6.5 Hz, H-7), 4.30 (d, J = 8.5 Hz, H-20a), 4.17 (dd, J = 8.5 Hz, H-20b), 3.77 (d, *J* = 7.0 Hz, H-3), 3.36 (s, 2'-OH), 2.55 (m, H-6a), 2.49 (s, 7-OH), 2.37 (s, Ac), 2.35-2.15 (m, H-14a + H-14b), 1.90 (m, H-6b), 1.82 (br s, H-18), 1.67 (s, H-19), 1.32 (s, BOC), 1.20 (s, H-17), 1.09 (s, H-16); Succinate: 2.32 (m, 4H). HRMS (EI): M^+, found 1497.6515 $C_{82}H_{99}NO_{25}$ requires 1497.6506.

REFERENCES AND NOTES

1. Part XXXIII in the Series "The Chemistry and Occurrence of Taxane Derivatives". Part XXXII: Barboni, L.; Lambertucci, C.; Ballini, R.; Appendino, G.; Bombardelli, E. *Tetrahedron Lett.* **1998**, *39*, 7177-7180.
2. Ford, J.M.; Hait, W.N. *Pharmacol. Rev.* **1990**, *42*, 155-192
3. Endicott, J.A.; Ling, V. *Annu. Rev. Biochem.* **1989**, *58*, 137-171.
4. Lautier, D.; Canitrot, Y.; Deeley, R.G.; Cole, S.P.C. *Biochem. Pharmacol.* **1996**, *52*, 967-977.
5. a) Reddy, D.S. *Drugs Fut.* **1997**, *22*, 653-660. b) Robert, J. *Drugs Fut.* **1997**, *22*, 149-158.
6. Spencer, C.M.; Faulds, D. *Drugs* **1994**, *48*, 794-847.
7. Fulton, B.; Spencer, C.M. *Drugs* **1996**, *51*, 1075-1092.
8. Wills, P.; Phung-Ba, V.; Warnery, A.; Lechardeur, D.; Raissi, S.; Hidalgo, I.J.; Schermann, D. *Biochem. Pharm.* **1994**, 48, 1528-1530. Non-P-gl-mediated mechanisms of resistance to paclitaxel are also known: Parekc, H.; Wiesen K.; Simpkins, H. *Biochem. Pharmacol.* **1997**, *53*, 461-470.
9. a) Kobayashi, J.; Hosoyama, H.; Wang, X.-X.; Shigemori, H.; Koiso, Y.; Iwasaki, S.; Sasaki, T.; Naito, M.; Tsuro, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 393. b) Ojima, I.; Bounaud, P.-Y.; Takeuchi, C.; Pera, P.; Bernacki, R.J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 189-194.
10. Liang, J.-Y.; Min, Z.-D-; Niwa, M. *Acta Chim. Sin.* **1988**, *46*, 1053-1055.

11. Alloatti, G.; Penna, C.; Levi, R.C.; Gallo, M.P.; Appendino, G.; Fenoglio, I. *Life Sci.* **1996**, *58*, 845-852.
12. Bourgignon, J.-J. In *The Practice of Medicinal Chemistry*, Wermuth, C.G., Ed.; Academic Press, 1996, 261-293.
13. For reviews, see: (a) Chen, S.-H.; Farina, V. In *The Chemistry and Pharmacology of Taxol® and Related Compounds*; Farina, V., Ed.; Elsevier, 1995, pp.165-253. (b) Georg, G.I.; Boge, T.C.; Cheruvallath, Z.S.; Clowers, J.S.; Harriman, G.C.B.; Hepperle, M.; Park, H. in *Taxol: Science and Applications*; Suffness, M., Ed.; CRC, Boca Raton, 1995, pp. 317-375.
14. Ojima, I.; Slater, J.C.; Michaud, E.; Kuduk, S.D.; Bounaoud, P.-Y.; Vrignaud, P.; Bissery, M.C.; Veith, J.M.; Pera, P.; Bernacki, R.J. *J. Med. Chem.* **1996**, *39*, 3889-3896.
15. a) Isolation of **4** from the European yew: Denis, J.-N.; Greene, A.E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917-5919. b) Isolation of **5** from *T. x media* Rehd.: Fenoglio, I.; Nano, G.M.; Vander Velde, D.G.; Appendino, G. *Tetrahedron Lett.* **1996**, *37*, 3203-3206.
16. Paclitaxel itself could not be directly employed for the synthesis of **3a**, since its 2'-protected- and 2',7-diprotected (TES, Cbz) derivatives could not be selectively deacetylated at C-10.
17. The diol **9c** was unreactive toward succinic anhydride. No reaction took also place when 7,10-diTES-10-deacetylbaccatin III was treated with this reagent.
18. Marder-Karsenti, R.; Dubois, J.; Bricard, L.; Guénard, D.; Guéritte-Voegelein, F. *J. Org. Chem.* **1997**, *62*, 6631-6637.
19. a) Wiegerinck, P.H.G.; Fluks, L.; Hammink, J.B.; Mulders, S.J.E.; de Groot, F.M.H.; van Rozendaal, H.L.M.; Scheeren, H.W. *J. Org. Chem.* **1996**, *61*, 7092-7100. b) Poujol, H.; Mourabit, A.A.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1997**, *53*, 12575-1294.
20. The silylation or the **4** requires a large excess (20 mol. equiv.) of TES-Cl when carried out in pyridine,[15a] but can be efficiently carried out in DMF with only 1.1 equivalents of TES-Cl and imidazole.
21. Guéritte-Voegelein, F.; Sénilh, V.; David, B.; Guénard, D.; Potier, P. *Tetrahedron* **1986**, *42*, 4451-4460.
22. Stoemer, D.; Caron, S.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9115-9125.
23. a) ZiChen, S.-H.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805-2828. b) Johnson, R.A.; Nidy, E.G.; Dobrowolski, P.J.; Gebhard, I.; Qualls, S.J.; Wicnienski, N.A.; Kelly, R.C. *Tetrahedron Lett.* **1994**, *35*, 7893-7896. c): Zheng, Q.Y.; Darbie, L.G.; Cheng, X.; Murray, C.K. *Tetrahedron Lett.* **1995**, *36*, 2001-2004.
24. Appendino, G.; Cravotto, G.; Enriù, R.; Gariboldi, P.; Barboni, L.; Torregiani, E.; Gabetta, B.; Zini, G.; Bombardelli, E. *J. Nat. Prod.* **1994**, *57*, 607-613.
25. Chattopadhyay, S.K.; Sharma, R.P. *Phytochemistry* **1995**, *39*, 935-936.
26. Ettouati, L.; Ahond, A.; Convert, O. Laurent, D.; Poupat, C.; Potier, P. *Bull. Soc. Chim. Fr.* **1988**, 749-755.
27. See for instance: Datta, A.; Jayasinghe, L.R.; Georg, G.I. *J. Org. Chem.* **1994**, *59*, 4689-4690.
28. Bathini, Y.; Micetich, R.G.; Daneshtalab, M. *Synth. Commun.* **1994**, *24*, 1513-1517. This selective removal of α,β-unsaturated esters has also been extensively used in the chemistry of zaragozic acids.[22]
29. Only the less hindered 7-TES group could be selectively removed with 1 mol. equiv. TBAF.
30. For a review on the synthesis of the side chain of antitumour taxoids, see: Kant, J. In *The Chemistry and Pharmacology of Taxol® and Related Compounds*; Farina, V., Ed.; Elsevier, 1995, pp.255-300.
31. Discrepancies of this type were first reported for a 11(15→1)*abeo* analogue of paclitaxel (Samaranayake, G.; Magri, N.F.; Jitrangsri, C.; Kingston, D.G.I. *J. Org. Chem.* **1991**, *56*, 5114-5119). Synthetic paclitaxel analogues which improved tubulin affinity but a remarkably reduced cytotoxicity have been recently reported (Kalr, U.; Graf, H.; Schenk., O.; Röhr, B.; Schulz, H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1397-1402).
32. These assays were carried out according to: All, S.M.; Hoemann, M.Z.; Aubé, J.; Mitscher, L.A.; Georg, G.I.; McCall, R.; Jayasinghe, L.R. *J. Med. Chem.* **1995**, *38*, 2821-2828.