genated as for **22**, affording a mixture of components: yield 76.5 mg, from which **5** was isolated via chromatotron with use of ethyl acetate/hexane (4:1); total yield of **5** from **20b**, 43.5 mg, 42%; mp 219-220 °C; ^1H NMR ($CDCl_3$) δ 6.75 (1 H, s, H7), 6.5 (1 H, s, H4), 6.31 (2 H, s, H2′, 6′), 6.00 (2 H, AB q, OCH_2O), 5.48 (1 H, s, ArOH), 4.74 (1 H, d, H3), 4.37 (2 H, AB q, CH_2OCO), 3.87 (2 H, br d, CH_2OH), 3.82 (6 H, s, $OCH_3 \times 2$), 3.57 (1 H, d, H2), 1.81 (1 H, br t, OH); HRMS (FAB/HRP), calcd for $C_{21}H_{20}O_8$ 400.1156, found 400.1162. Anal. ($C_{21}H_{20}O_8$) C, H; C: calcd, 62.98; found, 61.04.

Biological Assay. Cells were grown in RPMI 1640 supplemented with 10% fetal calf serum. Test compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted first with Earle's Balanced Salt Solution, followed by culture medium, to twice the highest concentration of compound to be tested. From this concentrated stock, 2-fold serial dilutions were prepared in 96-well microtiter trays. Each concentration was tested in triplicate and compared to triplicate drug-free controls. A 100-μL aliquot of cells (2.5×10^3 cells) was added to the wells of the microtiter plate containing 100 μL of growth medium with or without test drugs. Plates were incubated for 72 h at 37 °C in a humidified atmosphere containing 5% CO_2. After 72 h, 20 μL of 5 mg/mL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added, and cells were incubated for 90 min to allow reduction of the formasan by the surviving cells. Following washing and solubilization by DMSO, absorbance of each well was measured spectrophotometrically at 570 nm. The IC_{50} is determined as the concentration of compound tested required to reduce the absorbance to 50% of non-drug-treated control values.

Acknowledgment. We are grateful to Dr. R. Stephens in the Analytical division for helpful NOE analysis on several of our compounds and also thank Dr. M. Bures of CAMD division for molecular modeling analyses.

Supplementary Material Available: Microanalysis and mass spectra for several compounds mentioned in the text (31 pages). Ordering information is given on any current masthead page.

Relationships between the Structure of Taxol Analogues and Their Antimitotic Activity[§]

Françoise Guéritte-Voegelein,*[,†] Daniel Guénard,[†] François Lavelle,[‡] Marie-Thérèse Le Goff,[†] Lydie Mangatal,[†] and Pierre Potier[†]

Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France, and Centre de Recherches de Vitry, Rhône-Poulenc Santé, 94403 Vitry-sur-Seine, France. *Received April 2, 1990*

A variety of synthetic analogues of taxol, a naturally occurring antitumor diterpene, were examined for their potency to inhibit microtubule disassembly. For some of the compounds, the in vitro cytotoxic properties showed a good correlation with the tubulin assay. This structure-activity relationship study shows that inhibition of microtubule disassembly is quite sensitive to the configuration at C-2′ and C-3′. A correlation between the conformation of the side chain at C-13 and the activity is suggested. Of all the compounds examined, one of the most potent in inhibiting microtubule disassembly and in inhibiting murine P388 leukemic cells, *N*-debenzoyl-*N*-*tert*-(butoxycarbonyl)-10-deacetyltaxol, named taxotere, was selected for evaluation as a potential anticancer agent.

Several antitumor drugs prevent the formation of the mitotic spindle during cell division by interfering with the tubulin-microtubules system. Among the different classes of natural "mitotic spindle poisons", the anticancer diterpene taxol[1] promotes the assembly of microtubules and inhibits the disassembly process of microtubules to tubulin[2,3] in contrast to the vinblastine and colchicine type compounds which prevent microtubule assembly. Among natural substances, relationships between structure and microtubule assembly in vitro have been reported mostly for vinblastine,[4] colchicine,[5] maytansine,[6] podophyllotoxin,[7] and steganacine.[8] A good correlation between the inhibition of tubulin assembly and cytotoxicity has been shown for some of these compounds. In the vinblastine series, a new hemisynthetic "Vinca alkaloid", 5′-noranhydrovinblastine or Navelbine[9] was selected by using this in vitro assay as a possible useful chemotherapeutic agent and this compound is now used in clinics.[10]

In the taxol series, investigation of the structure-activity relationships has been limited because of the poor availability of taxol (**1**) from natural sources (only 50-150 mg/kg of dried trunk bark can be isolated from several species of yew (genus Taxus, family Taxaceae)[1,11]). However, some closely related taxol congeners, mostly

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[§] Dedicated to Professor G. B. Marini-Bettolo on the occasion of his 75th anniversary.

[†] Centre National de la Recherche Scientifique.

[‡] Centre de Recherches de Vitry.

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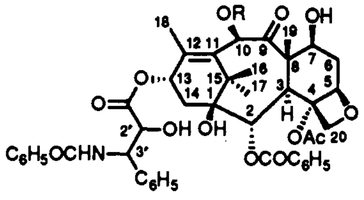
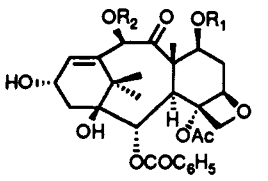
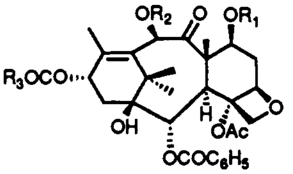
Table I. Structures of Taxol Analogues and Their Inhibition of Pig Brain Microtubule Disassembly[a]



1 (2'R,3'S): R = Ac
14a (2'R,3'S): R = H



2a: $R_1 = R_2 = H$
3a: $R_1 = H$, $R_2 = Ac$
2b: $R_1 = R_2 = COCH_2CCl_2$
3b: $R_1 = COOCH_2CCl_3$, $R_2 = Ac$



compd	ref	R_1	R_2	R_3	ID_{50}/ID_{50} (taxol)[b]
4	20b, 21	H	H	$CH{=}CHC_6H_6$	23
5	20b	H	$COCH_3$	$CH{=}CHCH_3$	100
7[c]	20b	H	H	$CH(OH)CH(OH)C_6H_6$	3
8[c]	20b	H	$COCH_3$	$CH(OH)CH(OH)CH_3$	60
11a	20, 21	$CO_2CH_2CCl_3$	$CO_2CH_2CCl_3$	$CH{=}CHC_6H_6$	1000
11b	20, 21	$CO_2CH_2CCl_3$	$COCH_3$	$CH{=}CHC_6H_6$	-

[a] The isolation of tubulin from pig brain and inhibition studies were carried out as previously described.[13] [b] ID_{50} is the concentration of drugs leading to a 50% inhibition of the rate of microtubule disassembly. The ratio ID_{50}/ID_{50} (taxol) gives the activity with regard to taxol itself (taxol: ID_{50} (μM) = 0.4). [c] Threo compounds 2'*R*,3'*R* + 2'*S*,3'*S*.

acylated at C-2' and/or C-7,[12-16] have been prepared as have water-soluble taxol derivatives, thereby showing that esters at C-2' can serve as prodrugs of taxol.[16]

Although previous studies have mostly highlighted the importance of the side chain in the 13-position for the in vitro disassembly[13]–assembly[14] process and for the cytotoxic activity,[1,14] we were interested in studying in more details the effects of structural and/or configurational modifications at carbons 2' and 3' of the side chain and carbons 7 and 10 of the taxane skeleton, on the biological activity.

To overcome the serious problems posed by the poor availability of taxol (**1**) and its derivatives, we have used simpler natural taxane-type compounds as "chemical precursors" to synthesize more complex taxol-like products. In this way, 10-deacetylbaccatin III (**2a**), easily extracted from the yew leaves[17,13b] and baccatin III (**3a**), isolated from the heartwood[18] or prepared from **2a**,[19] can be used as starting materials for the preparation of taxol and derivatives. Recently, we reported two partial syntheses of taxol (**1**) and structural analogues from **2a** and **3a**. One approach relies on the double bond functionalization of cinnamoyl derivatives of taxane,[20,21] the other makes use of the direct esterification of a taxol-like side chain on 10-deacetylbaccatin III.[19,21c]

Using these two synthetic approaches, we have been able to prepare a number of new taxol-like substances and consequently to further study the structure–activity relationships in this series. The potential antimitotic activities of these new compounds have been investigated by using the in vitro tubulin assay. For some of the compounds, the in vitro cytotoxic properties were also determined.

Chemistry

Structures of compounds, literature references concerning their preparation together with their activity on tubulin are given in Tables I and II.

Esterification of cinnamic, crotonic, and 3-phenylpropionic acids with compounds **2b** or **3b**, followed by

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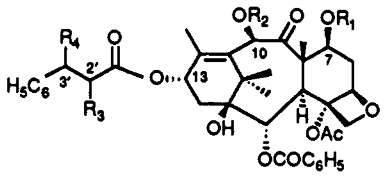
Table II. Inhibition of Pig Brain Microtubule Disassembly by Taxol Analogues at 4 °C[a]



compd	ref	R_1	R_2	R_3	R_4	ID_{50}/ID_{50}(taxol)
6		H	H	H	H	17
9a (2′*R*)		H	H	OH	H	4.5
9b (2′*S*)		H	H	OH	H	3.5
10a (3′*S* or 3′*R*)		H	H	H	$NHCO_2tBu$	2.3
10b (3′*R* or 3′*S*)		H	H	H	$NHCO_2tBu$	4.1
12a (2′*R*,3′*S*)	20a	H	H	OH	NHTs	5
12b (2′*S*,3′*R*)	20a	H	H	OH	NHTs	-
12c (2′*R*,3′*S*)	20a	H	H	NHTs	OH	15
12d (2′*S*,3′*R*)	20a	H	H	NHTs	OH	-
13a (2′*R*,3′*S*)	21	H	H	OH	$NHCO_2tBu$	0.5
13b (2′*S*,3′*R*)	21	H	H	OH	$NHCO_2tBu$	30
13c (2′*R*,3′*S*)	21	H	H	$NHCO_2tBu$	OH	10
13d (2′*S*,3′*R*)	21	H	H	$NHCO_2tBu$	OH	160
13e[a]		H	H	OH	$NHCO_2tBu$	1.8
13f[a]		H	H	OH	$NHCO_2tBu$	4.3
14a (2′*R*,3′*S*)	21	H	H	OH	NHCOPh	1.3
14b (2′*S*,3′*R*)	21	H	H	OH	NHCOPh	4
14c (2′*R*,3′*S*)	21	H	H	NHCOPh	OH	10
14d (2′*S*,3′*R*)	21	H	H	NHCOPh	OH	170
14e[a]		H	H	OH	NHCOPh	1.3
14f[a]		H	H	OH	NHCOPh	1.3
15 (2′*R*,3′*S*)	21*c*	H	H	OH	NH_2	-
16a (2′*R*,3′*S*)	21	H	$COCH_3$	OH	$NHCO_2tBu$	0.5
16b (2′*S*,3′*R*)	21	H	$COCH_3$	OH	$NHCO_2tBu$	30
16c (2′*R*,3′*S*)	21	H	$COCH_3$	$NHCO_2tBu$	OH	10
16d (2′*S*,3′*R*)	21	H	$COCH_3$	$NHCO_2tBu$	OH	108
1a (2′*R*,3′*S*)	21	H	$COCH_3$	OH	NHCOPh	1
17b (2′*S*,3′*R*)	21	H	$COCH_3$	OH	NHCOPh	4.5
17c (2′*R*,3′*S*)	21	H	$COCH_3$	NHCOPh	OH	10
17d (2′*S*,3′*R*)	21	H	$COCH_3$	NHCOPh	OH	110
18 (2′*R*,3′*S*)		H	$COCH_3$	OH	NH_2	44
19a[a]		H	H	OH	NH_2	30
19b[a]		H	H	OH	NH_2	30
20 (2′*R*,3′*S*)		H	H	OH	$NHCO(CH_2)_3CO_2H$	1
21 (2′*R*,3′*S*)		H	H	OH	$NHCO(C_6H_4)SO_3H$	5.5
22 (2′*R*,3′*S*)		$CO(CH_2)_3CO_2H$	$COCH_3$	OH	NHCOPh	1
23 (2′*R*,3′*S*)		$CO(CH_2)_3CO_2H$	$CO(CH_2)_3CO_2H$	OH	$NHCO_2tBu$	2
24 (2′*R*,3′*S*)		$COCH_2NH_2$	$COCH_2NH_2$	OH	$NHCO_2tBu$	1.2
25 (2′*R*,3′*S*)		$COCH(NH_2)CH_2C_6H_5$	H	OH	$NHCO_2tBu$	1

[a] Erythro compounds 2′*R*,3′*R* or 2′*S*,3′*S*.

deprotection, led, respectively, to esters **4**, **5**, and **6**. 2′,3′-Dihydroxy derivatives **7** and **8** were easily obtained from esters **4** and **5**. Coupling of racemic *O*-(1-ethoxyethyl)-3-phenyllactic acid with **2b** led, after deprotection, to a mixture of esters **9a** and **9b** in a 82/18 ratio showing that an asymmetric induction in favor of the 2′*R* isomer took place during esterification.[21c] Under the same conditions, coupling of L-*O*-(1-ethoxyethyl)-3-phenyllactic acid yielded compounds **9a** and **9b** in a 60/40 ratio, showing that epimerization at C-2′ also occurred during esterification. Racemic *N*-*tert*-(butoxycarbonyl)-3-aminopropionic acid yielded the C-3′ functionalized derivatives **10a** and **10b** after removal of the protecting groups.

Application of the Sharpless vicinal oxyamination reaction[22] to cinnamate derivatives such as **11a** using chloramine T or *tert*-butyl-*N*-chloro-*N*-argentocarbamate followed by deprotection of the C-7 and C-10 hydroxyl groups afforded, respectively, a mixture of threo hydroxy *p*-toluenesulfonamide isomers **12a–d** and threo hydroxycarbamates **13a–d**. Compound **13a** was correlated with 10-deacetyltaxol (**14a**) while 2′-epi,3′-epi, 10-deacetyltaxol **14b** was obtained from **13b**. In the same way regioisomers **14c** and **14d** were prepared from the oxyaminated compounds **13c** and **13d**. Amino alcohol **15** was prepared from hydroxycarbamate **13a** after deprotection of the amino group. The same reactions were applied to the cinnamate derivative of baccatin III **11b** to provide oxycarbamates **16a–d**, *N*-benzoyl-3-phenylisoserine isomers **1** (taxol), **17b–d**, and amino alcohol **18**. Taxol (**1**), 10-deacetyltaxol (**14a**), and hydroxycarbamates were also obtained by direct esterification.

Erythro isomers **13e,f** and **14e,f** were prepared from cinnamate ester **11a**. Epoxidation of **11a** yielded a mixture of two diastereoisomers which were treated with sodium azide. After reduction and deprotection with zinc dust in acetic acid, two amino alcohols **19a** and **19b** were obtained. Treatment of compounds **19a** and **19b** with benzoyl chloride or di-*tert*-butyl dicarbonate yielded, respectively, the erythro isomers of 10-deacetyltaxol **14e,f** and the erythro hydroxycarbamates **13e,f**. Compounds **20** and **21** were obtained by condensing the appropriate anhydride with the amino alcohol **15**. Esterification of taxol (**1**) and compound **13a** with glutaric anhydride led, respectively,

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[22] Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305–2307.

to products **22** and **23**. Finally, acylation of **13a** with suitably protected amino acids such as glycine and phenylalanine gave compounds **24** and **25**. All new compounds were principally characterized by NMR and MS.

Results and Discussion

Different in vitro assays have been used to determine the activity of taxol congeners on tubulin (promotion of microtubule assembly in the absence of GTP,[14] inhibition of binding of tritiated taxol to microtubules,[14] and inhibition of microtubule disassembly at 4 °C[13,21c]). Concerning the drug–tubulin interaction, the two procedures involving inhibition of microtubule assembly or inhibition of microtubule disassembly gave the same results. However, because of the rapidity of the latter method (5 min per sample), all the compounds described in Tables I and II were assayed for their ability to inhibit the disassembly process of microtubules at 4 °C.

Previous structure–activity studies have shown that (a) the side chain at C-13 is necessary for a good drug–receptor interaction,[1,13,14] and (b) modification of substituents at C-10 and/or C-7 such as replacement of a hydroxyl group by an acyl or xylosyl group has little effect on the activity.[12b,13,14]

With respect to structural modifications on the side chain, structural modifications have mainly been made at C-2′ and have shown that acylation of this carbon results in a loss of activity in the tubulin assay[12b,13] but not in the cytotoxicity assay. These observations recently led to the preparation of water soluble derivatives of taxol.[16]

The ID_{50} values obtained in this study (Tables I and II) are in good agreement with those previously described and also provide much more information concerning the specific influence of configuration and structural modifications of the side chain on the activity of taxol-type molecules: (a) Replacement of the C-10 acetoxy group with a hydroxyl group did not lead to loss of potency in different series of taxane derivatives (Compare series **13a–d** with **16a–b**, and **14a–d** and **1,17b–d**). (b) Replacement of a 3′-phenyl group with a methyl group resulted in a major loss of activity. Thus the 2′,3′-dihydroxycrotonyl ester **8** is 20-fold less potent than its cinnamoyl analogue **7**. (c) Branching of large groups such as [(trichloroethyl)oxy]carbonyl at C-7 and/or C-10 (**11a,b**) resulted in a loss of activity whereas compounds with polar substituents such as xylosyl,[13] glutaryl (**22,23**), or aminoacyl (**24,25**) are as potent as taxol in the tubulin assay. (d) No loss of potency was observed for compounds having different kinds of hydrophobic substituents on the amido group at C-3′. Thus, replacement of the phenyl group in taxol with tiglyl (cephalomanine),[14] tosyl (**12a**), or hexanoyl groups[13b] gave compounds as active as taxol. Moreover, the *tert*-butyloxycarbonyl compounds (**13a,16a**) were shown to be the most potent inhibitors of microtubule disassembly so far prepared by us. In contrast, compounds having a free amino group at C-3′ are less potent than their *N*-amido analogues (compare **18** and taxol (**1**)).

More interesting are the results obtained with compounds having different configurations at C-2′ and/or C-3′. Both threo ((2′*R*,3′*S*) **13a,14a,16a** and **1**; (2′*S*,3′*R*) **13b,14b,16b**, and **17b**) and erythro ((2′*R*,3′*R*; 2′*S*,3′*S*) **13e**, **13f**, **14e**, and **14f**) diastereoisomers were assayed, showing that inhibition of microtubule disassembly is quite sensitive to these two configurations. Thus in all cases, the 2′*R*,3′*S* diastereoisomer (natural configuration), was found to be the most potent. If this is true, then one question remains unanswered with regard to our observations: do the differences in activity seen among the various analogues synthesized arise from the presence or absence of particular functionalities per se or are these the result of differences in the side chain conformations imposed by these modifications, resulting in a favorable or unfavorable fit to the activity site?

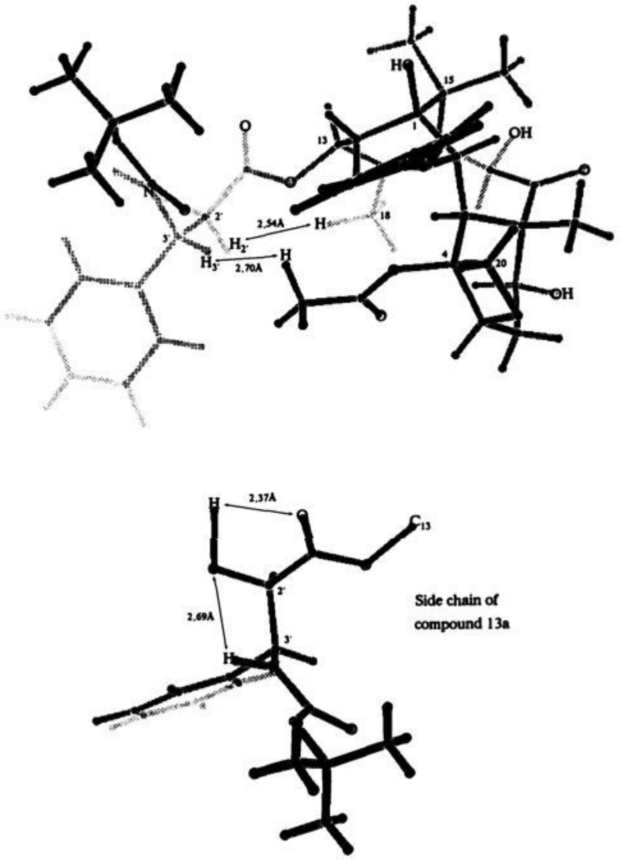

Figure 1. Three-dimensional view of compound **13a**.

The conformation of taxol-like compounds is imposed by the three-ring system having the highly strained eight-membered ring B cis-fused to ring A and trans-fused to ring C and, in addition, a bridgehead double bond, a hindering geminal dimethyl group, and a planar oxetane ring. This particular structure gives rise to a "caged-type conformation". A recent X ray analysis of the 2′*R*,3′*S* compound **13a**,[24] giving interatomic bond lengths, showed that the side chain adopts a particular conformation due to intramolecular hydrogen bonds and repulsive interaction between the substituents at carbons 2′ and 3′ and those of the taxane skeleton (Figure 1). Moreover, recent ROESY experiments[23] with threo isomers showed that compounds having a 2′*R*,3′*S* configuration exhibit a number of NOE's, indicating interactions between C-3′H and the C-4 acetyl group and between C-2′H and C-18H_3. In contrast, the 2′*S*,3′*R* diastereoisomers are characterized by NOE involving C-2′H/C-4 acetyl group and C-3′H/C-18H_3. Though these observations can also be predicted by molecular modeling, they need to be confirmed by other NMR experiments under different conditions of temperature and solvent. Configurations at C-2′ and/or C-3′ of compounds **10a,b** and erythro isomers **13e,f** and **14e,f** are still unknown

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Table III. Cytotoxicity of Taxol Analogues

compd	P388[a] IC_{50}	IC_{50}/IC_{50}(**13a**)[b]	ID_{50}/ID_{50}(**13a**)[c]
taxol (**1**)	0.27	2	2
taxotere (**13a**)	0.13	1	1
13b	>10	>77	60
13c	4	31	20
16a	0.17	1.3	1
17b	7	54	9
17c	6	46	20
21	>4	>31	11
24	0.19	1.5	1.4
25	0.12	1	2

[a] Murine P388 leukemic cells were obtained from the tumor bank of the National Cancer Institute. P388 cells were grown at 37 °C as suspensions in RPMI 1640 medium containing 10 μM 2-mercaptoethanol, 2 mM L-glutamine, 200 U/mL penicillin, 200 μg/mL streptomycin, and supplemented with 10% (v/v) fetal calf serum. Exponentially growing P388 cells suspended in complete medium were seeded in tubes at 10^5 cells/mL. the compounds were added at different concentrations on day 0 (3 tubes/concentration). Cells were allowed to grow for 3 or 4 days at 37 °C under 5% CO_2. Final cell numbers were measured by using a Coulter counter. The results were expressed as the concentration (μg/mL) which inhibits 50% of the cell proliferation (IC_{50}). The IC_{50} were estimated by regression analysis concentration–response data. [b] Cytotoxicity of drugs in comparison to compound 13a. [c] ID_{50} for disassembly of microtubule: see Table II. The ratio ID_{50}/ID_{50}(13a) gives the activity with regard to 13a itself(13a: ID_{50} (μM) = 0.2).

but some information can also be provided by ROESY experiments.[23] These studies could show the direct influence of the side-chain conformation on the inhibition of microtubule disassembly. It is already interesting to note that the gain in activity, in going from compound **6**, having no substituent at C-2′ and C-3′, to compound **13a**, bearing hydroxyl and hydroxycarbamate groups at C-2′ and C-3′, may be the product of the separate contributions brought by the substituents at carbons 2′ (compound **9**) and 3′ (compound **10**).

Other structural features such as the benzoate group at C-2 or the oxetane ring are probably essential for exhibiting a good activity. Indeed, products lacking these groups, though identified by others in yew extracts (i.e. taxanes with C4–C20 double bond),[26] were not isolated by using the tubulin bioassay guided fractionation.[11b,13b]

Previous results have shown that taxanes lacking the side chain at C-13 have the same affinity as taxol for Physarum tubulin.[13a] This may be the result of a point mutation on the peptide chain in the neighborhood of the binding site, allowing a specific noncovalent bond between the side chain and mammalian tubulin; moreover, the side chain by itself is inactive and has no effect on the binding of taxol or its analogues. These two observations allow us to imagine the binding process to occur as follows: (a) the taxane skeleton is recognized and binds to its site on tubulin, and (b) the drug–tubulin bond is stabilized by the specific interaction of the side chain, a situation which is probably not restricted to the field of taxane derivatives.

Concerning the in vitro cytotoxic activity, a generally good correlation with the tubulin assay may be noted: compounds such as **1**, **13a**, **16a**, **24**, and **25** have the ability to inhibit both cell growth and disassembly of microtubules (Table III). However, the C-2′ esters, less active in disassembling microtubules, are promptly hydrolysed in intra- or extracellular media, resulting in good cytotoxic activity.[12b,13,14,16]

Some attempts have been made to solubilize taxol derivatives in water, but the conditions used to obtain solubilization are incompatible with the stability of the final products (i.e. acidic or basic medium). The diglycine derivative **24**, soluble in water as its hydrochloride salt, is a potent inhibitor of microtubule disassembly and in vitro cellular proliferation but has no effect in vivo on murine leukemia.[27] The other amino acid or acid derivatives are good inhibitors of disassembly but they are only partially soluble in an ethanol–water mixture.

Conclusion

About 40 synthetic taxane-type compounds have been tested as potential inhibitors of disassembly of mammalian tubulin. The tubulin assay has proven to be a convenient method for studying structure–activity relationships, particularly in regard to the conformations of the "active" molecules. Correlation with activity against P388 murine leukemia shows that the tubulin assay is also a very efficient tool for a preliminary evaluation of new active products in the taxane family.

Of all the compounds examined in Tables I and II, one of the most potent, *N*-debenzoyl-*N*-(*tert*-butoxycarbonyl)-10-deacetyltaxol (**13a**) named taxotere, was selected for evaluation as a potential anticancer agent and so far has shown excellent antitumor activity against several models of grafted murine tumors.[25] Moreover taxotere (**13a**) showed a better solubility in excipient system (polysorbate 80/ethanol, 1:1) than the two others most active compounds taxol (**1**) and *N*-debenzoyl-*N*-(*tert*-butoxycarbonyl)taxol (**16a**).

Experimental Section

The purity of the samples was checked by chromatographic methods (HPLC and TLC) and careful analysis of NMR spectra. Melting points were taken on a Kofler hot bench and are uncorrected. Optical rotations (*c*, cg/mL) were determined on a Perkin-Elmer 141 MC polarimeter using a 10 cm path length cell. Infrared spectra (cm^{-1}, $CHCl_3$ or Nujol) were recorded on a Perkin-Elmer 257 spectrophotometer. ^1H and ^{13}C NMR were recorded on a Bruker AM 200 or AM 400 spectrometer. Chemical shifts are in ppm relative to TMS (0.00). Multiplicities are indicated in parentheses with coupling constants expressed in hertz. Mass spectra were recorded on an AEI MS9 (CI) or on a Kratos MS80 (FAB). The 10-deacetylbaccatin III used in this study was isolated from the leaves of the yew tree *Taxus baccata L.*

General procedures for esterification of 7,10-bis[[(2,2,2-trichloroethyl)oxy]carbonyl]-10-deacetylbaccatin III (**2b**) with different acids and for the deprotection of C-7 and/or C-10 troc group are described in refs 20b and 21.

3-(Phenylpropionyl)-10-deacetylbaccatin III (6). Esterification of **2b** (500 mg, 0.56 mmol) with 3-phenylpropionic acid (330 mg, 2.2 mmol) gave 93% of the corresponding ester which was deprotected to yield compound **6** (70%): MS-CI *m/z* 677 (MH^+); ^1H NMR ($CDCl_3$) δ 1.11 (s, C-17H_3), 1.21 (s, C-16H_3), 1.74 (s, C-19H_3), 1.82 (s, C-18H_3), 2.20 (s, $OCOCH_3$), 2.74 (m, C-2′H_2), 3.05 (m, C-3′H_2), 3.91 (d, J = 7, C-3H_2), 4.18 and 4.31 (s d, J = 9, C-20H_2), 4.23 (m, C-7H), 4.95 (d, J = 9, C-5H), 5.20 (s, C-10H), 5.67 (d, J = 7, C-2H), 6.17 (t, J = 8, C-13H), 7.25 and 7.33 (C_6H_5), 7.50, 7.62, and 8.06 ($OCOC_6H_5$).

Compounds 9a and 9b. *O*-(1-Ethoxyethyl)-3-phenyllactic acid was prepared by classical procedures from 3-phenyllactic acid (first, protection of the carboxyl group as a benzyl ester (MS-EI *m/z* 256 ($M^{\cdot+}$)), second, protection of the hydroxyl group as ethoxyethyl ether (MS-EI *m/z* 328 ($M^{\cdot+}$)), third, cleavage of the benzyl ester by hydrogenolysis).

Esterification of **2b** (669 mg, 0.75 mmol) with DL-*O*-(1-ethoxyethyl)-3-phenyllactic acid (714 mg, 3 mmol) gave 98% of a mixture of two esters which were deprotected to give **9a** (56%) and **9b** (12%). Diastereoisomers were separated by silica gel column chromatography using hexane/ethyl acetate (2:8) as

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(27) Lavelle, F. Personal communication.

eluant. Under the same conditions, esterification of **2b** with L-*O*-(1-ethoxyethyl)-3-phenyllactic acid gave after deprotection a 60/40 mixture of **9a** and **9b**.

9a: $[\alpha]^{22}_{\mathrm{D}} = -57°$ (c = 1.00, MeOH); MS-FAB$^+$ m/z 693 (MH$^+$); ^{1}H NMR (CDCl$_3$) δ 1.11 (s, C-17H$_3$), 1.22 (s, C-16H$_3$), 1.72 and 1.73 (2s, C-19H$_3$ and C-18H$_3$), 1.82 (m, C-6H), 2.12 (m, C-14H$_2$), 2.21 (s, OCOCH$_3$), 2.55 (m, C-6H), 3.12 (m, C-3′H$_2$), 3.85 (d, J = 7, C-3H), 4.18 (m, C-7H), 4.15 and 4.27 (2 d, J = 8, C-20H$_2$), 4.50 (m, C-2′H), 4.92 (d, J = 9, C-5H), 5.17 (s, C-10H), 5.62 (d, J = 7, C-2H), 6.11 (t, J = 9, C-13H), 7.18, 7.25, 7.30 (C$_6$H$_5$), 7.48, 7.60, and 8.05 (OCOC$_6$H$_5$).

9b: $[\alpha]^{22}_{\mathrm{D}} -37°$ (c = 1.00, MeOH); MS-FAB$^+$ m/z 693 (MH$^+$); ^{1}H NMR (CDCl$_3$ + CD$_3$OD) δ 1.11 (s, C-17H$_3$), 1.22 (s, C-16H$_3$), 1.75 (s, C-19H$_3$), 1.84 (s, C-18H$_3$), 1.92 (m, C-6H), 2.15 (dd, J = 15 and 9, C-14H), 2.26 (s, OCOCH$_3$), 2.28 (m, C-14H), 2.53 (m, C-6H), 3.03 and 3.24 (2 dd, C-3′H$_2$), 3.84 (d, J = 7, C-3H), 4.15 (m, C-7H), 4.18 and 4.28 (2 d, J = 9, C-20H$_2$), 4.47 (dd, J = 8 and 4.5, C-2′H), 4.96 (d, J = 9, C-5H), 5.20 (s, C-10H), 5.66 (d, J = 7, C-2H), 6.17 (t, J = 9, C-13H), 7.25 (C$_6$H$_5$), 7.45, 7.60, and 8.00 (OCOC$_6$H$_5$).

Compounds 10a and 10b. DL-3-[(*tert*-Butoxycarbonyl)-amino]-3-phenylpropionic acid was prepared in 86% from DL-3-amino-3-phenylpropionic acid.[21c] Esterification of this acid (999 mg, 3.77 mmol) with **2b** (838 mg, 0.94 mmol) gave a mixture of two diastereoisomeric esters in 98% yield. Removal of the protecting groups at C-7 and C-10 provided diastereoisomers **10a** (60%) and **10b** (40%) after purification by HPLC (RP-18; mobile phase, H$_2$O/MeOH 36:64; flow rate; 2 mL min^{-1}).

10a: mp 160 °C (MeOH); $[\alpha]^{22}_{\mathrm{D}} = -18°$ (c = 1.10, CHCl$_3$); MS-FAB$^+$ m/z 792 (MH$^+$), 774, 692, 527, 509, 266; ^{1}H NMR (CDCl$_3$) δ 1.08 (s, C-17H$_3$), 1.15 (s, C-16H$_3$), 1.42 (s, tBu), 1.72 (C-18H$_3$ and C-19H$_3$), 1.82 (m, C-6H), 2.13 (m, C-14H$_2$), 2.28 (s, OCOCH$_3$), 2.56 (m, C-6H), 2.93–3.10 (m, C-2′H$_2$), 3.85 (d, J = 7, C-3H), 4.18 (m, C-7H), 4.15 and 4.25 (2 d, J = 9, C-20H$_2$), 4.94 (d, J = 9, C-5H), 5.15 (s, C-10H), 5.18 (br d, C-3′H), 5.60 (br d, NH), 5.70 (d, J = 7, C-2H), 6.05 (t, J = 8, C$_{13}$H), 7.30 (C$_6$H$_5$), 7.50, 7.60, and 8.05 (OCOC$_6$H$_5$); ^{13}C NMR (CDCl$_3$) δ9.90 (C19), 14.40 (C18), 20.40 (C17), 22.60 (CH$_3$-acetate), 26.50 (C16), 28.40 (CH$_3$-tBu), 36.00 (C14), 36.80 (C6), 41.60 (C-2′), 43.00 (C15), 46.70 (C3), 54.7 (C3′), 57.80 (C8), 70.30 (C7), 71.90 (C13), 74.60 (C10), 75.10 (C2), 76.50 (C20 and C-1), 78.80 (C-tBu), 81.20 (C4), 84.30 (C5), 126.10, 127.70, 128.70, 128.80, 130.10, 133.70 (*o*-Bz, *m*-Bz, *p*-Bz, *o*-Ph, *m*-Ph, *p*-Ph), 129.50 (C1-Bz), 135.90, 138.70 and 138.50 (C11, C12, and C1-Ph), 155.20 (C=O of carbamate), 166.90 (C=O of Bz), 169.80 (C=O of Ac), 170.60 (C1′), 211.13 (C9).

10b: mp 156 °C (MeOH); $[\alpha]^{22}_{\mathrm{D}} = -12°$ (c = 0.90, CHCl$_3$); MS-FAB$^+$ m/z 792 (MH$^+$), 774, 692, 527, 509, 266; ^{1}H NMR (CDCl$_3$) δ 1.10 (s, C-17H$_3$), 1.18 (s, C-16H$_3$), 1.43 (s, tBu), 1.73 (s, C-19H$_3$ and C-18H$_3$), 1.84 (m, C-6H), 2.08 (m, C-14H$_2$), 2.15 (s, OCOCH$_3$), 2.55 (m, C-6H), 2.80–3.10 (m, C-2′H$_2$), 3.85 (d, J = 7, C-3H), 4.20 (m, C-7H), 4.15 and 4.28 (2d, J = 9, C-20H$_2$), 4.93 (d, J = 9, C-5H), 5.10 (m, C-3′H), 5.16 (m, C-10H), 5.63 (d, J = 7, C-2H), 6.08 (t, J = 8, C$_{13}$H), 7.27–7.30 (C$_6$H$_5$), 7.50, 7.60, and 8.05 (OCOC$_6$H$_5$); ^{13}C NMR (CDCl$_3$) δ identical with **10a**.

Erythro Amino Alcohols 19a and 19b. A solution of 7,10-bis[[(2,2,2-trichloroethyl)oxy]carbonyl]-13 cinnamoyl-10 deacetylbaccatin III (**11a**) (3.9 g, 3.82 mmol) in 150 mL of dry methylene chloride was treated under argon with *m*-chloroperbenzoic acid (8.4 g, 49 mmol) and anhydrous sodium carbonate (3.4 g). The mixture was stirred at 20 °C for 22 h. After filtration through Celite the filtrate was washed with an aqueous solution of sodium bisulfite. Evaporation of the solvent and purification of the residue by column chromatography with 50% ether in hexane gave 1.92 g of diastereoisomeric epoxides (2′*R*,3′*R* + 2′*S*,3′*S*): MS-CI m/z 1039 (MH$^+$); ^{1}H NMR (CDCl$_3$) δ 1.19 (s, C-17H$_3$), 1.28 (s, C-16H$_3$), 1.88 (s, C-19H$_3$), 2.10 and 2.11 (2 s, C-18H$_3$), 2.26 and 2.33 (2 s OCOCH$_3$), 3.63 and 3.68 (2 d, J = 1, H oxirane), 3.99 (d, J = 7, C-3H), 4.19 and 4.36 (2 d, J = 9, C-20H$_2$), 4.26 (2 d, J = 1, H oxirane), 4.66 and 4.99 (2 d, J = 12) and 4.86 (s) (2CH$_2$ of the protecting groups), 4.99 (d, J = 9, C-5H), 5.64 (m, C-7H), 5.76 (d, J = 7, C-2H), 6.29 and 6.37 (2 t, J = 9, C-13H), 6.33 (s, C-10H), 7.37–8.26 (C$_6$H$_5$ and OCOC$_6$H$_5$).

To a solution of 164 mg of sodium azide and 134 mg of ammonium chloride in 25 mL of ethanol was added a solution of 1.92 g (1.85 mmol) of the diastereoisomeric epoxides in 75 mL of ethanol. The mixture was stirred under reflux for 15 h. Water (150 mL) was then added. The ethanol was removed under reduced pressure. Extraction with methylene chloride and purification of the resulting residue by column chromatography with 1% methanol in methylene chloride yielded 630 mg and 570 mg of two azido alcohols (IR 3550, 2950, 2120, 1765, 1735 cm^{-1}; MS-CI m/z 1054 (MH$^+$ − N$_2$)).

A 0.14 mmol (150 mg) sample of the first compound to elute in 10 mL acetic acid was treated with 150 mg of zinc dust and vigorously stirred under argon at 60 °C. After 1 h the mixture was filtered and the filtrate washed with ethyl acetate. The solvent was then removed under reduced pressure; the resulting residue was dissolved in ethyl acetate, and the solution was neutralized with an aqueous solution of sodium bicarbonate. The organic layer was washed with water and brine and dried (MgSO$_4$). Filtration gave 75 mg of C-7, C-10-deprotected amino alcohol **19a**. Under the same conditions, concomitant reduction of the azido group and removal of the protecting group of the second azido alcohol to elute gave compound **19b**.

19a: $[\alpha]^{22}_{\mathrm{D}} = -46°$ (c = 0.80, CH$_3$OH); MS-FAB$^+$ m/z 708 (MH$^+$), 692, 527, 509, 461, 369, 277, 182; ^{1}H NMR (CDCl$_3$–CD$_3$OD) δ 1.11 (s, C-17H$_3$), 1.19 (s, C-16H$_3$), 1.65 (s, C-19H$_3$), 1.71 (C-18H$_3$), 2.18 (s, OCOCH$_3$), 3.82 (d, J = 7, C-3H), 4.20 (m, C-7H), 4.21 and 4.32 (2 d, J = 9, C-20H$_2$), 4.38 and 4.52 (2 d, J = 4, C-2′H and C-3′H), 4.96 (d, J = 9, C-5H), 5.19 (s, C-10H), 5.64 (d, J = 7, C-2H), 6.09 (t, J = 9, C$_{13}$H), 7.39 (C$_6$H$_5$), 7.59, 7.71, and 8.16 (OCOC$_6$H$_5$).

19b: $[\alpha]^{22}_{\mathrm{D}} = -27°$ (c = 0.50, CH$_3$OH); MS-FAB$^+$ m/z 730 (MNa$^+$), 708 (MH$^+$), 527, 509, 182; ^{1}H NMR (CDCl$_3$–CD$_3$OD) δ 1.10 (s, C-17H$_3$), 1.16 (s, C-16H$_3$), 1.68 (s, C-19H$_3$), 1.72 (s, C-18H$_3$), 2.23 (s, OCOCH$_3$), 3.82 (d, J = 7, C-3H), 4.19 (m, C-7H), 4.21 and 4.31 (2d, J = 9, C-20H$_2$), 4.39 and 4.57 (2d, J = 4.5, C-2′H and C-3′H), 4.98 (d, J = 9, C-5H), 5.21 (s, C-10H), 5.65 (d, J = 7, C-2H), 6.02 (t, J = 9, C$_{13}$H), 7.39 (C$_6$H$_5$), 7.54, 7.70, and 8.09 (OCOC$_6$H$_5$).

***tert*-Butoxycarbonylation of Amino Alcohols 19a and 19b. Erythro Compounds 13e and 13f.** Amino alcohols **19a** and **19b** (60 mg, 0.085 mmol) in 5 mL of pyridine were individually treated with 20 mg of di-*tert*-butyl dicarbonate at room temperature. After 30 min, the pyridine was removed under reduced pressure. The residue was purified by TLC (CHCl$_3$/MeOH 95:5) giving, respectively, 38.4% of **13e** and 32.5% of **13f**.

13e: MS-FAB$^+$ m/z 808 (MH$^+$), 790, 752, 734, 527, 509, 226; ^{1}H NMR (CDCl$_3$) δ 1.10 (s, C-17H$_3$), 1.16 (s, C-16H$_3$), 1.43 (s, tBu), 1.76 (s, C-19H$_3$) and C-18H$_3$), 2.30 (s, OCOCH$_3$), 3.82 (d, J = 7, C-3H), 4.23 (m, C-7H), 4.14 and 4.29 (2d, J = 9, C-20H$_2$), 4.63 (1 H, d, J = 2.5, C-2′H), 4.93 (d, J = 9, C-5H), 5.16 (m, C-10H and C-3′H), 5.63 (d, J = 7, C-2H), 5.73 (d, J = 9, NH), 5.96 (t, J = 8, C$_{13}$H), 7.26–8.09 (C$_6$H$_5$ and OCOC$_6$H$_5$).

13f: MS-FAB$^+$ m/z 808 (MH$^+$), 790, 752, 734, 527, 509, 226; ^{1}H NMR (CDCl$_3$) δ 1.10 (s, C-17H$_3$), 1.16 (s, C-16H$_3$), 1.43 (s, tBu), 1.73 (s, C-19H$_3$), 1.75 (s, C-18H$_3$), 2.30 (s, OCOCH$_3$), 3.91 (d, J = 7, C-3H), 4.21 (m, C-7H), 4.21 and 4.25 (2d, J = 9, C-20H$_2$), 4.67 (1 H, d, J = 2.5, C-2′H), 4.96 (d, J = 9, C-5H), 5.18 (m, C-10H and C-3′H), 5.64 (d, J = 9, NH), 5.68 (d, J = 7, C-2H), 6.04 (t, J = 8, C$_{13}$H), 7.37–8.09 (C$_6$H$_5$ and OCOC$_6$H$_5$).

Benzoylation of Amino Alcohols 19a and 19b. Erythro Compounds 14e and 14f. Amino alcohols **19a** and **19b** (80 mg, 0.12 mmol) in 2 mL of pyridine were individually treated at 0 °C by 18 mg (0.14 mmol) of benzoyl chloride. The reaction mixture was then allowed to warm to room temperature. After being stirred for 10 min, the mixture was hydrolyzed and extracted with chloroform. Evaporation and purification of the resulting residue by preparative TLC (CHCl$_3$/MeOH 95:5) gave 82% of **14e** and **14f**, respectively.

14e: $[\alpha]^{22}_{\mathrm{D}} = -17°$ (c = 0.40, CH$_3$OH); MS-FAB$^+$ m/z 812 (MH$^+$), 527, 509, 461, 286, 268, 240, 210; ^{1}H NMR (CDCl$_3$) δ 1.12 (s, C-17H$_3$), 1.18 (s, C-16H$_3$), 1.68 (s, C-19H$_3$), 1.75 (s, C-18H$_3$), 2.39 (s, OCOCH$_3$), 3.91 (d, J = 7, C-3H), 4.26 (m, C-7H), 4.21 and 4.38 (2d, J = 8, C-20H$_2$), 4.84 (1 H, br s, C-2′H), 4.99 (d, J = 9, C-5H), 5.23 (s, C-10H), 5.71 (br d, C-2H (J = 7) and C-3′H (J = 9)), 6.09 (t, J = 9, C$_{13}$H), 7.40–8.19 (C$_6$H$_5$, OCOC$_6$H$_5$, and NHCOC$_6$H$_5$).

14f: $[\alpha]^{22}_{\mathrm{D}} = -21°$ (c = 0.40, CH$_3$OH); MS-FAB$^+$ m/z 812 (MH$^+$), 527. 509, 286, 268, 240, 210; ^{1}H NMR (CDCl$_3$) δ 1.11 (s, C-17H$_3$), 1.16 (s, C-16H$_3$), 1.62 (s, C-19H$_3$), 1.75 (s, C-18H$_3$), 2.41 (s, OCOCH$_3$), 3.91 (d, J = 7, C-3H), 4.29 (m, C-7H), 4.19 and 4.36 (2 d, J = 9, C-20H$_2$), 4.88 (1 H, d, J = 3.5, C-2′H), 4.99 (d, J = 9, C-5H), 5.23 (s, C-10H), 5.69 (d, J = 7, C-2H), 5.82 (dd, J = 9 and 3.5, C-3′H), 6.06 (t, *J* = 9, $C_{13}H$), 7.44–8.14 (C_6H_5, $OCOC_6H_5$, and $NHCOC_6H_5$).

Threo Amino Alcohol 18. β-Amino alcohol **18** was obtained after cleavage of the C-3′ BOC group with iodotrimethylsilane at 0 °C,[21c,21d] and deprotection of the C-7 and C-10 [[(trichloroethyl)oxy]carbonyl] groups of hydroxycarbamate **16a** (C-7 [[(trichloroethyl)oxy]carbonyl] protected).

18: $[\alpha]^{22}_D = -17°$ (*c* = 0.40, CH_3OH); MS-CI *m/z* 750 (MH^+), 527, 509, 491, 449, 447, 387, 369, 327, 123; ^1H NMR ($CDCl_3$) δ 1.10 (s, C-17H_3), 1.20 (s, C-16H_3), 1.55 (s, C-19H_3), 1.90 (s, C-18H_3), 2.10 (s, $OCOCH_3$ on C-10), 2.25 (s, $OCOCH_3$ on C-4), 3.65 (d, *J* = 7, C-3H), 4.10 and 4.25 (2 d, *J* = 9, C-20H_2), 4.30–4.40 (m, C-7H, C-2′H, and C-3′H), 4.90 (d, *J* = 9, C-5H), 5.60 (d, *J* = 7, C-2H), 6.00 (t, *J* = 8, $C_{13}H$), 6.25 (s, C-10H), 7.30 (C_6H_5), 7.45–8.00 ($OCOC_6H_5$).

Compound 20. To a solution of β-amino alcohol **15**[21c,d] (50 mg, 0.07 mmol) in dry pyridine (4 mL) was added 8 mg (0.07 mmol) of glutaric anhydride. The reaction mixture was stirred at room temperature for about 30 min, and then worked up by standard methods. After purification using preparative TLC (CH_2Cl_2/MeOH, 90:10), compound **20** was obtained in 80% yield.

20: $[\alpha]^{22}_D = -31°$ (*c* = 1.09, CH_3CH_2OH); MS-FAB$^+$ *m/z* 860 (M + K^+), 844 (M + Na^+), 822 (MH^+), 804, 708, 527, 509, 296; ^1H NMR ($CDCl_3/CD_3OD$) δ 1.12 (s, C-17H_3), 1.19 (s, C-16H_3), 1.73 (s, C-19H_3), 1.87 (s, C-18H_3), 2.35 (s, $OCOCH_3$), 3.83 (d, *J* = 7, C-3H), 4.20 (q, *J* = 7 and 12, C-7H), 4.21 and 4.30 (2d, *J* = 9, C-20H_2), 4.63 (d, *J* = 2.5, C-2′H), 4.94 (d, *J* = 9, C-5H), 5.22 (s, C-10H), 5.52 (d, *J* = 2.5, C-3′H), 5.67 (d, *J* = 7, C-2H), 6.15 (t, *J* = 9, $C_{13}H$), 7.36 (C_6H_5), 7.47, 7.57, 8.07 ($OCOC_6H_5$).

Compound 21. To a solution of β-amino alcohol **15** (bis-[[(trichloroethyl)oxy]carbonyl]-protected at C-7 and C-10)[21c,d] (0.2 mmol, 210 mg) in dry methylene chloride (10 mL) and pyridine (0.1 mL) was added 41 mg (0.22 mmol) of *O*-sulfobenzoic cyclic anhydride. The reaction mixture was stirred at room temperature for about 2 h. The solvent was removed under reduced pressure. Purification by preparative TLC gave 170 mg of a pure compound which was deprotected on C-7 and C-10 to give compound **21** in 85% yield.

21: MS-FAB$^+$ *m/z* 930 (M + K^+), 914 (M + Na^+), 404, 388; ^1H NMR (CD_3OD) δ 1.14 (s, C-17H_3), 1.19 (s, C-16H_3), 1.71 (s, C-19H_3), 1.92 (s, C-18H_3), 2.26 (s, $OCOCH_3$), 3.84 (d, *J* = 7, C-3H), 4.20 (s, C-20H_2), 4.21 (m, C-7H), 4.64 (d, *J* = 7, C-2′H), 5.00 (m, C-5H), 5.32 (s, C-10H), 5.63 (d, *J* = 7, C3′H and C-2H), 6.20 (t, *J* = 9, C-13H), 7.32–8.12 (C_6H_5, $OCOC_6H_5$, and $NHCOC_6H_4SO_3H$).

Compound 22. Taxol (40 mg, 0.05 mmol) was treated for 3 h at room temperature with 2,2,2-trichloroethyl chloroformate in pyridine to give 2′-[[(trichloroethyl)oxy]carbonyl]taxol[13b] in 56% yield. The 2′-protected taxol (80 mg, 0.077 mmol)), 4-(dimethylamino)pyridine (2 mg, 0.016 mmol), and glutaric anhydride (88 mg, 0.77 mmol) were stirred in pyridine (2 mL) for 7 h at 60 °C and at room temperature for 15 h. Purification by preparative TLC (ether/hexane, 8:2) gave the protected 7-glutaryltaxol (20 mg). Removal of the [(trichloroethyl)oxy]carbonyl group gave a quantitative yield of compound **22**.

22: MS-FAB$^+$ *m/z* 968 (MH^+), 908, 286; ^1H NMR ($CDCl_3$) δ 1.14 (s, C-17H_3), 1.18 (s, C-16H_3), 1.67 (s, C-19H_3), 1.77 (m, $COCH_2CH_2$), 1.82 (s, C-18H_3), 2.13 (s, $OCOCH_3$ on C-10), 2.30 (m, $COCH_2CH_2CH_2$), 2.35 (s, $OCOCH_3$ on C-4), 3.84 (d, *J* = 7, C-3H), 4.12 and 4.25 (2 d, *J* = 9, C20H_2), 4.78 (br s, C-2′H), 4.90 (d, *J* = 9, C-5H), 5.50 (m, C-7H), 5.62 (d, *J* = 7, C-2H), 5.75 (br d, *J* = 9, C-3′H), 6.12 (t, *J* = 9, C-13H), 6.17 (s, C-10H), 7.15–8.05 (NH, C_6H_5, $OCOC_6H_5$, and $NHCOC_6H_5$).

Compound 23. Hydroxycarbamate **13a** (170 mg, 0.21 mmol) was treated for 1 h at room temperature with 2,2,2-trichloroethyl chloroformate (1.2 equiv) in pyridine to give the 2′-[(trichloroethyl)oxy]carbonyl hydroxycarbamate in 47% yield (preparative TLC purification in CH_2Cl_2/MeOH, 97:3). This compound (70 mg, 0.071 mmol), 4-(dimethylamino)pyridine (9 mg), and glutaric anhydride (104 mg, 0.91 mmol) were stirred in pyridine (4 mL) for 28 h at 60 °C. After workup and purification by preparative TLC (methylene chloride/methanol, 92:8), the 2′-protected 7,10-diglutaryl hydroxycarbamate was obtained (45 mg). Removal of the [(trichloroethyl)oxy]carbonyl group gave compound **22** in 48% yield (preparative TLC purification in CH_2Cl_2/MeOH/AcOH, 95:5:0.5).

23: MS-FAB$^+$ 1058 (M + Na^+), *m/z* 1036 (MH^+), 980, 282, 226; ^1H NMR ($CDCl_3/CD_3OD$) δ 1.09 (s, C-17H_3), 1.14 (s, C-16H_3), 1.28 (s, tBu), 1.70 (s, C-19H_3), 1.82 (s, C-18H_3), 2.22 (m, $COCH_2CH_2CH_2$), 2.30 (s, $OCOCH_3$ on C-4), 3.82 (d, *J* = 7, C-3H), 4.11 and 4.23 (2 d, *J* = 9, C20H_2), 4.52 (br s, C-2′H), 4.85 (d, *J* = 9, C-5H), 5.13 (br s, C-3′H), 5.45 (m, C-7H), 5.58 (d, *J* = 7, C-2H), 6.07 (t, *J* = 9, C-13H), 6.21 (s, C-10H), 7.22–8.05 (C_6H_5, $OCOC_6H_5$, and $NHCOC_6H_5$).

Compound 24. Compound **13a** was 2′-protected as its [(trichloroethyl)oxy]carbonyl derivative (see preparation of compound **23**). A 200 mg (0.203 mmol) sample of the 2′-protected hydroxycarbamate in toluene (3 mL) was treated with (carbobenzyloxy)glycine (170 mg, 0.81 mmol), DCC (157 mg, 0.76 mmol), and 4-(dimethylamino)pyridine (25 mg, 0.203 mmol) for one night at 70 °C. The reaction was worked up by standard methods. Preparative TLC (CH_2Cl_2/MeOH, 95:5) gave 135 mg of the 2′-[[(trichloroethyl)oxy]carbonyl] 7,10-bis(carbobenzyloxy)glycyl derivative. Removal of the [(trichloroethyl)oxy]carbonyl group yielded the 7,10-bis(carbobenzyloxy)glycyl derivative in 94% yield. This compound (70 mg) was treated with H_2/10% Pd/C (20 mg) in MeOH (6 mL) and HCl (mM, 0.35 mL) with stirring at room temperature for 5 h. The solution was filtered and washed with MeOH, and the solvent was evaporated. Extraction at pH 7 with $CHCl_3$ and evaporation of the solvent gave compound **24** in 79% yield.

24: MS-FAB$^+$ *m/z* 922 (MH^+), 865, 809, 527, 509; ^1H NMR ($CDCl_3$) δ 1.14 (s, C-17H_3), 1.23 (s, C-16H_3), 1.35 (s, tBu), 1.80 (s, C-19H_3), 1.93 (s, C-18H_3), 2.38 (s, $OCOCH_3$), 3.61 (m, $COCH_2NH2$), 3.91 (d, *J* = 7, C-3H), 4.16 and 4.33 (2 d, *J* = 9, C-20H_2), 4.63 (br s, C-2′H), 4.94 (d, *J* = 9, C-5H), 5.27 (m, C-7H), 5.46 (br d, *J* = 9, C-3′H), 5.66 (m, C-2H), 6.13 (t, *J* = 9, C-13H), 6.24 (s, C-10H), 7.30–8.07 (C_6H_5 and $OCOC_6H_5$).

The hydrochloride salt was prepared by addition of 2 equiv of HCl to a solution of **24** in CH_3OH/H_2O.

Compound 25. By use of similar reactions as for the preparation of **24**, compound **25** was obtained from **13a** in 9.5% yield after protection at C-2′, esterification with 1.2 equiv of (carbobenzyloxy)-L-phenylalanine, and removal of the [(trichloroethyl)oxy]carbonyl and carbobenzyloxy groups.

25: $[\alpha]^{22}_D = -15°$ (*c* = 1.00, CH_3OH); MS-FAB$^+$ *m/z* 955 (MH^+); ^1H NMR (CD_3OD) δ 1.11 (s, C-17H_3), 1.17 (s, C-16H_3), 1.41 (s, tBu), 1.83 (s, C-19H_3), 1.92 (s, C-18H_3), 2.37 (s, $OCOCH_3$), 2.91 and 3.37 (2 dd, *J* = 15 and 10 and *J* = 15 and 4, -CH_2Ph), 3.97 (d, *J* = 7, C-3H), 4.23 (s, C-20H_2), 4.28 (dd, *J* = 10 and 4, -$COCH(NH_2)$)), 4.49 (br s, C-2′H), 5.00 (d, *J* = 9, C-5H), 5.11 (br s, C-3′H), 5.42 (s, C-10H), 5.64 (m, C-7H), 5.67 (d, *J* = 7, C-2H), 6.16 (t, *J* = 9, C-13H), 7.30–8.11 (C_6H_5 and $OCOC_6H_5$).

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