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Synthesis, biology, and modeling of a C-4 carbonyl C,D-*seco*-taxoid

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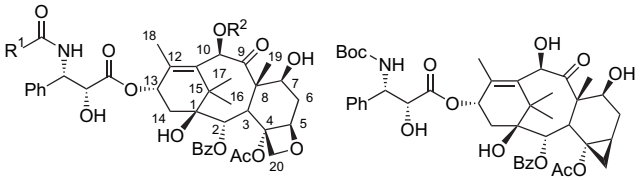
Dedicated with profound respect and affection to the memory of Professor Pierre Potier

Abstract—A C,D-*seco*-paclitaxel derivative **26** was prepared from taxine and tested for biological activity. Chemical reactivity of the *seco*-compounds proved to be substantially modified, with respects to taxoids. The corresponding C,D-*seco*-taxoid does not show tubulin stabilizing activity or cytotoxicity. Explanation of these observations based on molecular modeling is provided.

1. Introduction

Taxol **1**[1,2] and Taxotere **2**[2,3] are currently considered as the most efficient therapeutic agents for the treatment of several types of cancer. In order to understand better their unique mechanism of action, which would allow for design of the analogs of reduced structural complexity, yet with improved properties (i.e., higher activity, better solubility, activity against multidrug-resistant (MDR) tumors, etc.), extensive structure–activity relationship (SAR) studies have been performed. These studies indicated that the oxetane ring may be one of the crucial structural units of biologically active taxoids; its exact role, however, remained a matter of debate.[4] According to one explanation, the four-membered ring may serve purely as a rigidifying element, that imposes a proper conformational bias to the taxane core, thus forcing the functional groups at C-2, C-4, and C-13 to assume the appropriate positions for productive interactions with tubulin receptor. Alternatively, electronic effects may be important, with the heteroatom being involved in stabilizing dipolar, or hydrogen bonding, interactions with tubulin protein. For both hypotheses—'conformational' and 'electronic'—experimental support exists, as well as some contradictory data. Thus, substitution of oxygen in ring D by nitrogen,[5]



sulfur,[6] or selenium[6b] results in the loss of activity, although the geometries of the corresponding azetidine, thietane, and selenetane derivatives do not differ very much, as compared to the parent oxetane. These findings infer the prevalence of the electronic factors. On the other hand, the lack of bioactivity of most of D-*seco*-taxoids with various degree of oxygenation at positions C-4, C-5, and C-20, suggests that the role of the oxetane ring may be 'the conformational lock' of the diterpene scaffold.[7,4b] In line with this hypothesis, a taxoid **3**, containing cyclopropane ring in place of oxetane, showed the tubulin polymerizing activity comparable to that of docetaxel.[8] Recently, it was shown that, contrary to long

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lasting belief, no ring D is required for tubulin polymerizing activity of taxoids: on the basis of molecular modeling it was predicted that **4** would have a strong microtubule stabilizing activity, which was subsequently experimentally confirmed.[9] However, it should be noted that both **3** and **4** are at least by two orders of magnitude less cytotoxic with respect to paclitaxel or docetaxel; thus, while not necessary for the tubulin stabilizing activity, the oxetane ring still might be essential for cytotoxicity.

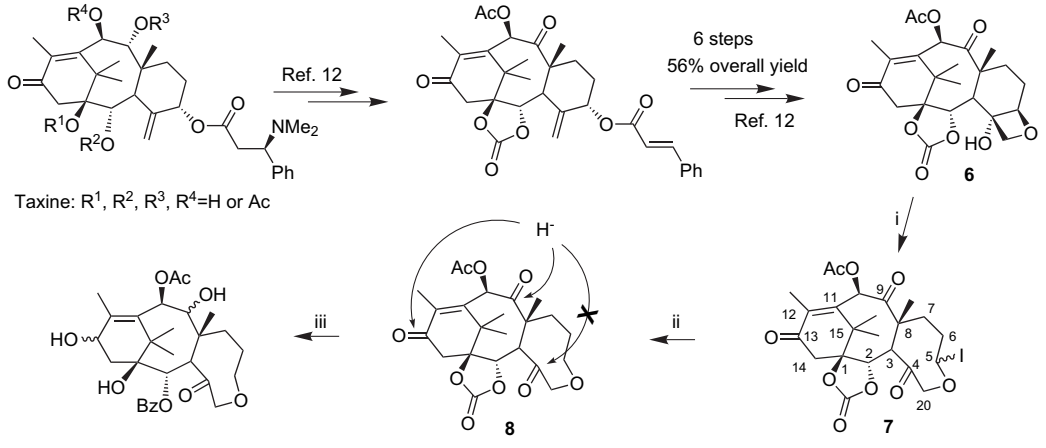
2. Results and discussion

In order to discern between the conformational and electronic effects of the oxetane ring, we endeavored to synthesize a C,D-*seco*-taxoid of type **5** and to evaluate its biological activity. While conformationally more flexible, the *seco*-derivative maintains the functionalization pattern of paclitaxel. The lack of biological activity of the compound would point to a conformational constraint as the principal (if not the sole) effect of the oxetane ring; on the contrary, eventual cytotoxicity of the *seco*-derivative would indicate the importance of the oxygenation pattern (i.e., the electronic effect of the oxetane oxygen atom). We decided to perform our study on 7-deoxy-taxoids: given that a 7-hydroxyl group is not required for cytotoxicity,[10] synthetic transformations could be performed on derivatives that require less protective group manipulation. In addition, others[11] and we[12] have shown that taxine B[13]—a pseudo-alkaloid readily isolated from the renewable needles of the European yew (*Taxus baccata*)—constitutes a suitable starting material, amenable to structural patterns relevant for this study.[14]

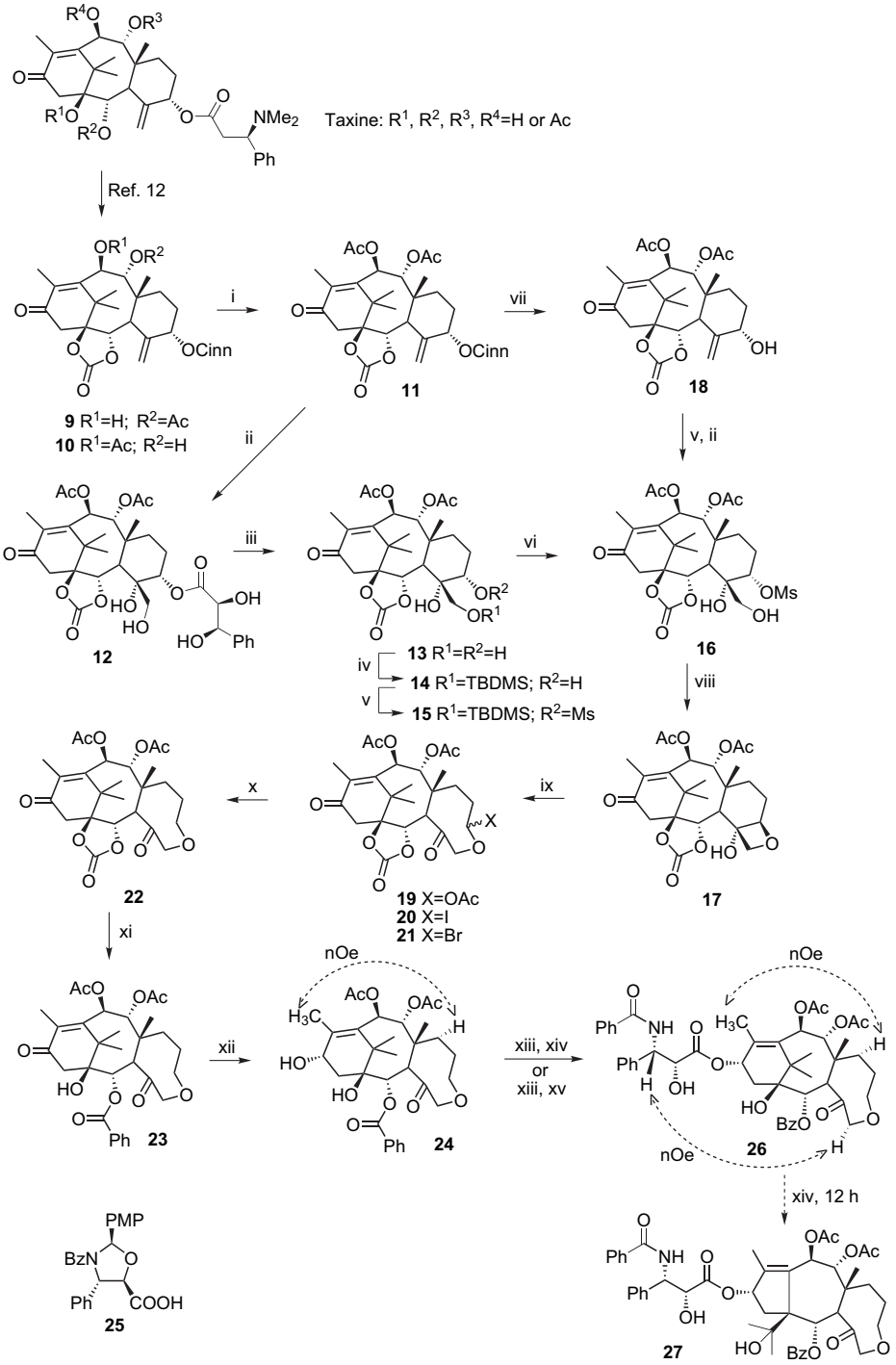
Our initial plan called for the scission of the central C-4–C-5 bond in previously described alcohol **6**,[12] via a fragmentation of the corresponding alkoxyl radical (Scheme 1). After some experimentation, the iodine-transfer fragmentation was cleanly effected using diacetoxyiodobenzene (DIB)/iodine reagent under photolytic conditions.[15] Subsequent reduction with tributyltin hydride (TBTH) afforded the desired intermediate **8** in good yield. For the reaction to proceed efficiently, a high concentration and an excess of TBTH are needed (under the conventional conditions for reductions with TBTH, rearrangements occur and unidentified products are formed). This skeletal transformation reversed the order of reactivity of carbonyl groups, with respect to the parent taxane: while C-9 carbonyl group in paclitaxel is resistant even to $LiAlH_4$,[16] in 4,5-*seco*-derivative it underwent rapid, but stereorandom reduction with $NaBH_4$, as well as C-13 carbonyl. On the contrary, the newly formed ketone at C-4 proved resistant toward $NaBH_4$, $NaBH_4/CeCl_3$, or $NaBH_3CN$, while a large excess of $NaBH_4$ resulted in decomposition of material.

In order to overcome this difficulty, the target structure was modified by substituting the C-9 α-acetate for the C-9 carbonyl group: a change that should simplify the synthetic procedure without affecting the biological activity of the final product (Scheme 2).[17] After the acetylation of a mixture of cinnamoyltaxicines **9** and **10**, selective removal of the cinnamoyl side chain in **10**, in the presence of two acetate units and a cyclic carbonate, was accomplished using our previously developed procedure:[12] dihydroxylation of **11** with OsO_4 resulted in stereoselective introduction of two requisite hydroxyl groups into the taxane core, while simultaneously activating (by intramolecular hydrogen bonding in **12**) the intermediate 2,3-dihydroxy-3-phenylpropanoate side chain toward alcoholysis in a buffered methanolic solution. The resulting triol **13** was converted into oxetane **17** by a slightly modified four-step protocol developed by the CNRS group[11a] (the cyclization step had to be performed with DIPEA in refluxing toluene; the reagents described in the literature proved unsuccessful). Alternatively, the conversion of **11** into the advanced cyclization precursor **16** could be effected via a three-step procedure based on hydroxylamine promoted selective cinnamate cleavage.[6a,18] The latter route is shorter and avoids the use of protective groups; however, the overall yield of **17** is lower (calculated yields for the transformation **11**→**17**, via tetraol **12**: 38%; via allylic alcohol **18**: 23%).

With compound **17** in hand, several reagents for the generation of tertiary alkoxyl radicals were tried for the fragmentation step. Surprisingly, the major product in the reaction with DIB/iodine was acetate **19** (29%), accompanied by the desired iodide **20** (17%); this is in sharp contrast to the same reaction with **6**, which proceeded in 73% yield without



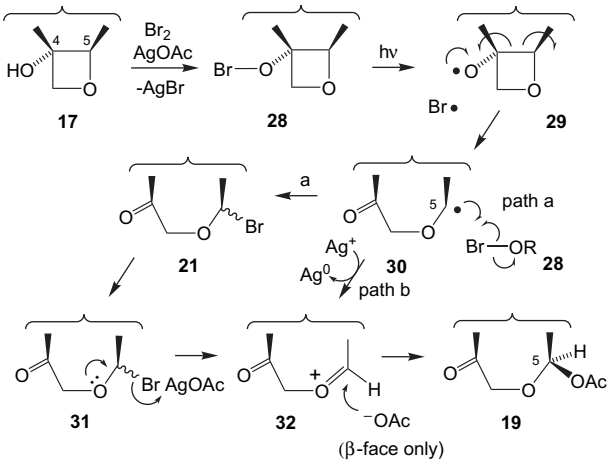
Scheme 1. Reagents and conditions: (i) $PhI(OAc)_2$ (1.5 equiv), I_2 (1.5 equiv), benzene, 15 °C, 250 W Xenophot lamp, 73%; (ii) Bu_3SnH (10 equiv, 0.4 M), benzene, 15 °C, 250 W Xenophot lamp, 80%; (iii) $NaBH_4$, $CeCl_3$, EtOH, rt.



Scheme 2. Reagents and conditions: (i) Ac_2O, pyridine, CH_2Cl_2, DMAP, 93%; (ii) OsO_4, NMO, THF, H_2O, *t*-BuOH; (iii) KOAc, MeOH, 73% over two steps; (iv) TBDMSCl, DMAP, Et_3N, CH_2Cl_2; (v) MsCl, pyridine; (vi) TBAF, THF, 58% from **13**; (vii) NH_2OH, HCl, Et_3N, THF, EtOH, H_2O, 50%; (viii) DIPEA, PhMe, Δ, 24 h, 90%; (ix) AgOAc, Br_2, PhH, hν, see text for conditions, **19** (60%) or **21** (61%); (x) Bu_3SnH, AIBN, PhH, hν, 61% over two steps; (xi) (a) PhLi, THF, −80 °C; (b) Ac_2O, DMAP, CH_2Cl_2, 62%; (xii) $NaBH_4$, MeOH, 72%; (xiii) **25**, DCC, DMAP, PhMe, 75 °C; (xiv) 5% *p*-TsOH, MeOH, 30 min, 70% from **24**; (xv) CAN, H_2O, CH_3CN, 40 °C, 2.5 h, 61% from **24**.

complication. Reagents such as mercuric oxide/iodine,[19] or silver oxide/bromine,[20] were also unsuccessful, afforded **20**, or **21**, in very low yield (<10%), along with some unidentified products. Finally, we found that the fragmentation step could be accomplished with silver acetate/bromine reagent,[19a,b] under carefully controlled conditions. As a result both bromide **21** and acetate **19** could be obtained chemoselectively, depending on the stoichiometry of reactants. When the reaction was performed with 1.4 equiv of AgOAc and 2.5 equiv of Br_2, the required bromide **21** was the predominant product isolated as a 1:1 mixture of stereoisomers. With 4 equiv of AgOAc and 2 equiv of Br_2 the chemoselectivity of the reaction is reversed and only acetate **19** is obtained. Interestingly, the acetate was formed stereoselectively, with strong predominance of the β-isomer (β:α=10.5:1), as determined by NOESY experiment.

The formation of bromide mixture **21** and acetate **19** can be understood as the consequence of different mechanistic pathways. In the first case, the AgOAc/Br_2 reagent produces a hypobromite at C-4 (C_4OBr), which is cleaved to an alkoxyl radical **29** under the influence of light (Scheme 3). As part of the chain reaction process, hypobromite **28** delivers bromine to both faces of the ring-opened radical **30** (path a) accountable for the product mixture. An MM3* Monte Carlo conformational search[21,22] of the flexible eight-membered ring radical corresponding to **30** with the C-5 carbon center modeled as a carbon free radical shows that both faces of the ring are free to react with **28** to give **21** (Fig. 1).[23]



Scheme 3. Proposed hypobromite reaction of **17** to give **21** and subsequent formation of oxonium cation **32** in the presence of excess AgOAc. Intermediate **32** is proposed to lead chemoselectively to β-acetate **19**.

The stereospecific formation of acetate **19** proceeds with a two-fold excess of AgOAc over Br_2. We speculate that under these conditions the 50:50 mixture of bromides **21** (Schemes 2 and 3) is likewise formed. However, the Lewis acid silver ion or silver acetate then coordinates with bromine to give complex **31** (Scheme 3, path a). Facile elimination can then provide the stabilized oxonium cation **32**. Alternatively, in the presence of excess AgOAc electron-transfer may predominate over the bromine transfer reaction, which results in direct oxidation of radical intermediate **30** to carbocation **32** (Scheme 3, path b).[24] The C–C=O^+–CH moiety introduces an element of rigidity in the *seco*-C,D eight-membered ring as suggested by a Monte Carlo conformational search of the analog of **32** modeled as the corresponding alkene. Unlike in the radical, the ring adopts a low energy conformation that presents only the face corresponding to the β-isomer as available for capturing the acetate nucleophile (**32**, Scheme 3 and Fig. 2). Bromide does not reassociate with the cation as it is removed as insoluble AgBr.

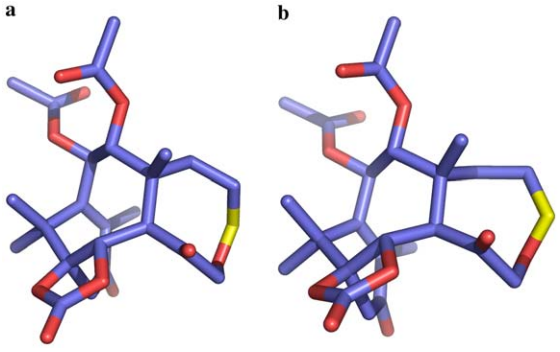


Figure 1. The first (a) and second (b) low energy MM3* conformers of the radical intermediate **30** (Scheme 3). The C-5 free radical carbon is highlighted in yellow.

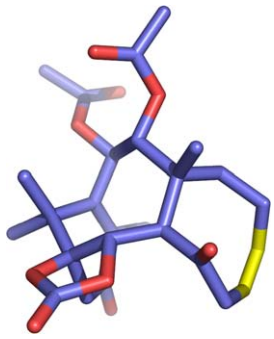


Figure 2. Low energy conformer of oxonium cation **32** (Scheme 3) modeled as the corresponding alkene-**21**. Only the β-face is exposed to nucleophilic attack. The O=C^+ bond modeled by C=C is highlighted in yellow.

Due to its instability on silica-gel, the crude bromide **21** was not purified, but directly reduced with TBTH to afford ketone **22** in 60% yield (from **17**). The installation of benzoate ester into C-2 position was effected by treatment with phenyllithium,[25] followed by reacetylation and the reduction of the C-13 carbonyl group in **23** with $NaBH_4$. At this stage we planned the reduction of the C-4 carbonyl group in **24** followed by acetylation of the so formed secondary alcohol. To our surprise, **24** proved unreactive toward a variety of reducing agents, such as $NaBH_4$ (20 equiv, rt), $NaBH_4/CeCl_3$, $BH_3 \cdot Me_2S$ (rt), L-Selectride (−70→0 °C), Red-Al (−60→+50 °C), or Noyori transfer-hydrogenation (performed separately with both (*R*,*R*)- and (*S*,*S*)-enantiomers of TsDPEN ligand).[26] Under the conditions of reduction with Et_3SiH/BF_3 only the formation of products of the Lewis acid-catalyzed rearrangement were observed. With $LiAlH_4$ a complex mixture of products was obtained. At low temperatures, DIBALH in excess induced only the reductive hydrolysis of the acetate groups, while a very complex mixture of products was formed at rt. The attempted Noyori reduction of **22** was very slow and resulted only in reductive deprotection of the cyclic carbonate unit. With other reducing reagents occasional reduction of the C-13 carbonyl group was observed, but the C-4 carbonyl remained intact. Thus, similar to compound **8**, fragmentation of the central bond in the condensed C,D-system of **17** brought about a major conformational change in the taxane core and rendered the newly formed carbonyl group inaccessible to reducing agents.

To understand the remarkable lack of reactivity at the C-4 carbonyls of **22** and **24**, we examined the conformational profile of the molecules to learn what structural features might contribute to sequester the C=O groups at C-4. In a preliminary communication,[14] we performed a 10,000-step

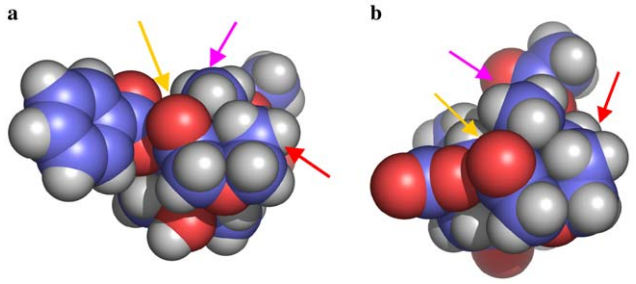


Figure 3. The lowest energy conformations for taxanes **24** and **22** and the disposition of the C-4 carbonyl. (a) For **24**, the C_4=O (yellow arrow) is surrounded by the C-2 phenyl (left), the C-8 methylene (red arrow) and the C-19 methyl (top, magenta arrow); (b) for **22**, the cyclic carbonate effectively replaces the C-2 phenyl in **24** as a shielding unit for C_4=O.

MMFF/GBSA/H_2O conformational search for ketone **24** and located a boat-chair (BC) conformation as the global minimum with a predicted population of 99.5% at 298 K. This form is identical to the lowest energy torsional isomer of cyclooctanone.[27] The BC conformer, embedded in the taxane architecture, occludes approach to either face of the C_4=O group (center, yellow arrow) by reducing agents (Fig. 3a). The plane of the carbonyl is shielded on three sides by the C-2 phenyl group (left), the C-8 CH_2 group (right, red arrow), and the C-19 Me group (top, magenta arrow) causing the C-4 carbon to be buried within the folds of the taxane. This observation is substantiated by calculation of zero solvent accessible surface for C-4.

In Figure 3a the C-2 phenyl of **24** is shown as a bulky impediment to the approach of a reducing agent to the α-face of the C-4 carbonyl. By comparison, the cyclic carbonate in **22** is both smaller and, to some extent, twisted away from the C-4 position by virtue of attachment at C-1 (Fig. 3b). Yet, it too prevents reduction. To understand this, we performed an MMFF conformational search of the C,D-ring of **22** similar to that of **24**. The lowest energy conformer likewise sustains the BC shape. Surprisingly, the cyclic carbonate oxygen, though much smaller than a phenyl ring, blocks approach to C-4 equally effectively. The distance between the C-4 carbon and the C-2 carbonate oxygen atom is 2.7 Å, indicating that the two atoms are most likely crowded (van der Waals sum=3.5 Å).[28] The steric repulsion might, nonetheless, be mediated by a LP→π* interaction from O to C(=O). Similar to the benzoyl ester **24**, the solvent accessible surface area for C-4 in **22** is estimated to be a diminutive 0.35 $Å^2$. One implication of the C_4=O shielding from C-2 is that reduction of the C-4 carbonyl in the absence of either the carbonate or the C-2 phenyl ring, namely the bare C-2 OH, is likewise predicted to fail.

Thus, the reluctance of **24** toward reduction hampered the introduction of acetoxy substituent into C-4 position. Although this structural feature is known to be important for the biological activity of taxoids, we proceeded further with the appendage of the side chain and the conversion of **24** into a derivative suitable for biological evaluation. Esterification of the C-13 hydroxyl group was achieved through the coupling of **24** with the protected side chain **25**, using a previously described procedure.[29,12] Acidic hydrolysis of *p*-methoxybenzylidene protective group afforded the required C,D-*seco*-derivative **26** in good yield (70% over two steps). However, prolonged reaction times (12 h instead of 30 min) lead to the rearrangement of the A-ring in **26** and formation of 11(15-1)-abeotaxane **27**. We found that, alternatively, the deprotection step could be performed oxidatively, with CAN in aqueous acetonitrile, which obviates the need for close monitoring of the progress of the reaction.

For the evaluation of biological activity, compound **26** was submitted to the tubulin test,[30] as well as to cytotoxicity assays against rat glioma C6 cell lines,[31] and these results were compared to those obtained with paclitaxel. The result of the tubulin test showed **26** to be devoid of microtubule stabilizing activity. At 11.9 mM concentration, **26** effected only 7% inhibition of the microtubule disassembly process (for comparison, paclitaxel showed 50% inhibition at 1 μM concentration). The staining with crystal violet showed that paclitaxel reduced the number of C6 glioma cells in a dose-dependent manner, with an LC_{50} value of approx. 5 nmol (Fig. 4a). In contrast, compound **26** failed to display significant cytotoxicity in the same concentration range (Fig. 4a). The absence of cytotoxic activity of **26** was also confirmed in the MTT assay for mitochondrial respiration (Fig. 4b). Therefore, the observed lack of microtubule stabilizing

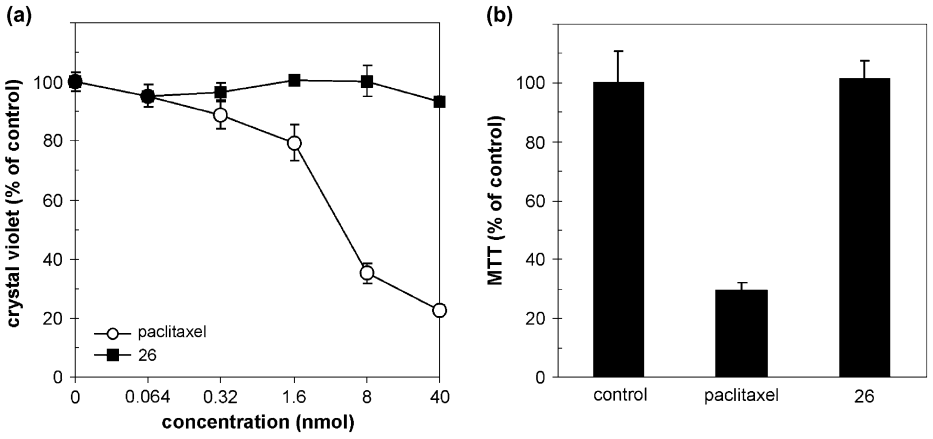


Figure 4. Cytotoxicity of paclitaxel and compound **26**. (a) C6 cells were incubated alone (control) or with various doses of paclitaxel or **26**; (b) C6 cells were incubated in the absence (control) or presence of 40 nmol of paclitaxel or **26**. Cell viability was assessed after 48 h by crystal violet (a) or MTT assay (b). The results from the representative of three separate experiments are presented as mean±SD of triplicate observations.

activity of **26** can be associated with the complete loss of cytotoxicity at pharmacologically relevant concentrations.

These findings confirmed the importance of the precise conformation of the C,D-ring system in taxoids for the biological activity. However, the fact that compound **26** lacks the C-4 acetate group makes interpretations of the biological tests somewhat ambiguous, as it is difficult to estimate, which of the two structural features in **26** (the conformational change, or the absence of the C-4 acetate) contributes more to the loss of biological activity.

Another factor concerns the relocation of the oxetane oxygen and the adjacent carbons. A conformation of compound **26** was constructed to incorporate the global minimum BC conformation of the *seco*-C,D unit as depicted in Figure 3a. In addition, the C-13 side chain was oriented in the T-Taxol conformation.[32,33] The corresponding structure was rigidly docked with the Glide protocol[34,22] into the taxane pocket of β-tubulin. The pose that resembles most closely the electron crystallographic structure of paclitaxel is depicted in Figure 5.

A significant difference between the structures of T-Taxol and **26** is the conformational reorganization of atoms in the *seco*-C,D rings. In paclitaxel (PTX), the C-4 acetate is found on the α-face of the molecule and directed into the concave region of the baccatin core. Simultaneously, the oxygen of the oxetane ring is oriented upward toward the β-face and outward forming weak contact with Thr274 of β-tubulin.[4a,32] In striking contrast, compound **26**, to a first approximation, inverts the roles of these two functionalities. The C═O replacement for the C-4 acetate is β oriented, while the oxetane oxygen along with its adjacent methylene groups is folded α and found deep within the concave baccatin cavity. The relative docking poses for PTX and **26** (Fig. 5) reflect the inside-out relationship operating within the C,D region of the molecules. One critical difference is that the C-4 acetate of PTX enjoying close contact with the C-3′ phenyl ring in the hydrophobic basin of the tubulin binding site[32] is lost in **26**. Another stems from the latter's α orientation of the bulky *seco*-C,D moiety. As a result of steric clashes with binding pocket residues Leu371, Pro274, and Phe272, the molecule is obligated to sit much higher in the pocket than PTX as depicted in Figure 5. Unfortunately, this results in the loss of pivotal hydrophobic interactions between ligand and protein. For example, instead of surrounding His229 in a stacked arrangement, the C-3′ benzamido and C-2 benzoyl moieties of **26** are moved much further up in the pocket and well outside of van der Waals contact. The situation is reminiscent of bridged taxanes proposed to be similarly dislodged from deep residence in the tubulin binding cleft as a result of ligand/protein steric encounters. The compounds are 10 to 30-fold less active than PTX.[35]

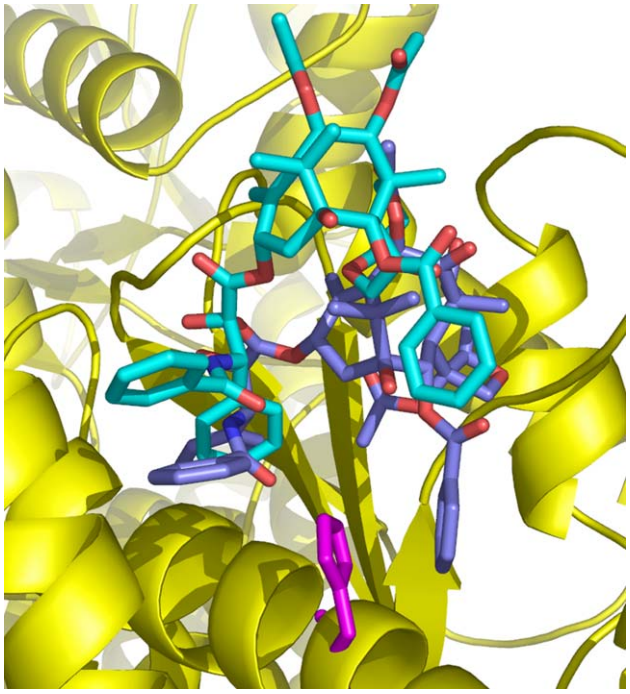


Figure 5. Docking poses of Taxol (blue) and **26** (cyan) within the taxane/tubulin binding pocket.

The proposed conformation of **26** (Fig. 5) is corroborated with the results of NOESY experiments (Scheme 2). A cross peak between H-20α and H-3′ is in agreement with the modeled conformation with C-20 curled into the concave region of the baccatin core and with a H-20α to H-3′ distance of 2.8 Å in the docked conformation. In addition, NOESY cross peaks between H-7α and H-18 are observed for both **26** and **24**, in accord with the concave conformation of the molecules. Taken together these observations support the proposal that the molecule adopts the pose pictured in Figure 5 and consequently experiences the steric clash suggested.

To summarize, a method is developed for the efficient preparation of C,D-*seco*-taxoids. The conformational change, induced by the scission of the C-4–C-5 bond in the taxane core, brings about important modifications in chemical reactivity of the 4,20-*seco*-derivatives and results in the loss of biological activity of the corresponding C,D-*seco*-taxoid.

3. Experimental

3.1. General

All chromatographic separations were performed on silica, 10–18 μm, 60A, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents. NMR spectra were recorded on a Varian Gemini 200 spectrometer, ^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz, for samples in deuterated chloroform. Chemical shifts are expressed in parts per million using tetramethylsilane as internal standard, coupling constants (*J*) are in hertz. The NOESY spectra were acquired on a Varian Inova Unity 600 MHz spectrometer in deuterated chloroform at 25 °C, with mixing times of 400 ms and 500 ms for compounds **26** and **24**, respectively. IR spectra were recorded on a Perkin–Elmer 457 grating FT instrument, and are expressed in cm^{-1}. Mass spectrometric analysis was provided by the Emory University Mass Spectrometry Center using an ACQ Advantage mass spectrometer. Microanalyses were

performed at the Vario EL III instrument CHNOS Elementar Analyzer, Elementar Analysensysteme GmbH, Hanau, Germany. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

3.1.1. Compound 8. In a Pyrex, external water-cooled reactor, a deaerated suspension of **6** (30 mg, 0.067 mmol), diacetoxyiodobenzene (32 mg, 0.1 mmol), and iodine (25.4 mg, 0.1 mmol) in benzene (3 mL) was irradiated for 20 min with a 250 W Xenophot sun-lamp focalized light, with stirring under an argon atmosphere. The reaction mixture was diluted with CH_2Cl_2, washed successively with 5% aq $Na_2S_2O_3$ and water, and dried over anhyd $MgSO_4$. After the solvent was removed under reduced pressure, the crude **7** (60 mg) was used in the next step without further purification.

In a Pyrex, external water-cooled reactor, a deaerated solution of crude iodide **7** (60 mg), TBTH (101 mg, 0.348 mmol), AIBN (2 mg), and benzene (0.9 mL) was irradiated for 10 min with a 250 W Xenophot sun-lamp focalized light, with stirring under an argon atmosphere. After removal of the solvent under reduced pressure, the crude product was purified by dry flash chromatography (eluent: benzene/ethyl acetate=8/2) to give compound **8** (17.8 mg, 59%) as a colorless film. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.72 (1H, s, H-10), 4.42 (2H, br s, H-2 superimposed with H-3), 3.94 (1H, d, J=17.2 Hz, H-20), 3.86–3.72 (1H, m, H-5), 3.64–3.62 (1H, m, H-5), 3.52 (1H, d, J=17.2 Hz, H-20), 2.99 (1H, d, J=19.6 Hz, H-14), 2.76 (1H, d, J=19.4 Hz, H-14), 2.29 (3H, s, H-18), 2.25 (3H, s, Ac), 1.97–1.30 (4H, m, H-6 and H-7), 1.35 (3H, s, H-17 or H-16), 1.28 (3H, s, H-16 or H-17), 1.25 (3H, s, H-19). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 205.24 (C, C-4), 202.15 (C, C-9), 195.31 (C, C-13), 169.30 (C, Ac), 151.55 (C, CO), 147.02 (C, C-11), 141.99 (C, C-12), 88.41 (C, C-1), 78.77 (CH, C-2), 76.18 (CH_2, C-20), 75.99 (CH, C-10), 72.55 (CH_2, C-5), 57.28 (C, C-8), 48.49 (CH, C-3), 41.41 (CH_2, C-15), 40.68 (C, C-14), 36.00 (CH_2, C-7), 31.26 (CH_3, C-17 or C-16), 21.93 (CH_2, C-6), 20.74 (CH_3, Ac), 18.34 (CH_3, C-16 or C-17), 16.96 (CH_3, C-19), 15.28 (CH_3, C-18). IR (film) ν_{max}: 2960, 1820, 1749, 1694, 1270, 1236, 1028. HRMS (MALDI-FTMS) calcd for $C_{23}H_{27}O_9Na$ (M+Na$^+$) 471.1631, found 471.1641.

3.1.2. Compound 11. A mixture of 9-*O*-acetyl-5-*O*-cinnamoyltaxicine 1,2-carbonate **9** and 10-*O*-acetyl-5-*O*-cinnamoyltaxicine 1,2-carbonate **10** (200 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (6 mL) and treated with acetic anhydride (160 mg, 1.57 mmol), pyridine (80 mg, 1.01 mmol), and DMAP (5 mg, 0.04 mmol). The reaction mixture was stirred at rt for 2.5 h, diluted with CH_2Cl_2, washed with 1.5 N HCl and water, dried over anhyd $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by dry flash chromatography (eluent: petroleum ether/ethyl acetate=7/3) afforded 9-*O*,10-*O*-diacetyl-5-*O*-cinnamoyltaxicine 1,2-carbonate **11** (210 mg, 93%) as a white amorphous solid (mp 233–235 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.76–7.72 (2H, m), 7.67 (1H, d, J=16.0 Hz), 7.46–7.42 (3H, m), 6.31 (1H, d, J=15.9 Hz), 6.07 (1H, d, J=10.2 Hz), 5.77 (1H, d, J=10.2 Hz), 5.55 (1H, br s), 5.39 (1H, s), 5.37 (1H, s), 5.02 (1H, d, J=5.8 Hz), 3.40 (1H, d, J=5.5 Hz), 2.96 (2H, br s), 2.32 (3H, s), 2.11 (3H, s), 2.07 (3H, s), 2.10–1.60 (4H, m), 1.70 (3H, s), 1.35 (3H, s), 1.01 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 196.38 (C), 169.87 (C), 169.43 (C), 165.76 (C), 152.25 (C), 150.14 (C), 146.00 (CH), 141.96 (C), 139.49 (C), 134.22 (C), 130.42 (CH), 128.85 (CH), 128.31 (CH), 118.60 (CH_2), 117.16 (CH), 88.60 (C), 79.06 (CH), 76.93 (CH), 75.29 (CH), 72.74 (CH), 44.46 (C), 42.99 (CH), 40.93 (CH_2), 40.86 (C), 32.54 (CH_3), 27.26 (CH_2), 27.02 (CH_2), 20.60 (CH_3), 20.41 (CH_3), 19.94 (CH_3), 17.19 (CH_3), 14.24 (CH_3). IR (KBr) ν_{max}: 2998, 2958, 1818, 1750, 1714, 1686, 1638, 1374, 1310, 1270, 1202, 1163, 1032. HRMS (FAB) calcd for $C_{34}H_{39}O_{10}$ (MH$^+$) 607.2543, found 607.2579. $[\alpha]_D^{25}$ +251 (*c* 1.0, CH_2Cl_2).

3.1.3. Compound 13. To a solution of **11** (800 mg, 1.32 mmol) in a mixture of THF (19 mL) and water (9.5 mL) was added NMO (910 mg, 6.74 mmol), followed by osmium tetraoxide (1.27 mL, 2.5% solution in *t*-BuOH). The reaction mixture was stirred for 6 h at rt, then Florisil (900 mg), sodium dithionite (2.5 g), and water (10 mL) were added, and stirring was continued for 30 min. The reaction mixture was filtered and the filtrate was extracted with CH_2Cl_2. The organic extract was dried over anhyd $MgSO_4$ and concentrated under reduced pressure. Crude **12** (800 mg, 90%) was used in the next step without further purification.

To a solution of **12** (800 mg) in methanol (104 mL) was added methanolic KOAc (4.93 mL, 0.1 M solution) and the reaction mixture was stirred and heated to reflux for 15 min. The solvent was evaporated under reduced pressure and the residue was diluted with water, extracted with CH_2Cl_2, the extract was dried over anhyd $MgSO_4$ and concentrated under reduced pressure. Purification by dry flash chromatography (eluent: benzene/ethyl acetate=1/1) afforded compound **13** (490 mg, 81%) as a colorless film. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.04 (1H, d, J=10.4 Hz), 5.62 (1H, d, J=10.2 Hz), 4.86 (1H, d, J=4.6 Hz), 4.05 (1H, br s), 3.98 (1H, d, J=19.3 Hz), 3.98 (1H, d, J=10.6 Hz), 3.80–3.60 (1H, m), 3.65 (1H, br s), 3.54 (1H, d, J=10.6 Hz), 3.01 (1H, br s), 2.93 (1H, d, J=4.6 Hz), 2.81 (1H, d, J=19.2 Hz), 2.21 (3H, s), 2.10 (3H, s), 2.04 (3H, s), 1.97–1.48 (4H, m), 1.67 (3H, s), 1.32 (3H, s), 0.89 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 198.07 (C), 170.33 (C), 169.36 (C), 153.38 (C), 148.73 (C), 143.25 (C), 89.09 (C), 80.20 (CH), 75.36 (CH), 74.85 (C), 72.58 (CH), 70.21 (CH), 62.34 (CH_2), 43.50 (C), 41.59 (CH), 41.39 (C), 40.93 (CH_2), 32.50 (CH_3), 24.40 (CH_2), 23.58 (CH_2), 20.69 (CH_3), 20.56 (CH_3), 20.03 (CH_3), 18.63 (CH_3), 13.80 (CH_3). IR (film) ν_{max}: 3611, 3477, 2995, 2960, 1808, 1748, 1688, 1474, 1401, 1375, 1272, 1238, 1025. HRMS (FAB) calcd for $C_{25}H_{35}O_{11}$ (MH$^+$) 511.2179, found 511.2170. $[\alpha]_D^{25}$ +178 (*c* 1.0, CH_2Cl_2).

3.1.4. Compound 14. A solution of **13** (470 mg, 0.92 mmol), triethylamine (540 mg, 5.35 mmol), DMAP (15 mg, 0.12 mmol), and TBDMSCl (660 mg, 4.41 mmol) in CH_2Cl_2 (13 mL) was stirred for 5 days at rt under an argon atmosphere. The reaction mixture was diluted with CH_2Cl_2, washed with ice-cold satd aq NH_4Cl and water, and dried over anhyd $MgSO_4$. The solvent removal under reduced pressure followed by purification by dry flash chromatography (eluent: benzene/ethyl acetate=8/2) afforded silyl

ether **14** (523 mg, 91%) as a white foam. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.05 (1H, d, J=10.3 Hz), 5.62 (1H, d, J=10.3 Hz), 4.81 (1H, d, J=4.7 Hz), 4.01 (1H, d, J=19.4 Hz), 3.98 (1H, d, J=9.4 Hz), 3.94 (1H, br s), 3.56 (1H, br s), 3.49 (1H, d, J=9.2 Hz), 2.95 (1H, d, J=4.5 Hz), 2.79 (1H, d, J=19.2 Hz), 2.70 (1H, br s), 2.22 (3H, s), 2.09 (3H, s), 2.04 (3H, s), 2.00–1.50 (4H, m), 1.65 (3H, s), 1.31 (3H, s), 0.90 (9H, s), 0.86 (3H, s), 0.14 (3H, s), 0.10 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 197.96 (C), 170.24 (C), 169.29 (C), 152.70 (C), 148.57 (C), 143.27 (C), 88.45 (C), 79.80 (CH), 75.38 (CH), 74.76 (C), 72.56 (CH), 70.01 (CH), 63.29 (CH_2), 43.48 (C), 41.41 (C), 41.11 (CH), 40.99 (CH_2), 32.48 (CH_3), 25.69 (CH_3), 24.44 (CH_2), 23.49 (CH_2), 20.69 (CH_3), 20.54 (CH_3), 20.01 (CH_3), 18.59 (CH_3), 18.12 (C), 13.82 (CH_3), −5.58 (CH_3). IR (film) ν_{max}: 3479, 2956, 2934, 1813, 1750, 1690, 1470, 1373, 1237, 1091, 1023. HRMS (FAB) calcd for $C_{31}H_{49}O_{11}Si$ (MH^+) 625.3044, found 625.3028.

3.1.5. Compound 15. To a cold (0 °C) solution of **14** (40 mg, 0.064 mmol) in pyridine (2 mL) was added mesyl chloride (110 mg, 0.96 mmol). The reaction mixture was stirred at 0 °C for 15 min and then for 24 h at rt. The reaction mixture was diluted with CH_2Cl_2, washed successively with ice-cold 2.5% HCl, aq $NaHCO_3$, and water, and dried over anhyd $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by dry flash chromatography (eluent: benzene/ethyl acetate=8/2) to give mesylate **15** (34 mg, 77%) as a colorless film. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.04 (1H, d, J=10.4 Hz), 5.64 (1H, d, J=10.2 Hz), 4.79 (1H, d, J=4.6 Hz), 4.75 (1H, br s), 4.01 (1H, d, J=19.1 Hz), 3.99 (1H, d, J=9.8 Hz), 3.92 (1H, s), 3.54 (1H, d, J=9.7 Hz), 2.96 (3H, s), 2.89 (1H, d, J=4.9 Hz), 2.83 (1H, d, J=19.9 Hz), 2.27 (3H, s), 2.11 (3H, s), 2.10–1.50 (4H, m), 2.05 (3H, s), 1.65 (3H, s), 1.33 (3H, s), 0.92 (9H, s), 0.90 (3H, s), 0.16 (3H, s), 0.12 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 197.56 (C), 170.20 (C), 169.22 (C), 152.43 (C), 149.52 (C), 143.44 (C), 88.36 (C), 81.22 (CH), 79.24 (CH), 75.20 (CH), 73.87 (C), 72.63 (CH), 63.18 (CH_2), 43.46 (C), 42.61 (CH), 41.48 (C), 41.01 (CH_2), 38.66 (CH_3), 32.67 (CH_3), 25.68 (CH_3), 25.13 (CH_2), 25.06 (CH_2), 20.65 (CH_3), 20.54 (CH_3), 19.99 (CH_3), 18.99 (CH_3), 18.06 (C), 13.77 (CH_3), −5.51 (CH_3), −5.57 (CH_3). IR (film) ν_{max}: 3481, 2957, 2935, 1815, 1750, 1688, 1472, 1370, 1265, 1235, 1174, 1094, 1025. HRMS (FAB) calcd for $C_{32}H_{51}O_{13}SSi$ (MH^+) 703.2820, found 703.2814.

3.1.6. Compound 16. To a solution of **15** (320 mg, 0.45 mmol) in THF (27 mL) was added a solution of tetrabutylammonium fluoride trihydrate (156 mg, 0.49 mmol) in THF (3 mL). The reaction mixture was stirred at rt for 5 min and ethyl acetate was added. The resulting solution was washed with aq $NaHCO_3$ and water and dried over anhyd $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by dry flash chromatography (eluent: benzene/ethyl acetate=6/4) to give **16** (216 mg, 83%) as a colorless film. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.03 (1H, d, J=10.2 Hz), 5.63 (1H, d, J=10.4 Hz), 4.87 (1H, d, J=4.4 Hz), 4.79 (1H, br s), 4.11 (1H, br s), 3.99 (1H, d, J=19.3 Hz), 3.99 (1H, d, J=11.3 Hz), 3.85 (1H, br s), 3.62 (1H, d, J=10.9 Hz), 3.00 (3H, s), 2.85 (1H, d, J=4.4 Hz), 2.83 (1H, d, J=19.3 Hz), 2.25 (3H, s), 2.11 (3H, s), 2.05 (3H, s), 2.10–1.65 (4H, m), 1.66 (3H, s), 1.33 (3H, s), 0.92 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 197.64 (C), 170.29 (C), 169.31 (C), 153.12 (C), 149.68 (C), 143.33 (C), 88.94 (C), 81.75 (CH), 79.57 (CH), 75.20 (CH), 73.85 (C), 72.63 (CH), 62.16 (CH_2), 43.44 (C), 43.01 (CH), 41.44 (C), 40.91 (CH_2), 38.60 (CH_3), 32.66 (CH_3), 24.93 (2×CH_2), 20.63 (CH_3), 20.54 (CH_3), 19.96 (CH_3), 18.90 (CH_3), 13.75 (CH_3). IR (film) ν_{max}: 3563, 3455, 2967, 2934, 1806, 1750, 1685, 1414, 1375, 1346, 1273, 1238, 1033. HRMS (FAB) calcd for $C_{26}H_{37}O_{13}S$ (MH^+) 589.1955, found 589.1998. $[\alpha]_D^{25}$ +152 (*c* 1.0, ethyl acetate).

3.1.7. Compound 17. A solution of **16** (62 mg, 0.1 mmol) and DIPEA (95 mg, 0.74 mmol) in anhyd toluene (15.2 mL) was heated to reflux with stirring for 24 h. The solvent was removed under reduced pressure and the residue was purified by dry flash chromatography (eluent: benzene/ethyl acetate=6/4) to give compound **17** (47 mg, 90%) as a colorless film. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.96 (1H, d, J=10.4 Hz), 5.73 (1H, d, J=10.6 Hz), 4.94 (1H, d, J=5.1 Hz), 4.81–4.76 (1H, m), 4.64 (1H, d, J=9.0 Hz), 4.47 (1H, d, J=9.2 Hz), 3.73 (1H, d, J=19.1 Hz), 3.12 (1H, s), 2.80 (1H, d, J=19.3 Hz), 2.19 (1H, d, J=5.3 Hz), 2.14 (3H, s), 2.11 (3H, s), 2.40–1.60 (4H, m), 2.06 (3H, s), 1.70 (3H, s), 1.43 (3H, s), 1.32 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 197.47 (C), 170.22 (C), 169.42 (C), 152.92 (C), 149.53 (C), 142.52 (C), 88.42 (C), 87.83 (CH), 80.00 (CH_2), 79.42 (CH), 75.25 (CH), 74.52 (C), 72.67 (CH), 46.56 (CH), 42.68 (C), 41.35 (C), 40.71 (CH_2), 32.41 (CH_3), 27.82 (CH_2), 26.40 (CH_2), 20.70 (CH_3), 20.60 (CH_3), 20.05 (CH_3), 16.32 (CH_3),13.93 (CH_3). IR (film) ν_{max}: 3479, 2993, 2965, 1812, 1750, 1690, 1375, 1271, 1238, 1022. HRMS (FAB) calcd for $C_{25}H_{33}O_{10}$ (MH^+) 493.2074, found 493.2317. $[\alpha]_D^{25}$ +147 (*c* 1.0, ethyl acetate).

3.1.8. Compound 18. To a solution of **11** (300 mg, 0.49 mmol) in a mixture of THF, EtOH, and water (1:1:1, 54 mL) were added hydroxylamine hydrochloride (170 mg, 2.47 mmol) and triethylamine (250 mg, 2.47 mmol). The solution was stirred and heated at 80 °C for 30 h. The reaction mixture was diluted with CH_2Cl_2 and water, the organic layer was separated and dried over anhyd $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by dry flash chromatography (eluent: petroleum ether/ethyl acetate=6/4) to give compound **18** (120 mg, 50%) as a colorless film. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.11 (1H, d, J=10.2 Hz), 5.71 (1H, d, J=10.2 Hz), 5.39 (1H, br s), 5.18 (1H, br s), 4.95 (1H, d, J=5.7 Hz), 4.20 (1H, br s), 3.61 (1H, d, J=5.5 Hz), 2.90 (2H, br s), 2.25 (3H, s), 2.10 (3H, s), 2.07 (3H, s), 1.85–1.60 (4H, m), 1.68 (3H, s), 1.32 (3H, s), 0.96 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 196.86 (C), 170.09 (C), 169.62 (C), 152.74 (C), 148.74 (C), 144.79 (C), 142.56 (C), 114.87 (CH_2), 88.78 (C), 79.71 (CH), 75.52 (CH), 74.49 (CH), 72.63 (CH), 44.72 (2×C), 40.80 (CH and CH_2), 32.41 (CH_3), 29.42 (CH_2), 26.16 (CH_2), 20.63 (CH_3), 20.45 (CH_3), 19.96 (CH_3), 17.04 (CH_3), 14.28 (CH_3). IR (KBr) ν_{max}: 2998, 2958, 1818, 1750, 1714, 1686, 1638, 1374, 1310, 1270, 1202, 1163, 1032. HRMS (FAB) calcd for $C_{25}H_{32}O_9Na$ (MNa^+) 499.1944, found 499.1930. $[\alpha]_D^{25}$ +179 (*c* 1.1, CH_2Cl_2).

3.1.9. Compound 19. In a Pyrex, external water-cooled reactor, to a deaerated suspension of **17** (96 mg, 0.195 mmol), silver acetate (130 mg, 0.778 mmol), and benzene (8.8 mL) was added a solution of bromine (62 mg, 0.387 mmol) in benzene (0.7 mL). The reaction mixture was irradiated for 5 min with a 250 W Xenophot sun-lamp focalized light, with stirring under an argon atmosphere. The reaction mixture was filtered and diluted with CH_2Cl_2, washed successively with 5% $Na_2S_2O_3$, aq $NaHCO_3$, and water, and dried over anhyd $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by dry flash chromatography (eluent: benzene/ethyl acetate=7/3) to give acetate **19** (β/α=10.5/1) (65 mg, 60%) as a colorless film. Spectroscopic data for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.08 (1H, d, J=10.5 Hz, H-10), 5.96–5.94 (1H, m, H-5), 5.75 (1H, d, J=10.5 Hz, H-9), 4.94 (1H, d, J=7.1 Hz, H-2), 4.16 (1H, d, J=17.6 Hz, H-20), 3.95 (1H, d, J=7.1 Hz, H-3), 3.74 (1H, d, J=17.6 Hz, H-20), 2.98 (1H, d, J=19.4 Hz, H-14), 2.73 (1H, d, J=19.4 Hz, H-14), 2.29 (3H, s, H-18), 2.15–2.05 (1H, m, H-7), 2.13 (3H, s, Ac), 2.09 (3H, s, Ac), 2.08 (3H, s, Ac), 1.85–1.72 (1H, m, H-6), 1.70 (3H, s, H-16 or H-17), 1.60–1.50 (1H, m, H-7), 1.50–1.40 (1H, m, H-6), 1.34 (3H, s, H-17 or H-16), 1.02 (3H, s, H-19). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.94 (C, C-4), 195.06 (C, C-13), 169.65 (C, Ac), 169.33 (C, Ac), 168.82 (C, Ac), 151.60 (C, CO), 148.75 (C, C-11), 142.09 (C, C-12), 95.71 (CH, C-5), 88.49 (C, C-1), 77.37 (CH, C-2), 74.54 (CH, C-9), 71.99 (CH, C-10), 69.12 (CH_2, C-20), 47.52 (CH, C-3), 45.76 (C, C-8), 40.99 (CH_2, C-14), 40.82 (C, C-15), 32.30 (CH_3, C-16 or C-17), 28.73 (CH_2, C-7), 24.98 (CH_2, C-6), 20.91 (CH_3, Ac), 20.71 (CH_3, Ac), 20.52 (CH_3, Ac), 20.09 (CH_3, C-17 or C-16), 18.25 (CH_3, C-19), 14.94 (CH_3, C-18). IR (film) ν_{max}: 2998, 1821, 1750, 1693, 1375, 1235, 1025. HRMS: $C_{27}H_{34}O_{12}Na$ 573.1948, found 573.1959.

3.1.10. Compound 22. In a Pyrex, external water-cooled reactor, to a deaerated suspension of **17** (220 mg, 0.447 mmol), silver acetate (112 mg, 0.670 mmol), and benzene (21 mL) was added a solution of bromine (143 mg, 0.894 mmol) in benzene (1.9 mL). The reaction mixture was irradiated for 5 min with a 250 W Xenophot sun-lamp focalized light, with stirring under an argon atmosphere. The reaction mixture was filtered and diluted with CH_2Cl_2, washed successively with 5% $Na_2S_2O_3$, aq $NaHCO_3$, and water, and dried over anhyd $MgSO_4$. After concentration under reduced pressure, the crude **21** (260 mg, equimolar mixture of diastereoisomers) was used in the next step without further purification.

In a Pyrex, external water-cooled reactor, a deaerated solution of bromides **21** (260 mg, 0.447 mmol), TBTH (1.3 g, 4.47 mmol), AIBN, and benzene (8 mL) was irradiated for 15 min with a 250 W Xenophot sun-lamp focalized light, with stirring under an argon atmosphere. After removal of the solvent under reduced pressure, the crude product was purified by dry flash chromatography (eluent: benzene/ethyl acetate=8/2) to give compound **22** (135 mg, 61%) as a colorless film. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.10 (1H, d, J=10.5 Hz, H-10), 5.74 (1H, d, J=10.5 Hz, H-9), 4.94 (1H, d, J=7.0 Hz, H-2), 4.06 (1H, d, J=7.0 Hz, H-3), 3.91 (1H, d, J=17.2 Hz, H-20), 3.78–3.64 (1H, m, H-5), 3.59–3.52 (1H, m, H-5), 3.48 (1H, d, J=17.2 Hz, H-20), 2.98 (1H, d, J=19.3 Hz, H-14), 2.73 (1H, d, J=19.4 Hz, H-14), 2.26 (3H, s, H-18), 2.12 (3H, s, Ac), 2.25–2.10 (1H, m, H-7), 2.07 (3H, s, Ac), 1.69 (3H, s, H-16 or H-17), 1.72–1.30 (3H, m, H-6 and H-7), 1.33 (3H, s, H-17 or H-16), 0.99 (3H, s, H-19). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 207.14 (C, C-4), 195.49 (C, C-13), 169.80 (C, Ac), 169.38 (C, Ac), 151.81 (C, CO), 148.93 (C, C-11), 141.91 (C, C-12), 88.45 (C, C-1), 77.38 (CH, C-2), 75.91 (CH_2, C-20), 74.80 (CH, C-9), 72.47 (CH_2, C-5), 71.97 (CH, C-10), 46.90 (CH, C-3), 44.97 (C, C-8), 40.82 (CH_2, C-14), 40.70 (C, C-15), 32.19 (CH_3, C-16 or C-17), 31.63 (CH_2, C-7), 21.20 (CH_2, C-6), 20.56 (CH_3, Ac), 20.32 (CH_3, Ac), 19.90 (CH_3, C-17 or C-16), 17.83 (CH_3, C-19), 14.66 (CH_3, C-18). IR (film) ν_{max}: 2958, 1818, 1747, 1692, 1373, 1268, 1234, 1026. HRMS (MALDI-FTMS) calcd for $C_{25}H_{32}O_{10}Na$ (M+Na$^+$) 515.1888, found 515.1885. $[\alpha]_D^{25}$ +180 (*c* 1.0, ethyl acetate).

3.1.11. Compound 23. A cold (−80 °C) solution of **22** (70 mg, 0.142 mmol) in THF (15 mL) was treated with PhLi (240 mg, 1.5 mL of a 1.9 M solution in toluene) and stirred at −80 °C for 6 h under an argon atmosphere. The reaction mixture was quenched with satd aq NH_4Cl (10 mL) and then allowed to warm to rt. After dilution with CH_2Cl_2, the organic layer was separated, dried over anhyd $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (6 mL) and acetic anhydride (147 mg, 1.42 mmol) and DMAP (87 mg, 0.71 mmol) was added. The mixture was stirred for 30 min at rt and diluted with CH_2Cl_2. The resulting solution was washed with satd aq $NaHCO_3$, 1.5 M HCl and water, and dried over anhyd $MgSO_4$. After removal of the solvent under reduced pressure the residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate=7/4) to give benzoate **23** (47 mg, 58%, 62% based on recovered carbonate **22**) as a colorless film, followed by the starting compound **22** (4 mg). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.86–7.82 (2H, m), 7.61–7.53 (1H, m), 7.47–7.39 (2H, m), 6.20 (1H, d, J=10.5 Hz), 6.01 (1H, d, J=10.6 Hz), 5.88 (1H, d, J=7.7 Hz), 4.32 (1H, d, J=7.7 Hz), 3.87 (1H, d, J=16.0 Hz), 3.78–3.64 (1H, m), 3.53–3.45 (1H, m), 3.37 (1H, d, J=16.1 Hz), 2.94 (1H, d, J=19.6 Hz), 2.80 (1H, d, J=19.4 Hz), 2.26 (3H, s), 2.11 (3H, s), 2.09 (3H, s), 2.05–1.45 (4H, m), 1.76 (3H, s), 1.27 (3H, s), 1.00 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 211.00 (C), 198.55 (C), 169.73 (C), 169.62 (C), 165.14 (C), 151.45 (C), 140.03 (C), 133.28 (CH), 129.53 (C), 129.47 (CH), 128.45 (CH), 77.98 (C), 77.36 (CH_2), 74.71 (CH), 72.72 (CH_2), 72.21 (CH), 72.17 (CH), 50.84 (CH), 44.17 (CH_2 and C), 42.50 (C), 33.83 (CH_3), 31.45 (CH_2), 21.54 (CH_2), 20.78 (CH_3), 20.54 (CH_3), 20.01 (CH_3), 17.88 (CH_3), 13.99 (CH_3). IR (film) ν_{max}: 3497, 2986, 1746, 1680, 1451, 1374, 1269, 1231, 1096, 1026. HRMS (TOF MS ES+) calcd for $C_{31}H_{39}O_{10}$ (MH$^+$) 571.2543, found 571.2548. $[\alpha]_D^{25}$ +112 (*c* 1.0, ethyl acetate).

3.1.12. Compound 24. A solution of **23** (40 mg, 0.070 mmol) in methanol (5.7 mL) was treated with excess of $NaBH_4$ (53 mg, 1.40 mmol) for 1 h at rt. The reaction was quenched with satd aq NH_4Cl and the resulting mixture was stirred for 10 min. After dilution with water, the reaction mixture was extracted twice with CH_2Cl_2 and dried over anhyd $MgSO_4$. Concentration under reduced pressure, followed by purification of the residue by column chromatography (eluent: benzene/ethyl acetate=6/4) gave alcohol

24 (29 mg, 72%) as a white amorphous solid (mp 139–141 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.87–7.83 (2H, m), 7.59–7.51 (1H, m), 7.45–7.37 (2H, m), 6.11 (1H, d, J=10.4 Hz), 5.89 (1H, d, J=10.4 Hz), 5.76 (1H, d, J=7.1 Hz), 4.73–4.61 (1H, m), 4.40 (1H, d, J=6.9 Hz), 4.07 (1H, d, J=16.0 Hz), 3.95–3.77 (1H, m), 3.69–3.55 (1H, m), 3.47 (1H, d, J=16.2 Hz), 3.14 (1H, d, J=10.9 Hz), 2.63 (1H, dd, J_1=15.8 Hz, J_2=10.4 Hz), 2.29 (3H, s), 2.23–2.16 (1H, m), 2.10–1.28 (4H, m), 2.07 (3H, s), 2.05 (3H, s), 1.66 (3H, s), 1.07 (3H, s), 0.99 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 210.69 (C), 169.96 (C), 169.76 (C), 165.19 (C), 142.73 (C), 133.99 (C), 133.17 (CH), 129.85 (C), 129.51 (CH), 128.45 (CH), 77.09 (C), 76.49 (CH_2), 75.85 (CH), 73.56 (CH_2), 72.88 (CH), 72.41 (CH), 69.35 (CH), 51.11 (CH), 43.95 (C), 41.92 (CH_2), 41.53 (C), 31.87 (CH_2), 28.98 (CH_3), 21.62 (CH_2), 20.96 (CH_3), 20.61 (CH_3), 20.38 (CH_3), 17.94 (CH_3), 16.74 (CH_3). IR (film) ν_{max}: 3474, 2932, 2875, 1737, 1630, 1452, 1374, 1244, 1094, 1024. HRMS (TOF MS ES+) calcd for $C_{31}H_{40}O_{10}Na$ ($M+Na^+$) 595.2519, found 595.2493. $[\alpha]_D^{25}$ +41 (*c* 1.0, ethyl acetate).

3.1.13. Compound 26. To a solution of carboxylic acid **25** (73.0 mg, 0.181 mmol), alcohol **24** (26.0 mg, 0.045 mmol) and DMAP (22.2 mg, 0.181 mmol) in toluene (11.0 mL) was added DCC (37.4 mg, 0.181 mmol) in toluene (1.4 mL), at rt, under an argon atmosphere. The reaction mixture was stirred at 75 °C for 30 min. After filtration and removal of the solvent under reduced pressure, the product was roughly purified by short column chromatography (eluent: benzene/ethyl acetate=7/3) to give the protected ester (41.3 mg, 93%).

Acidic deprotection: the product from the previous step was treated with 5% methanolic *p*-TsOH (7.0 mL) at rt for 30 min. The reaction mixture was diluted with ethyl acetate, washed successively with aq $NaHCO_3$ and brine, dried over anhyd $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/ethyl acetate=1/1) to give ester **26** (26.9 mg, 75%) as a colorless film.

Deprotection with CAN: to a stirred solution of protected compound (15 mg, 0.015 mmol) in acetonitrile (0.9 mL) was added a solution of CAN (25.2 mg, 0.046 mmol) in water (0.9 mL). The resulting yellow mixture was stirred at 40 °C for 2.5 h, diluted with CH_2Cl_2, organic layer was separated and dried over anhyd $MgSO_4$. The residue was purified by column chromatography (eluent: hexane/ethyl acetate=1/1) to give compound **26** (8.7 mg, 66%) as a colorless film. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.03 (2H, dd, J_1=8.0 Hz, J_2=1.0 Hz, Ar), 7.81 (2H, dd, J_1=8.5 Hz, J_2=1.5 Hz, Ar), 7.54–7.48 (4H, m, Ar), 7.43 (2H, t, J=7.5 Hz, Ar), 7.40–7.30 (5H, m, Ar), 7.25 (1H, d superimposed with $CDCl_3$, J=9.5 Hz, N–H), 6.07 (1H, d, J=10.5 Hz, H-10), 6.06–6.03 (1H, m, H-13), 5.93 (1H, d, J=9.5 Hz, H-3′), 5.93 (1H, d, J=10.5 Hz, H-9), 5.79 (1H, d, J=7.5 Hz, H-2), 4.73 (1H, br s, H-2′), 4.65 (1H, d, J=16.0 Hz, H-20), 4.41 (1H, d, J=7.5 Hz, H-3), 3.88 (1H, br s, OH), 3.86–3.78 (1H, m, H-5), 3.68–3.65 (1H, m, H-5), 3.48 (1H, d, J=16.0 Hz, H-20), 2.46 (1H, dd, J_1=16.0 Hz, J_2=9.5 Hz, H-14), 2.39 (1H, dd, J_1=16.0 Hz, J_2=5.0 Hz, H-14), 2.15–2.00 (1H, m, H-7), 2.08 (3H, s, Ac), 2.05 (3H, s, Ac), 1.96 (3H, s, H-18), 1.70 (3H, s, H-17 or H-16), 1.65–1.50 (1H, m, H-7), 1.40–1.20 (2H, m, H-6), 1.13 (3H, s, H-16 or H-17), 0.99 (3H, s, H-19). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 211.21 (C, C-4), 171.79 (C-1′), 169.93 (C, Ac), 169.75 (C, Ac), 166.51 (C, Ar), 165.51 (C, Ar), 138.70 (C, Ar), 137.99 (C, C-12), 135.39 (C, C-11), 134.12 (C, Ar), 133.10 (CH, Ar), 131.79 (CH, Ar), 129.95 (CH, Ar), 129.67 (C, Ar), 128.69 (CH, Ar), 128.65 (CH, Ar), 128.40 (CH, Ar), 127.94 (CH, Ar), 127.00 (CH, Ar), 126.92 (CH, Ar), 77.31 (CH_2, C-20), 75.47 (CH, C-9), 74.09 (CH, C-2′), 73.07 (CH, C-2), 72.87 (CH_2, C-5), 72.32 (CH, C-13), 71.68 (CH, C-10), 54.20 (CH, C-3′), 51.55 (CH, C-3), 44.15 (C, C-8), 41.53 (C, C-15), 36.72 (CH_2, C-14), 31.24 (CH_2, C-7), 28.91 (CH_3, C-16 or C-17), 21.61 (CH_2, C-6), 20.94 (CH_3, Ac), 20.63 (2×CH_3, Ac and C-17 or C-16), 17.94 (CH_3, C-19), 16.04 (CH_3, C-18). The signal corresponding to C-1 could not be detected under the recording conditions. IR (film) ν_{max}: 3443, 2931, 1737, 1662, 1517, 1487, 1452, 1373, 1243, 1096, 1025. HRMS (ESI-TOF high acc) calcd for $C_{47}H_{54}NO_{13}$ (MH^+) 840.3589, found 840.3575. $[\alpha]_D^{25}$ +95 (*c* 1.6, ethyl acetate).

3.1.14. Spectroscopic data for 27. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (2H, dd, J_1=7.0 Hz, J_2=1.5 Hz, Ar), 7.78–7.75 (2H, m, Ar), 7.54–7.50 (3H, m, Ar), 7.46–7.36 (4H, m, Ar), 7.34–7.29 (2H, m, Ar), 7.20–7.17 (2H, m, Ar), 6.95 (1H, d, J=9.5 Hz, N–H), 6.41 (1H, d, J=9.5 Hz, H-2), 6.19 (1H, d, J=10.0 Hz, H-10), 5.89–5.87 (1H, m, H-3′), 5.88 (1H, d, J=10.0 Hz, H-9), 5.79 (1H, br t, J=6.5 Hz, H-13), 4.69 (1H, d, J=2.0 Hz, H-2′), 4.38 (1H, d, J=17.0 Hz, H-20), 4.34 (1H, d, J=9.0 Hz, H-3), 3.83–3.77 (1H, m, H-5), 3.60–3.57 (1H, m, H-5), 3.37 (1H, d, J=17.5 Hz, H-20), 2.52 (1H, dd, J_1=15.5 Hz, J_2=6.0 Hz, H-14), 2.44 (1H, dd, J_1=15.5 Hz, J_2=7.5 Hz, H-14), 2.08–2.03 (1H, m, H-7), 2.05 (3H, s, Ac), 2.03 (3H, s, Ac), 1.87 (3H, s, H-18), 1.65–1.20 (3H, m, H-7 and H-6), 1.13 (3H, s, H-17 or H-16), 1.11 (3H, s, H-16 or H-17), 1.05 (3H, s, H-19). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 212.12 (C, C-4), 172.51 (C-1′), 169.51 (C, Ac), 168.64 (C, Ac), 166.68 (C, Ar), 165.09 (C, Ar), 145.82 (C, C-11), 139.28 (C, Ar), 137.51 (C, C-12), 135.00 (C, Ar), 132.63 (CH, Ar), 131.65 (CH, Ar), 130.29 (C, Ar), 129.75 (CH, Ar), 128.78 (CH, Ar), 128.33 (CH, Ar), 128.00 (CH, Ar), 127.11 (CH, Ar), 127.06 (CH, Ar), 127.04 (CH, Ar), 81.68 (CH, C-13), 76.34 (CH, C-9), 76.17 (CH_2, C-20), 74.97 (C, C-15), 73.49 (CH, C-2′), 72.58 (CH_2, C-5), 69.11 (CH, C-10), 68.85 (C, C-1), 67.95 (CH, C-2), 54.38 (CH, C-3′), 50.28 (CH, C-3), 42.28 (C, C-8), 36.46 (CH_2, C-14), 32.36 (CH_2, C-7), 27.48 (CH_3, C-16 or C-17), 25.25 (CH_3, C-16 or C-17), 21.82 (CH_2, C-6), 20.86 (CH_3, Ac), 20.68 (CH_3, Ac), 18.14 (CH_3, C-19), 12.05 (CH_3, C-18). IR (film) ν_{max}: 3450, 2921, 1730, 1663, 1517, 1486, 1454, 1372, 1233, 1100, 1030. HRMS (ESI-TOF high acc) calcd for $C_{47}H_{53}NO_{13}Na$ (MH^+) 862.3409, found 862.3416. $[\alpha]_D^{25}$ −1.9 (*c* 0.53, ethyl acetate).

3.2. Biological assays

Tubulin test was performed according to the described procedure.[30]

3.2.1. Cell culture and determination of cell viability. The cells of the rat glioma cell line C6 (ATCC) were seeded in

96-well flat-bottom plates (2×10^4 cells/well) and incubated with paclitaxel or compound **26** for 48 h. The cells were cultivated at 37 °C in a humidified atmosphere with 5% CO_2, in a HEPES-buffered RPMI 1640 cell culture medium supplemented with 5% fetal calf serum, 2 mmol L-glutamine, 50 μmol 2-mercaptoethanol, 10 mmol sodium pyruvate and penicillin/streptomycin (all from Sigma, St. Louis, MO). Cell viability was analyzed by staining the viable cells with crystal violet, or by measuring the mitochondrial-dependent reduction of 3-[4,5-dimethyl thiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT) to formazan. Both crystal violet and MTT test were performed exactly as previously described,[31] and the results were presented as % viability relative to untreated control.

3.3. Modeling

All calculations including energy minimization, conformational searches, and Glide Docking were performed in Maestro (Schördinger Inc.).[22] With the exception of the free radical intermediate **30**, 10,000-step MMFF/GBSA/H_2O conformational searches were performed for taxane analogs within 7.0 kcal/mol of the global minimum. For C-5 of the C–O–C•–C radical unit of intermediate **30** (Scheme 3 and Fig. 2), a set of provisional force field parameters were employed in a 10,000-step gas phase MM3* conformational search.

A local modification of the refined electron crystallographic complex of PTX/β-tubulin[32] was made prior to docking. Thus, Arg284 on the M-loop was relocated from the electron crystallographic position so as to form a hydrogen bond with PTX's C-10 acetyl group. Without this modification, the Glide method (Schrödinger Inc.)[34,22] docks the taxane structures in an inverted binding pose that directs the two C-13 side chain phenyl rings out into solvent instead of deep within the hydrophobic pocket. With the M-loop modified protein, however, Glide is able to accurately predict the binding mode for PTX conformation as observed in the refined electron crystallographic complex.[32] Accordingly, taxane analogs **22** and **26** were constructed with the C-13 T-taxane geometry and the *seco*-C,D ring conformer illustrated in Figure 3 followed by rigid Glide Docking into the complex. The best docking poses were chosen on the basis of the Emodel scoring function together with visualization to ensure reasonable binding modes.

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References and notes

1. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327.
2. (a) Kingston, D. G. I.; Jagtap, P. G.; Yuan, H.; Samala, L. *Prog. Chem. Org. Nat. Prod.* **2002**, *84*, 53–225; (b) Gueritte, F. *Curr. Pharm. Des.* **2001**, *7*, 933–953; (c) *The Chemistry and Pharmacology of Taxol and its Derivatives, Pharmacochemistry Library*; Farina, V., Ed.; Elsevier: Amsterdam, 1995; Vol. 22.
3. Guenard, D.; Gueritte-Voegelin, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160–167.
4. (a) Wang, M.; Cornett, B.; Nettles, J.; Liotta, D. C.; Snyder, J. P. *J. Org. Chem.* **2000**, *65*, 1059–1068; (b) Boge, T. C.; Hepperle, M.; Vander Velde, D. G.; Gunn, C. W.; Grunewald, G. L.; Georg, G. I. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3041–3046.
5. Marder-Karsenti, R.; Dubois, J.; Bricard, L.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **1997**, *62*, 6631–6637.
6. (a) Merckle, L.; Dubois, J.; Place, E.; Thoret, S.; Gueritte, F.; Guenard, D.; Poupat, C.; Ahond, A.; Potier, P. *J. Org. Chem.* **2001**, *66*, 5058–5065; (b) Gunatilaka, A. L.; Ramdayal, F. D.; Sarragiotto, M. H.; Kingston, D. G. I.; Sackett, D. L.; Hamel, E. *J. Org. Chem.* **1999**, *64*, 2694–2703.
7. (a) Barboni, L.; Data, A.; Gutta, D.; Georg, G. I.; Vander Velde, D. G.; Himes, R. H.; Wang, M.; Snyder, J. P. *J. Org. Chem.* **2001**, *66*, 3321–3329; (b) Deka, V.; Dubois, J.; Thoret, S.; Gueritte, F.; Guenard, D. *Org. Lett.* **2003**, *5*, 5031–5034; (c) Beusker, P. H.; Veldhuis, H.; Brinkhorst, J.; Hetterscheid, D. G. H.; Feichter, N.; Bugaut, A.; Scheeren, H. W. *Eur. J. Org. Chem.* **2003**, 689–705; (d) Samaranayake, G.; Magri, N. F.; Jitrangsrei, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114–5119.
8. Dubois, J.; Thoret, S.; Gueritte, F.; Guenard, D. *Tetrahedron Lett.* **2000**, *41*, 3331–3334.
9. Barboni, L.; Giarlo, G.; Ricciutelli, M.; Ballini, R.; Georg, G. I.; Vander Velde, D. G.; Himes, R. H.; Wang, M.; Lakdawala, A.; Snyder, J. P. *Org. Lett.* **2004**, *4*, 461–464.
10. (a) Chaudhary, A. G.; Rimoldi, J. M.; Kingston, D. G. I. *J. Org. Chem.* **1993**, *58*, 3798–3799; (b) Chen, S.-H.; Huang, S.; Kant, J.; Fairchild, C.; Wei, J.; Farina, V. *J. Org. Chem.* **1993**, *58*, 5028–5029.
11. (a) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823–9838; (b) Wiegerinck, P. H. G.; Fluks, F.; 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; (c) Poujol, H.; Ahond, A.; Al Mourabit, A.; Chiaroni, A.; Poupat, C.; Riche, C.; Potier, P. *Tetrahedron* **1997**, *53*, 5169–5184; (d) Poujol, H.; Al Mourabit, A.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1997**, *53*, 12575–12594.
12. (a) Saicic, R. N.; Matovic, R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 59–65; (b) Matovic, R.; Saicic, R. N. *J. Chem. Soc., Chem. Commun.* **1998**, 1745–1746.
13. (a) Lucas, H. *Arch. Pharmacol.* **1856**, *85*, 145–149; (b) Appendino, G. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: 1996; Vol. 11, pp 237–268; (c) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *J. Nat. Prod.* **1991**, *54*, 1455–1458; (d) Jenniskens, L. H. D.; van Rosendaal, E. L. M.; van Beek, T. A.; Wiegerinck, P. H. G.; Scheeren, H. W. *J. Nat. Prod.* **1996**, *59*, 117–123.
14. For a preliminary report, see: Ferjancic, Z.; Matovic, R.; Cekovic, Z.; Snyder, J. P.; Saicic, R. N. *Tetrahedron Lett.* **2005**, *46*, 5049–5052.
15. (a) Moriarty, R. M.; Chang, C. J., II; Kosmeder, J. W., II. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, NY, 1995; Vol. 2, p 1484; (b) Moriarty, R. M.; Chang, C. J., II; Kosmeder, J. W., II;

Du Bois, J. *Electronic Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, NY, 2005; doi:10.1002/047084289x.rd005m; http://www.mrw.interscience.wiley.com/eros/articles/rd005m/frame.html; (c) Gonzalez, A. G.; Dorta, R. L.; Rovelo, A. G.; Luis, J. G. *J. Chem. Res., Synop.* **1988**, 150–151; (d) Concepcion, J. I.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1953–1956; (e) Freire, R.; Marrero, J. J.; Rodriguez, M. S.; Suarez, E. *Tetrahedron Lett.* **1986**, *27*, 383–386.

16. Georg, G. I.; Hariman, G. C. B.; Datta, A.; Ali, S.; Cheruvallath, Z.; Dutta, D.; Vander Velde, D. G. *J. Org. Chem.* **1998**, *63*, 8926–8934.
17. Klein, L. L. *Tetrahedron Lett.* **1993**, *34*, 2047–2050.
18. (a) Bathini, Y.; Micetich, R. G.; Daneshtalab, M. *Synth. Commun.* **1994**, *24*, 1513–1517; (b) Fenoglio, I.; Nano, G. M.; Vander Velde, G. M.; Appendino, G. *Tetrahedron Lett.* **1996**, *37*, 3203–3206.
19. (a) Saicic, R. N. *Tetrahedron Lett.* **1997**, *38*, 295–298; (b) Saicic, R. N.; Cekovic, Z. *J. Serb. Chem. Soc.* **1997**, *62*, 727–735; (c) Iwasa, S.; Rawal, V. H. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, NY, 1995; Vol. 5, pp 3261–3263.
20. West, F. G.; Bender, J. A. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, NY, 1995; Vol. 1, pp 688–689.
21. As MM3* does not incorporate force field parameters for the C–O–C$^{\bullet}$–C radical unit, we employed a set of generic parameters.
22. http://www.schrodinger.com/Products/macromodel.html.
23. The two lowest energy conformations of **30** (Scheme 3) fall within a 0.9 kcal/mol energy window. Both faces of C-5 are open to attack by Br$^{\bullet}$ within the two conformers.
24. The metallic silver precipitate observed in the reaction mixture upon completion of the reaction supports the latter mechanism. However, both mechanisms may operate simultaneously.
25. (a) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624–633; (b) Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599–1600.
26. (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522; (b) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285–288; (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102.
27. Langley, C. H.; Lii, J.-H.; Allinger, N. L. *J. Comput. Chem.* **2001**, *22*, 1451–1475.
28. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.
29. Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Chem. Soc., Chem. Commun.* **1994**, 2591–2592.
30. Chauviere, G.; Guenard, D.; Picot, F.; Senilh, V.; Potier, P. *C. R. Hebd. Seances Acad. Sci. Ser. II* **1981**, *293*, 501–503.
31. Kaludjerovic, G. N.; Miljkovic, D.; Momcilovic, M.; Djinovic, V. M.; Mostarica Stojkovic, M.; Sabo, T. J.; Trajkovic, V. *Int. J. Cancer* **2005**, *116*, 479–486.
32. Snyder, J. P.; Nettles, J. H.; Cornett, B.; Downing, K. H.; Nogales, E. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5312–5316.
33. (a) Ganesh, T.; Guza, R. C.; Bane, S.; Ravindra, R.; Shanker, N.; Lakdawala, A. S.; Snyder, J. P.; Kingston, D. G. I. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 10006–10011; (b) Kingston, D. G. I.; Bane, S.; Snyder, J. P. *Cell Cycle* **2005**, *4*, 279–289.
34. (a) Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shaw, D. E.; Shelley, M.; Perry, J. K.; Sander, L. C.; Shenkin, P. S. *J. Med. Chem.* **2004**, *47*, 1739–1749; (b) Halgren, T. A.; Murphy, R. B.; Friesner, R. A.; Beard, H. S.; Frye, L. L.; Pollard, W. T.; Banks, J. L. *J. Med. Chem.* **2004**, *47*, 1750–1759.
35. Metaferia, B. B.; Hoch, J.; Glass, T. E.; Bane, S. L.; Chatterjee, S. K.; Snyder, J. P.; Lakdawala, A.; Cornett, B.; Kingston, D. G. I. *Org. Lett.* **2000**, *3*, 2461–2464.