# Synthesis and Evaluation of 14-Nor-A-*seco*taxoids

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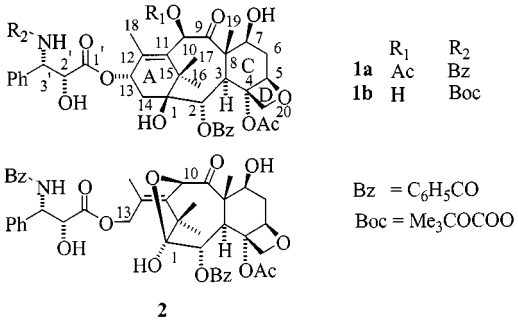
A series of 14-nor-A-secotaxoids has been prepared from 10-deacetyl-14β-hydroxybaccatin III (**3a**) and some unexpected and new reactivity of the taxane system has been revealed. The observation that the final compounds were considerably less active than taxol and their 1,10-oxygen-bridged analogues shows that the 1,10-oxygen tether can partially compensate for the opening of ring A, and suggests that 14-nor-A-secotaxoids warrant further investigation as simplified taxol mimics.

With the combined sales of taxol (**1a**) and taxotere (**1b**) approaching two billion dollars in 2000,[1] taxoids are the most successful anticancer agents ever, and no other class of natural products has received such worldwide and multidisciplinary attention over the past fifteen years.[2] In the chemical arena, the focus of taxoid research has gradually moved from the total synthesis of the natural product to the discovery of more powerful, better tolerated, and easier to administer newer-generation analogues.[3] Non-oncological potential applications of taxoids have also been discovered,[4] with powerful activity against severe conditions such as Alzheimer's disease,[4a] polycystic kidney disease,[4b] arthritis,[4c] and multiple sclerosis.[4d]

The emergence of new clinical targets suggests that the pharmacological potential of taxoids is still underexploited. This, as well as the uncertainties still shrouding the mechanism of the anticancer activity of these compounds[5] and the definition of a taxane pharmacophore,[6] has continued to inspire the search for new taxane leads. In this context, we have explored changes of connectivity within the taxane skeleton, a rigid scaffold, perturbation of which is expected to have profound effects on the biological activity.[7] The early observation that the cleavage of the oxetane D ring results in inactive compounds[8] has long deterred studies in this area. Nevertheless, both tubulin binding and cytotoxicity are substantially retained in 7,8-secotaxoids bearing norstatin-type side-chains,[9] while the A-seco analogue **2** maintains a considerable degree of activity, especially against multiply drug-resistant cell lines.[10]




**2**

The B-ring of **2** is constrained in a rigid conformation by the 1,10-oxido bridge, and it was therefore interesting to assess the contribution of this conformational lock to the overall activity of 14-nor-A-secotaxoids. The key reaction to cleave ring A is the periodate oxidation of 10-deacetyl-14β-hydroxybaccatin III (**3a**), a naturally occurring baccatin available from the Himalayan yew.[11] This generates a 1-one, which is trapped by the 10-hydroxy group with formation of a γ-lactol ring (Scheme 1). Acetylation of the 10-hydroxy group before the periodate oxidation would prevent formation of the oxido bridge, and further simplify comparison with taxol, in which the 10-hydroxy function is acetylated. The synthesis of ring B unconstrained A-nor-A-secobaccatins and their esterification with side-chains of the phenylisoserine and the norstatin types became the target of our investigation. As usual with highly functionalized molecules like taxoids, the synthesis of these compounds was plagued by unexpected reactions and complications.

10-Deacetyl-14β-hydroxybaccatin III (**3a**) has four acetylable hydroxy groups, the order of esterification of which under basic or nucleophilic catalysis conditions is 7 > 14 > 10 >> 13.[11] However, we were delighted to observe that the acyloin hydroxy group could be chemoselectively acetylated by Lewis acid catalysis under the Scheeren−Holton conditions (cat. $CeCl_3$, $Ac_2O$, THF).[12]

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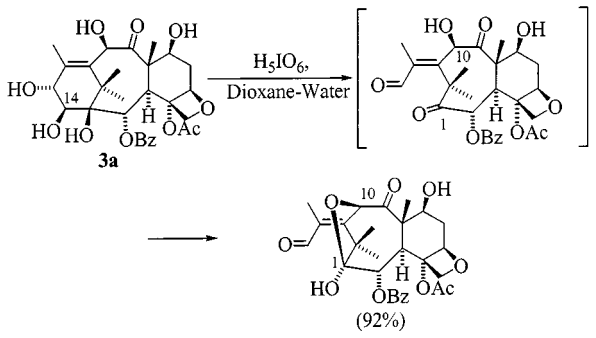
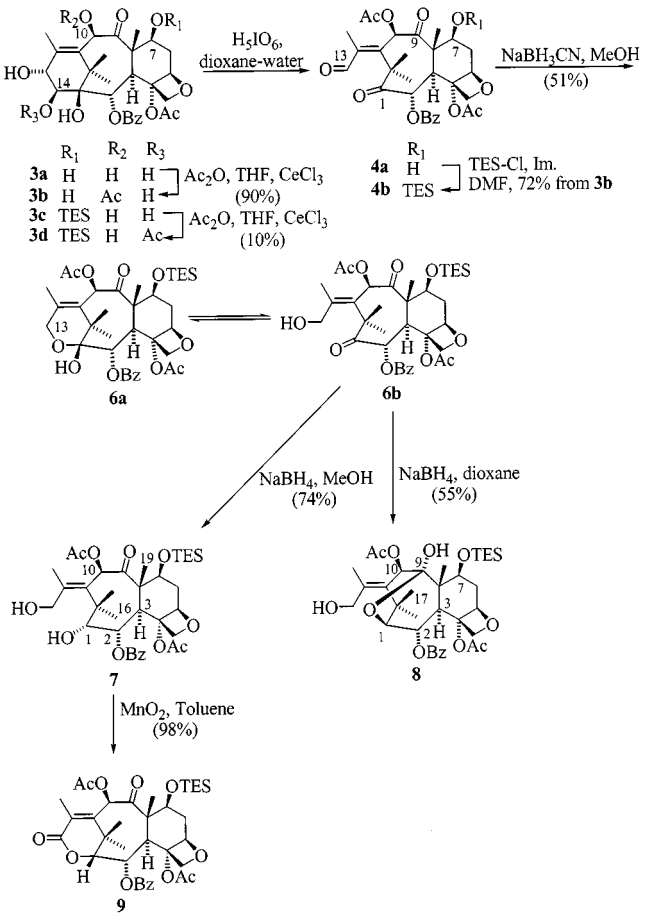



Scheme 1. Periodate cleavage of 10-deacetyl-14β-hydroxybaccatin III[10]

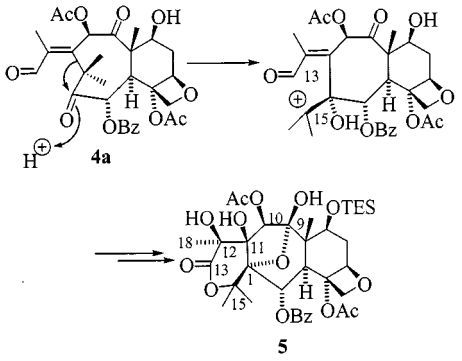
This gave the 10-acetyl derivative **3b** in 90% yield (Scheme 2). Remarkably, protection of the 7-hydroxy function as a silyl group changed the selectivity of the reaction, affording, in low yield (10%), the 14-acetyl derivative **3d** as the only reaction product (Scheme 2). A possible explanation for these observations is that the Lewis acid forms a chelate with the 10-hydroxy and the 9-carbonyl moieties and that formation of this complex somewhat activates the 10-hydroxy group toward esterification, possibly by coordination of the acetylating reagent to cerium and intramolecular acyl delivery. The capacity of Lewis acids to promote the esterification of acyloin-type hydroxy groups, even tertiary ones, had been observed previously,[13] and silylation of the 7-hydroxy group apparently prevents formation of the acyloin−Lewis acid complex, possibly because of steric hindrance.

Treatment of **3b** with periodic acid in dioxane/water gave the unstable nor-dioxoaldehyde **4a** (Scheme 2), which was contaminated by a more polar by-product (ca. 20%, $^1$H NMR analysis). The amount of the more polar impurity increased when the reaction was allowed to proceed after complete consumption of the starting material, suggesting that further oxidation and/or rearrangement of **4a** was taking place. After silylation, a mixture amenable to chromatographic purification was obtained, and the silylated dioxoaldehyde **4b** and the A-seco-14-nor-11(15→1)-*abeo* derivative **5** were obtained as pure compounds. The $^1$H NMR spectrum of **5** (Scheme 3) was at first glance similar to that of a baccatin derivative, lacking the signals of the 13- and 14-protons. However, the $^{13}$C NMR spectrum revealed dramatic differences. Thus, in comparison with the starting material, the endocyclic double bond was replaced by two oxygenated quaternary carbon atoms [δ = 88.2 and 88.3 (s)], the 9-carbonyl by an acetal group [δ = 106.3 (s)], and the oxymethine groups at C-13 and C-14 by an ester carbonyl group [δ = 172.7 (s)]. HRMS confirmed the nortaxoid nature of the compound and established the molecular formula as $C_{36}H_{50}O_{14}Si$, while HMBC experiments clarified the carbon−carbon connectivity and the 11→15-*abeo* nature of the nortaxane skeleton. Analysis of the long-range $^1$H-$^{13}$C correlations left the location of the two possible oxygen bridges required by the molecular formula undefined, since all potentially involved carbon atoms were nonprotonated. Of the possible alternatives, the 13,15-δ-lactone 1,9-ether **5** was preferred over the alternative arrangement, namely a 13,1-γ-lactone 9,15-ether, because the chemical shift of C-13 (δ = 172.7) was typical of a δ-lactone and not of a γ-lactone, which would have resonated at δ ≈ 178−180.[14] The very low field resonance of C-1 [δ = 101.1 (s)] could also be more easily accommodated in a tetrahydrofuran rather than in a tetrahydropyran structure.[15] Formation of the by-product **5** is presumably triggered by a Wagner−Meerwein rearrangement of **4a**. Closure of a 1,9-hemiacetal bridge, quenching of the 15-cation by the hydrate form of the 13-aldehyde carbonyl group and eventual lactol-to-lactone oxidation (Scheme 3) would then afford the final structure. It is not clear at what stage the dihydroxylation of the endocyclic double bond takes place. While the Wagner−Meerwein rearrangement of 1-oxygenated taxanes is well documented,[7,8] the dihydroxylation of a carbonyl-conjugated double bond under the conditions of periodate cleavage is, to the best of our knowledge, unprecedented. Also remarkable is the observation that no overoxidation took place during the periodate cleavage of **3a**, the 10-deacetyl derivative of **3b**. The compact shape of the rearranged product **5** resulted in many diagnostic NOE effects, which were instrumental in the assignment of its configuration. Especially useful were the NOE correlations be-




Scheme 2. Synthesis of the 14-nor-A-secobaccatins **6**−**8**

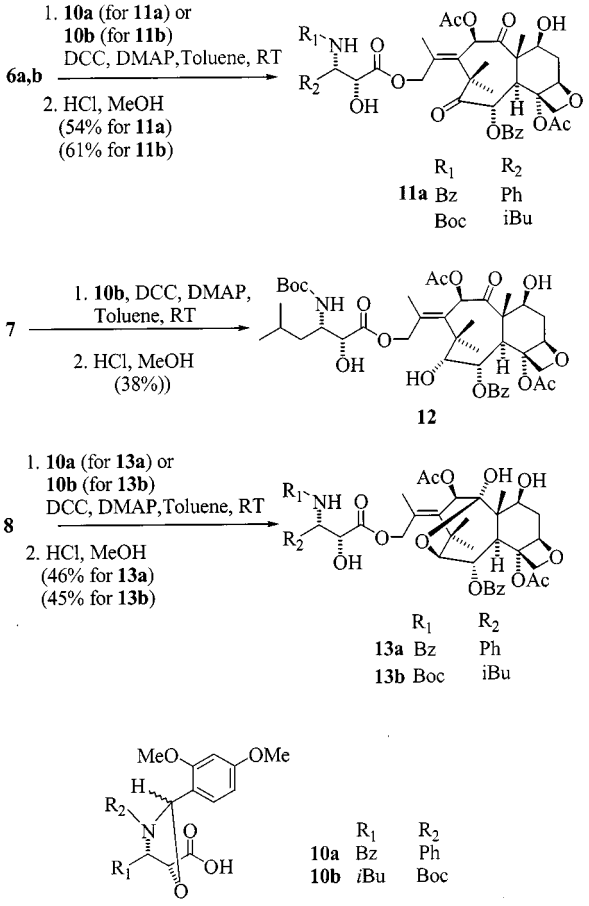
tween the 18-methyl group and 10-H and between the 15β-methyl group and 2-H.




Scheme 3. Possible mechanism of the formation of the 14-nor-A-seco-11(15→1)-*abeo*-taxane **5**

The aldehyde carbonyl group of **4b** could be chemoselectively reduced with $NaBH_3CN$ in the presence of the ketone carbonyl groups at C-1 and C-9, affording the corresponding 13-ol. This was shown by NMR to be a tautomeric mixture (4:1 in $CDCl_3$ at room temp.) of the δ-lactol **6a** and the hydroxy ketone **6b** (Scheme 2). The former was anomerically pure, because only one face of the cyclooctanone carbonyl group can be approached intramolecularly by the primary 13-hydroxy group. Reduction of the tautomeric mixture gave different compounds depending on the solvent. Thus, when the reaction was carried out in methanol, the 1-hydroxy derivative **7** was obtained as the only reaction product, and the same result was observed in ethanol and in 2-propanol. However, the hemiacetal **8** was selectively formed when methanol was replaced with dioxane. The reduction products **7** and **8** share the same molecular formula ($C_{36}H_{52}O_{10}Si$). The major difference in their $^{13}C$ NMR spectra was the replacement of the 9-carbonyl signal with an acetal carbon signal in **8** [δ = 97.9 (s)], showing that an acetal bridge had formed between C-9 and the hydroxy function at C-1. Since **7** and **8** did not interconvert in solution or in acidic medium, they thus had different configurations at C-1. The splitting pattern of 1-H was indeed different [δ = 3.40 (s) in **7**; δ = 4.01 (d, $J$ = 9.0 Hz) in **8**], but not diagnostic for a configurational assignment, which could, however, be done with the aid of NOE difference experiments. Thus, the detection in **8** of NOE effects between 7-H and 10-H and between 3-H and the α-methyl group at C-15 (17-$H_3$)[16] showed that these atoms were *syn*-oriented, a condition requiring a β-oxygen bridge between C-1 and C-9. Conversely, these NOE effects were absent in the α-alcohol **7**, the NOE effects pattern of which (16-$H_3$,19-$H_3$; 2-H,19-$H_3$; 10-H,3-H) showed an overall shape more similar to that of ring B of taxanes. We do not at present have a compelling explanation for the complementary stereochemical courses of the borohydride reduction in alcohol and in dioxane. The poor solubility and solvation of $NaBH_4$ in dioxane means that a 13-alkoxyborohydride might actually be the reducing species in dioxane, resulting in intramolecular hydride delivery from the α-face of the C-1 carbonyl group, the only one available for this type of process.[17] Treatment of **7** and **8** with activated $MnO_2$ took a very different course. While **7** afforded the crystalline δ-lactone **9** in almost quantitative yield, its isomer **8** gave a complex mixture that was not further investigated.

With the three A-secobaccatins **6**, **7**, and **8** to hand, their esterification with compact synthons of the aminoacyl side chains of first- and second-generation anticancer taxoids was investigated.[18] Treatment with the N,O-(2,4-dimethoxybenzal) derivatives **10a** and **10b**[19] was uneventful with all three compounds, the presence of the tautomeric equilibrium in **6** and of a free secondary hydroxy group at C-1 in **7** notwithstanding (Scheme 4).




Scheme 4. Esterification of the 14-nor-A-secobaccatins **6**–**8** with amino acid side chains

Deprotection with acidic methanol or formic acid eventually afforded the taxoids **11a**, **11b**, **12**, **13a**, and **13b**, which were evaluated for cytotoxicity in MCF7 breast cancer cells (Table 1). Compounds **11a**, **11b**, **13a**, and **13b** showed markedly decreased activities compared not only to taxol (500–800fold) but also to its 1,9-oxygen bridged A-seco analogue **2** (10–20fold),[10] while **12**, despite substantial retention of the taxane conformation in rings B and C, was inactive. These data show that the 1,10-oxygen bridge has an important effect on activity, acting as a partial surrogate for ring A. In sharp contrast to C-secotaxoids,[9] no major

differences in activity were observed between compounds bearing phenylisoserine and norstatin chains.

Table 1. Biological evaluation of the 14-nor-A-secotaxoids **11a**,**b**−**13a**,**b**

| Compound | $IC_{50}$ [nM] |
|---|---|
| Taxol (**1a**) | 1.7 |
| **2** | 79 |
| **11a** | 800 |
| **11b** | 900 |
| **12** | > 10000 |
| **13a** | 1500 |
| **13b** | 1100 |

## Conclusions

A series of five 14-nor-A-secotaxoids has been prepared from 10-deacetyl-14β-hydroxybaccatin III (**3a**), revealing some new and unexpected reactivity of taxane derivatives. The final compounds were either inactive or considerable less cytotoxic than their 1,10-bridged analogue **2** and taxol. Nevertheless, the preservation of a lower micromolar cytotoxicity and the existence of definite structure−activity relationships show that 14-nor-A-secotaxoids warrant further investigation as simplified taxol analogues.

## Experimental Section

**General:** Column chromatography: Merck silica gel. IR: Shimadzu DR 8001 spectrophotometer. Optical rotations: Perkin−Elmer 192 polarimeter, equipped with a sodium lamp (λ = 589 nm) and a 10-cm microcell. NMR: Bruker AM 500 (500 MHz and 125 MHz for $^1H$ and $^{13}C$, respectively). For $^1H$ NMR, $CDCl_3$ as solventand reference (δ = 7.26). For $^{13}C$ NMR, $CDCl_3$ as solvent and reference (δ = 77.0). The $^1H$ and $^{13}C$ NMR spectra of all final products and the key intermediates were fully assigned by a combination of 1D and 2D (COSY, HMBC, HMQC, ROESY) techniques. $CH_2Cl_2$ was dried by distillation from $CaH_2$, and THF by distillation from Na/benzophenone. $Na_2SO_4$ was used to dry solutions before concentration. Reactions were monitored by TLC on Merck 60 $F_{254}$ (0.25 mm) plates, which were viewed by UV inspection and/or staining with 5% $H_2SO_4$ in ethanol and heating. All compounds were crystallized from ether, unless indicated otherwise. Cytotoxicity assays were carried out according to an established literature procedure.[20]

**Acetylation of 10-Deacetyl-14β-hydroxybaccatin III (3a):** $Ac_2O$ (2.68 mL, 28.6 mmol, 4 mol-equiv.) and $CeCl_3{\cdot}7H_2O$ (266 mg, 0.71 mmol, 0.1 mol-equiv.) were added to a solution of **3a** (4.0 g, 7.14 mmol) in dry THF (25 mL). After stirring at room temp. for 18 h, the reaction mixture was worked up by dilution with EtOAc and washing with sat. $NaHCO_3$. The solid residue obtained after removal of the solvent was washed with ether to give 3.6 g (90%) of **3b** as a white powder, m.p. 230−234 °C. $[\alpha]_D^{25} = -48$ ($c$ = 0.42, $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3475, 1740, 1717, 1401, 1240, 1049, 716 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ = 1.13 (s, 16-$H_3$), 1.16 (s, 17-$H_3$), 1.68 (s, 19-$H_3$), 1.87 (m, 6b-H), 2.06 (br. s, 18-$H_3$), 2.26 (s, OAc), 2.31 (s, OAc), 2.55 (m, 6a-H), 2.68 (s, OH), 3.05 (s, OH), 3.30 (s, OH), 3.81 (d, $J$ = 8.0 Hz, 3-H), 4.01 (br. d, $J$ = 4.0 Hz, 14-H), 4.20 (d, $J$ = 8.0 Hz, 20b-H), 4.29 (d, $J$ = 8.0 Hz, 20a-H), 4.44 (m, 7-H), 4.76 (br. s, 13-H), 4.98 (br. d, $J$ = 8.0 Hz, 5-H), 5.81 (d, $J$ = 8.0 Hz, 2-H), 6.31 (s, 10-H), 7.44 (BB′-Bz); 7.61 (C-Bz); 8.08 (AA′-Bz). HRMS (70 eV): $m/z$ = 602.2371 (calcd. for $C_{31}H_{38}O_{12}$ 602.2363).

**Acetylation of 10-deacetyl-7-triethylsilyl-14β-hydroxybaccatin III (3c):** $Ac_2O$ (110 μL, 1.1 mmol, 4 mol-equiv.) and $CeCl_3{\cdot}7H_2O$ (ca. 5 mg) were added to a solution of **3c** (200 mg, 0.28 mmol) in dry THF (3 mL). After stirring at room temp. for 24 h, the reaction mixture was worked up by dilution with EtOAc and washing with sat. $NaHCO_3$. Removal of the solvent left a paste, which was purified by column chromatography (3 g of silica gel; hexane/EtOAc, 4:6, as eluent) to give 21 mg (10%) of **3d** and 149 mg of recovered **3c**. Compound **3d** was obtained as a white powder, m.p. 235 °C. $[\alpha]_D^{25} = -56$ ($c$ = 0.60, $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3490, 1760, 1740, 1530, 1220, 1100, 1025, 830 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ = 0.63 (m, TES), 0.94 (m, TES), 1.07 (s, 16-$H_3$), 1.14 (s, 17-$H_3$), 1.77 (s, 19-$H_3$), 1.90 (m, 6b-H), 1.99 (s, OAc), 2.18 (br. s, 18-$H_3$), 2.37 (s, OAc), 2.50 (m, 6a-H), 2.71 (s, OH), 3.14 (s, OH), 3.95 (d, $J$ = 8.0 Hz, 3-H), 4.24 (d, $J$ = 8.0 Hz, 20b-H), 4.28 (d, $J$ = 8.0 Hz, 20a-H), 4.30 (s, OH), 4.43 (dd, $J$ = 10.3, 6.2 Hz, 7-H), 4.73 (br. s, 13-H), 4.95 (br. d, $J$ = 9.0 Hz, 5-H), 5.20 (s, 10-H), 5.35 (d, $J$ = 5.1 Hz, 14-H), 5.79 (d, $J$ = 8.0 Hz, 2-H), 7.46 (BB′-Bz); 7.60 (C-Bz); 8.03 (AA′-Bz). HRMS (70 eV): $m/z$ = 602.2371 (calcd. for $C_{31}H_{38}O_{12}$ 602.2363).

**Periodate Cleavage of 14β-Hydroxybaccatin III (3b):** Aq. $H_5IO_6{\cdot}2H_2O$ (0.5 M, 34.3 mL, 17.20 mmol, 2.4 mol-equiv.) was added to a solution of **3b** (4.31 g, 7.14 mmol) in dioxane (40 mL). After stirring overnight, the reaction mixture was worked up by dilution with sat. $NaHCO_3$ (100 mL) and extraction with EtOAc. The organic phase was sequentially washed with 5% $Na_2S_2O_3$ and brine, and then dried. The solvents were evaporated to give 4.1 g of crude **4a** as an unstable, amorphous powder, containing ca. 20% ($^1H$ NMR analysis) of the overoxidation product. $^1H$ NMR ($CDCl_3$): δ = 1.38 (s, 16-$H_3$), 1.44 (s, 19-$H_3$), 1.48 (s, 17-$H_3$), 1.88 (s, 18-$H_3$), 1.88 (m, 6b-H), 2.06 (s, 4-OAc), 2.20 (s, 10-OAc), 2.55 (m, 6a-H), 3.06 (d, $J$ = 4.4 Hz, OH), 3.74 (d, $J$ = 11.1 Hz, 3-H), 4.42 (d, $J$ = 11.2 Hz, 20a-H), 4.69 (d, $J$ = 11.2 Hz, 20b-H), 4.74 (m, 7-H), 4.93 (dd, $J$ = 10.2 Hz, 5-H), 5.87 (d, $J$ = 11.1 Hz, 2-H), 6.44 (s, 10-H), 7.51 (BB′-Bz), 7.64 (C-Bz), 7.94 (AA′-Bz), 10.54 (s, H-13). HRMS (70 eV): $m/z$ = 570.2100 (calcd. for $C_{30}H_{34}O_{11}$ 570.2101).

**Silylation of the Secotaxoid 4a:** Imidazole (2.35 g, 34.50 mmol, 5 mol-equiv.) and triethylsilyl chloride (TES-Cl, 5.80 mL, 5.21 g, 34.51 mmol, 5 mol-equiv.) were added to a mixture of **4a** and its overoxidation product (3.94 g, 6.90 mmol based on the molecular mass of **4a**) in dry DMF (25 mL). After stirring at room temp. for 12 h, the reaction mixture was worked up by dilution with water (100 mL) and addition of Celite (2 g). The reaction mixture was then filtered through a bed of Celite, and the cake was washed several times with water to remove DMF, and eventually with EtOAc to recover the silylated products. After drying and concentration, the residue was purified by column chromatography (hexane/EtOAc gradient, from 9:1 to 7:3) to give **4b** (3.4 g, 72%) and **5** (779 mg, 15%). Compound **4b** was obtained as a white powder, m.p. 143−147 °C. $[\alpha]_D^{25} = -10$ ($c$ = 0.46; $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3453, 1755, 1738, 1732, 1728, 11689, 1675, 1586, 1376, 1227, 1090 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ = 0.63 (m, TES), 0.91 (m, TES), 1.44 (s, 16-H), 1.46 (s, 19-$H_3$), 1.50 (s, 17-$H_3$), 1.98 (s, 18-$H_3$), 2.11 (s, 4-OAc), 2.16 (s, 10-OAc), 3.94 (d, $J$ = 8.5 Hz, 3-H), 4.52 (d, $J$ = 8.6 Hz, 20b-H), 4.62 (m, 7-H), 4.63 (d, $J$ = 8.6 Hz, 20a-H), 4.92 (dd, $J$ = 8.3 Hz, 5-H), 5.72 (d, $J$ = 8.5 Hz, 2-H), 6.77 (s, 10-H),

10.24 (s, 13-H), 7.50 (BB′-Bz), 7.66 (C-Bz), 7.94 (AA′-Bz). HRMS (70 eV): *m*/*z* = 684.2956, (calcd. for $C_{36}H_{48}O_{11}Si$, 684.2966). Compound **5** was obtained as a white powder, m.p. 117−123 °C. $[\alpha]_D^{25}$ = +1 (*c* = 0.42; $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3429, 3228, 1777, 1738, 1453, 1375, 1267, 1244, 1200, 1088, 999 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ = 0.68 (m, TES), 0.97 (t, *J* = 7.0 Hz, TES), 1.14 (s, 17-$H_3$), 1.38 (s, 16-$H_3$), 1.56 (s, 18-$H_3$), 1.82 (s, 19-$H_3$), 2.01 (m, 6b-H), 2.26 (s, OAc), 2.35 (s, OAc), 2.41 (m, 6a-H), 3.41 (br. d, *J* = 9.0 Hz, 3-H), 4.09 (d, *J* = 8.0 Hz, 20b-H), 4.68 (dd, *J* = 10.8 Hz, 7-H), 4.88 (d, *J* = 8.0 Hz, 20a-H), 4.91 (dd, *J* = 9.2 Hz, 5-H), 5.74 (s, 10-H), 6.75 (d, *J* = 9.0 Hz, 2-H), 7.53 (BB′-Bz), 7.60 (br. s, OH), 7.67 (C-Bz), 8.12 (AA′-Bz). Selected HMBC correlations: 2-H,C-3; 2-H,C-8; 2-H,C=$O_{Bz}$; 3-H,C-19; 5-H,C-4; 5-H,C-7; 6a-H,C-8; 6b-H,C-7; 7-H,C-19; 10-H,C-11; 10-H,C-12; 10-H,C-1; 10-H,C-9; 10-H,C=$O_{Ac}$; 16-$H_3$,C-17; 16-$H_3$,C-15; 16-$H_3$,C-1; 18-$H_3$,C-11; 18-$H_3$,C-12; 18-$H_3$,C-13; 19-$H_3$,C-4; 19-$H_3$,C-8; 19-$H_3$,C-7; 19-$H_3$,C-9; OH,C-10. $^{13}C$ NMR ($CDCl_3$): δ = 5.0 (t, TES), 6.5 (q, TES), 9.9 (q, C-19), 14.7 (q, C-18), 19.3 (q, C-17), 21.0 (q, Ac), 21.5 (q, Ac), 22.8 (q, C-16), 36.4 (t, C-6), 42.6 (d, C-3), 48.5 (s, C-8), 68.8 (d, C-2), 70.4 (d, C-10), 72.8 (d, C-7), 75.6 (t, C-20), 79.3 (s, C-4), 83.6 (d, C-5), 88.3 (s, C-11*), 88.3 (s, C-12*), 90.5 (s, C-15), 101.1 (s, C-1), 106.3 (s, C-9), 128.7 (d, Bz), 128.9 (s, Bz), 130.2 (d, Bz), 134.3 (d, Bz), 165.3 (s, Bz), 167.6 (s, Ac), 169.8 (s, Ac), 172.7 (s, C-13). HRMS (70 eV): *m*/*z* = 734.2984 (calcd. for $C_{36}H_{50}O_{14}Si$ 734.2970).

**Reduction of 4b with $NaBH_3CN$:** An excess of $NaBH_3CN$ (3.4 g) was added portionwise over 2 h to a solution of **4b** (3.4 g, 5.01 mmol) in MeOH (22 mL)/acetate buffer (22 mL). After stirring at room temp. for an additional 4 h, the reaction mixture was worked up by dilution with sat. $NaHCO_3$ and extraction with EtOAc. After having been washed with brine, the residue was concentrated and the residue was purified by column chromatography (25 g of silica gel; hexane/EtOAc, 9:1, as eluent) to afford **6** (1.73 g, 51%) as a white powder, m.p. 134−139 °C. $[\alpha]_D^{25}$ = −49 (*c* = 0.5; $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3432, 1748, 1721, 1372, 1109, 826, 710; 825 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): Tautomer **6a**: δ = 0.58 (m, TES), 0.94 (m, TES), 1.19 (s, 17-$H_3$), 1.29 (s, 16-$H_3$), 1.69 (s, 19-$H_3$), 1.90 (m, 6b-H), 2.14 (br. s, 18-$H_3$), 2.20 (s, 4-OAc), 2.28 (s, 10-OAc), 2.57 (m, 6a-H), 3.87 (d, *J* = 7.2 Hz, 3-H), 3.99 (d, *J* = 16.1 Hz, 13a-H), 4.21 (d, *J* = 8.2 Hz, 20b-H), 4.29 (d, *J* = 8.2 Hz, 20a-H), 4.48 (dd, *J* = 10.0, 8.3 Hz, 7-H), 4.83 (d, *J* = 16.1 Hz, 13b-H), 4.98 (d, *J* = 7.9 Hz, 5-H), 5.67 (d, *J* = 7.2 Hz, 2-H), 6.43 (s, 10-H), 7.48 (BB′-Bz), 7.61 (C-Bz), 8.12 (AA′-Bz). Tautomer **6b**: δ = 0.58 (m, TES), 0.94 (m, TES), 1.35 (s, 16-$H_3$), 1.52 (s, 17-$H_3$), 1.62 (s, 19-$H_3$), 2.12 (br. s, 18-$H_3$), 2.19 (s, 4-OAc), 2.48 (s, 10-OAc), 4.14 (d, *J* = 8.0 Hz, 20b-H), 4.21 (d, *J* = 8.0 Hz, 20a-H), 4.54 (m, 7-H), 4.62 (d, *J* = 9.0 Hz, 13b-H), 4.74 (d, *J* = 9.0 Hz, 13a-H), 5.49 (d, *J* = 8.0 Hz, 5-H), 5.52 (d, *J* = 6.2 Hz, 2-H), 6.71 (s, 10-H), 7.49 (BB′-Bz), 7.61 (C-Bz); 8.03 (AA′-Bz).$^{13}C$ NMR ($CDCl_3$): Tautomer **6a**: δ = 5.4 (t, TES), 6.9 (q, TES), 10.1 (q, C-19), 17.2 (q, C-18), 20.9 (q, C-16), 21.6 (q, Ac), 22.0 (q, Ac), 25.4 (q, C-17), 38.0 (t, C-6), 42.4 (s, C-15), 45.0 (d, C-3), 59.1 (s, C-8), 69.8 (t, C-13), 72.8 (d, C-7), 72.9 (d, C-2), 75.1 (d, C-10), 76.6 (t, C-20), 80.9 (s, C-4), 84.1 (d, C-5), 102.2 (s, C-1), 128.6 (d, Bz), 129.0 (s, Bz), 130.2 (d, Bz), 132.6 (s, C-11), 133.6 (s, Bz), 134.2 (d, Bz), 146.6 (s, C-12), 165.6 (s, Ac), 170.4 (s, Ac), 202.2 (s, C-9). Diagnostic signal of tautomer **6b**: δ = 204.6 (s, C-1). HRMS (70 eV): *m*/*z* = 686.3118 (calcd. for $C_{36}H_{50}O_{11}Si$ 686.3122).

**Reduction of 6. − A) With $NaBH_4$ in Methanol:** An excess of $NaBH_4$ (100 mg) was added to a solution of **6** (200 mg, 0.29 mmol) in MeOH (5 mL). After stirring for 10 min at room temp., the reaction mixture was worked up by quenching with $NH_4Cl$ and extraction with EtOAc. The organic phase was washed with brine and the solvents were evaporated to give a white powder. Purification by column chromatography (5 g of silica gel; hexane/EtOAc, 8:2, as eluent) gave **7** (147 mg, 74%) as white crystals, m.p. 90−96 °C (toluene/ether). $[\alpha]_D^{25}$ = −72 (*c* = 0.58; $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3432, 1748, 1721, 1603, 1561, 1372, 1273, 111, 1016, 993, 713.7; 993 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ = 0.63 (q, TES), 0.92 (t, *J* = 7.4 Hz, TES), 1.19 (s, 17-$H_3$), 1.35 (s, 16-$H_3$), 1.53 (s, 19-$H_3$), 1.92 (m, 6b-H), 2.12 (s, 18-$H_3$), 2.15 (s, 4-OAc), 2.22 (s, 10-OAc), 2.63 (m, 6a-H), 3.40 (s, 1-H), 3.69 (s, OH), 4.11 (d, *J* = 9.0 Hz, 3-H), 4.22 (d, *J* = 12.0 Hz, 13b-H), 4.35 (d, *J* = 8.0 Hz, 20b-H), 4.53 (dd, *J* = 10.8 Hz, 7-H), 4.54 (d, *J* = 8.0 Hz, 20a-H), 4.85 (d, *J* = 12.0 Hz, 12a-H), 4.99 (br. d, *J* = 8.0 Hz, 5-H), 5.35 (d, *J* = 9.0 Hz, 2-H), 6.56 (s, 10-H), 7.47 (BB′-Bz), 7.61 (CBz), 7.98 (AA′-Bz). Selected NOEs: 2-H,1-H; 3-H,7-H; 10-H,7-H; 10-H,18-$H_3$; 16-$H_3$,1-H; 16-$H_3$,13a-H; 16-$H_3$,13b-H; 17-$H_3$,1-H; 2-H,10-OAc; 18-$H_3$,2-H; 6a-H,20a-H. $^{13}C$ NMR ($CDCl_3$): δ = 5.5 (t, TES), 7.0 (q, TES), 9.6 (q, C-17), 19.6 (q, C-18), 21.0 (q, Ac), 22.1 (q, Ac), 27.4 (q, C-19), 31.2 (q, C-16), 38.0 (t, C-6), 38.1 (d, C-3), 43.1 (s, C-15), 57.8 (s, C-8), 65.4 (t, C-13), 72.4 (d, C-7), 72.7 (d, C-2), 77.3 (t, C-20), 77.9 (d, C-10), 81.0 (d, C-1), 81.0 (s, C-4), 84.5 (d, C-5), 128.7 (d, Bz), 129.0 (s, Bz), 129.6 (d, Bz), 132.4 (s, C-11), 133.8 (d, Bz), 146.2 (s, C-12), 164.3 (s, Ac), 164.3 (s, Bz), 172.1 (s, Ac), 206.1 (s, C-9). HRMS (70 eV): *m*/*z* = 688.3280 (calcd. for $C_{36}H_{52}O_{11}Si$, 688.3279). − **B) With $NaBH_4$ in Dioxane:** An excess of $NaBH_4$ (825 mg) was added to a solution of **6** (658 mg, 0.96 mmol) in dioxane (7 mL). The suspension was stirred at room temp. for 48 h, and then worked up by washing with sat. $NH_4Cl$ and extraction with EtOAc. The organic phase was washed with brine and dried, and the solvents were evaporated to give recovered **6** (127 mg) and **8** (365 mg, 55%) as a white powder, m.p. 168−171 °C. $[\alpha]_D^{25}$ = −49 (*c* = 0.67; $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3453, 1748, 1721, 1603, 1372, 1273, 1235, 1112, 1017, 996, 714 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ = 0.76 (m, TES), 1.06 (t, *J* = 7.0 Hz, TES), 1.38 (s, 16-$H_3$), 1.43 (s, 17-$H_3$), 1.65 (s, 19-$H_3$), 1.95 (m, 6b-H), 2.04 (s, 18-$H_3$), 2.09 (s, OAc), 2.12 (s, OAc), 2.55 (m, 6a-H), 3.38 (d, *J* = 12.0 Hz, 3-H), 3.98 (d, *J* = 10.0 Hz, 13b-H), 4.01 (d, *J* = 9.0 Hz, 1-H), 4.31 (d, *J* = 8.0 Hz, 20b-H), 4.38 (d, *J* = 8.0 Hz, 20a-H), 4.55 (d, *J* = 10.0 Hz, 13a-H), 4.60 (dd, *J* = 10.8 Hz, 7-H), 4.68 (s, OH), 4.92 (d, *J* = 8.0 Hz, 5-H), 5.83 (dd, *J* = 12.0, 9 Hz, 2-H), 6.14 (s, 10-H), 7.46 (BB′-Bz), 7.59 (C-Bz), 8.03 (AA′-Bz). $^{13}C$ NMR ($CDCl_3$): δ = 5.5 (t, TES), 6.9 (q, TES), 9.4 (q, C-17), 20.1 (q, C-18), 21.2 (q, Ac), 21.5 (q, Ac), 27.7 (q, C-19), 32.2 (q, C-16), 36.6 (t, C-6), 39.9 (d, C-3), 40.1 (s, C-15), 46.7 (s, C-8), 63.9 (t, C-13), 69.2 (d, C-7), 69.7 (d, C-2), 71.8 (d, C-10), 73.4 (d, C-10), 80.6 (d, C-1), 84.0 (s, C-4), 84.0 (d, C-5), 98.0 (s, C-9), 128.9 (d, Bz), 129.0 (s, Bz), 129.6 (d, Bz), 133.4 (s, C-11), 134.7 (d, Bz), 137.5 (s, C-12), 165.5 (s, Bz), 170.0 (s. OAc), 170.3 (s, Ac). HRMS (EI): *m*/*z* = 688.3288 (calcd. for $C_{36}H_{52}O_{10}Si$ 688.3279).

**Oxidation of the Diol 7 to the Lactone 9:** Commercial (Merck) activated $MnO_2$ (1.4 g) was added to a solution of **7** (140 mg, 2.02 mmol) in toluene (5 mL). After stirring overnight at room temp., the reaction mixture was worked up by filtration to give **9** (136 mg, 98%) as a white powder, m.p. 122−124 °C. $[\alpha]_D^{25}$ = −129 (*c* = 0.50; $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 1725, 1603, 1586, 1279, 1250, 1165, 1065, 984, 714 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ = 0.58 (q, TES), 0.92 (t, *J* = 7.4 Hz, TES), 1.23 (s, 17-$H_3$), 1.31 (s, H-16/3), 1.67 (s,19-$H_3$), 1.89 (m, 6b-H), 2.21 (s, OAc), 2.25 (s, OAc), 2.36 (br. s, 18-$H_3$), 2.60 (m, 6a-H), 3.72 (d, *J* = 7.0 Hz, 3-H), 4.13 (d, *J* = 8.0 Hz, H-20b), 4.24 (s, 1-H), 4.40 (d, *J* = 8.0 Hz, H-20a), 4.53 (dd, *J* = 10.8 Hz, H-7), 4.54 (dd, *J* = 10.5, 8.0 Hz, H-7), 5.01 (br. d, *J* = 9.0 Hz, H-5), 5.55 (d, *J* = 7.0 Hz, H-2), 6.46 (s, H-10), 7.47 (BB′-Bz), 7.61 (CBz), 8.09 (AA′-Bz). $^{13}C$ NMR ($CDCl_3$) δ = 5.2 (t, TES), 7.0 (q, TES), 10.0 (q, C-19), 15.3 (q, C-18), 20.7 (q, Ac),

21.07 (q, C-16), 21.6 (q, Ac), 33.9 (q, C-17), 37.1 (s, C-15), 37.5 (t, C-6), 43.0 (d, C-3), 60.1 (s, C-8), 69.1 (d, C-7), 72.3 (d, C-10), 75.2 (t, C-20), 79.9 (s, C-1), 83.8 (d, C-5), 85.2 (s, C-1), 128.6 (d, Bz), 129.0 (s, Bz), 130.0 (d, Bz), 133.2 (d, Bz), 133.9 (s, C-12), 145.3 (s, C-11), 164.7 (s, C-13), 165.3 (s, Bz), 168.9 (s, OAc), 170.9 (s, Ac), 200.1 (s, C-9). HRMS (70 eV): *m/z* = 684.2990 (calcd. for $C_{36}H_{48}O_{11}Si$ 684.2966).

**Coupling of Secobaccatins 6−8 with Amino Acid Side-Chains:** Synthesis of **13a** as representative: (4*S*,5*R*)-*N*-Benzoyl-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolinecarboxylic acid (**10a**; 428 mg, 1.06 mmol, 2 mol-equiv.), DCC (219 mg, 1.06 mmol, 2 mol-equiv.), and DMAP (catalytic amount: 30 mg) were added to a solution of **8** (365 mg, 0.53 mmol) in dry toluene (4 mL). After stirring at room temp. for 1 h, the reaction mixture was filtered and dissolved in a solution of HCl in methanol (10 mL, obtained by addition of 140 μL of $Ac_2O$ to 20 mL of MeOH). The reaction mixture was worked up by washing with sat. $NaHCO_3$ and extraction with EtOAc. After having been washed with brine and concentrated, the residue was purified by column chromatography (hexane/EtOAC gradient from 8:2 to 6:4) to afford 206 mg (46%) of **13a**. The taxanes **11a**, **11b**, **12**, and **13b** were obtained in a similar way, in yields of 54%, 61%, 38%, and 45%, respectively.

**Compound 11a:** White powder, m.p. 61−65 °C. $[\alpha]_D^{25}$ = +32 (*c* = 0.58; $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3513, 3430, 1732, 1665, 1518, 1487, 1265, 1244, 1088, 1076, 988, 712 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ = 1.35 (s, 17-$H_3$), 1.44 (s, 19-$H_3$), 1.50 (s, 16-$H_3$); 1.81 (s, 18-$H_3$), 2.03 (s, OAc), 2.21 (s, OAc), 2.54 (m, 6a-H), 3.13 (d, *J* = 4.0 Hz, 2′-OH), 3.37 (d, *J* = 4.0 Hz, 7-OH), 3.78 (d, *J* = 10.0 Hz, 3-H), 4.44 (d, *J* = 8.0 Hz, 20b-H), 4.68 (m, 7-H), 4.72 (d, *J* = 12.0 Hz, 13b-H), 4.72 (d, *J* = 8.0 Hz, 20a-H), 4.72 (m, 2′-H), 4.90 (br. d, *J* = 9.0 Hz, 5-H), 5.58 (d, *J* = 12.0 Hz, 13a-H), 5.80 (dd, *J* = 8, 1.8 Hz, 3′-H), 5.85 (d, *J* = 10.0 Hz, 2-H), 6.40 (s, 10-H), 6.92 (d, *J* = 8.0 Hz, NH), 7.32 (m, arom), 7.58 (m, arom), 7.76 (AA′-NHBz), 7.96 (AA′-OBz). HRMS (70 eV): *m/z* = 839.3131 (calcd. for $C_{46}H_{49}NO_{14}$ 839.3153).

**Compound 11b:** White powder, m.p. 100−103 °C. $[\alpha]_D^{25}$ = +13 (*c* = 0.5 MeOH). IR (KBr): $\tilde{\nu}$ = 3524, 3389, 1732, 1603, 1508, 1452, 1370, 1246, 1173, 1090, 1050, 711.8; 1049.4. $^1H$ NMR ($CDCl_3$): δ = 0.97 (d, *J* = 7.4 Hz, *i*Bu), 0.99 (d, *J* = 7.4 Hz, *i*Bu), 1.35 (s, 16-$H_3$), 1.38 (s, Boc), 1.44 (s, 17-$H_3$), 1.79 (s, 19-$H_3$), 2.06 (br. s, 18-$H_3$), 2.21 (s, OAc × 2), 2.55 (m, 6a-H), 3.10 (br. s, 2′-OH), 3.14 (d, *J* = 4.0 Hz, 7-OH), 3.79 (d, *J* = 9.9 Hz, 3-H), 4.12 (br. d, *J* = 8.0 Hz, 3′-H), 4.16 (br. s, 2′-H), 4.44 (d, *J* = 8.2 Hz, 20b-H), 4.60 (d, *J* = 12.2 Hz, 13b-H), 4.63 (d, *J* = 8.0 Hz, NH), 4.69 (m, 7-H), 4.73 (d, *J* = 8.2 Hz, 20a-H), 4.93 (br. d, *J* = 7.9 Hz, 5-H), 5.58 (d, *J* = 12.2 Hz, 13a-H), 5.87 (d, *J* = 9.9 Hz, 2-H), 6.42 (s, 10-H), 7.54 (BB′-Bz), 7.63 (C-Bz), 7.98 (AA′-Bz). HRMS (EI): *m/z* = 815.3712 (calcd. for $C_{42}H_{57}NO_{15}$ 815.3728).

**Compound 12:** White powder, m.p. 158−161 °C. $[\alpha]_D^{25}$ = −12 (*c* = 0.58 $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3444, 1723, 1603, 1505, 1370, 1273, 1248, 1175, 1094, 713 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ = 0.94 (d, *J* = 7.4 Hz, *i*Bu), 0.96 (d, *J* = 7.4 Hz, *i*Bu), 1.19 (s, 16-$H_3$), 1.38 (s, 17-$H_3$), 1.42 (s, Boc), 1.56 (s, 19-$H_3$), 2.04 (br. s, 18-$H_3$), 2.18 (s, OAc), 2.24 (s, OAc), 2.61 (m, 6a-H), 2.9 (br. s, 1-OH), 3.21 (br. d, *J* = 4.0 Hz, 7-OH), 3.42 (br. s, 2′-OH), 3.85 (d, *J* = 4.0 Hz, 3-H), 4.31 (d, *J* = 8.0 Hz, 20b-H), 4.34 (d, *J* = 8.0 Hz, 20a-H), ca 4.15 (m, 1-H, 2′-H, 3′-H), 4.54 (d, *J* = 12.2 Hz, 13b-H), 4.65 (d, *J* = 8.0 Hz, NH), 5.08 (dd, *J* = 7.9, 2.9 Hz, 5-H), 5.37 (br. d, *J* = 4.0 Hz, 2-H), 5.74 (d, *J* = 12.2 Hz, 13a-H), 6.43 (s, 10-H), 7.49 (BB′-Bz), 7.62 (C-Bz), 7.98 (AA′-Bz). HRMS (70 eV): *m/z* = 817.3892 (calcd. for $C_{42}H_{59}NO_{15}$ 817.3885).

**Compound 13a:** White powder, m.p. 115−120 °C. $[\alpha]_D^{25}$ = −31 (*c* = 0.42; $CH_2Cl_2$) IR (KBr): $\tilde{\nu}$ = 3432, 1736, 1725, 1659, 1520, 1487, 1372, 1273, 1107, 1065, 713 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ = 1.28 (s, 16-$H_3$), 1.42 (s, 17-$H_3$), 1.66 (s, 19-$H_3$), 1.87 (s, 18-$H_3$), 2.10 (s, OAc), 2.16 (s, OAc), 3.19 (d, *J* = 12.0 Hz, 3-H), 4.02 (d, *J* = 4.0 Hz, 1-H), 4.32 (d, *J* = 8.0 Hz, 20b-H), 4.37 (d, *J* = 8.0 Hz, 20a-H), 4.58 (dd, *J* = 10.8 Hz, 7-H), 4.95 (d, *J* = 8.0 Hz, 5-H), 5.22 (d, *J* = 12.0 Hz, 13a-H), 5.74 (dd, *J* = 8.5, 2 Hz, 3′-H), 5.82 (dd, *J* = 12.4 Hz, 2-H), 6.21 (s, 10-H), 6.90 (d, *J* = 8.5 Hz, NH), 7.30 (m, arom.), 7.60 (m, arom), 7.73 (AA′-NHBz), 8.02 (AA′-OBz). HRMS (70 eV): *m/z* = 825.3351 (calcd. for $C_{46}H_{51}NO_{13}$ 825.3360).

**Compound 13b:** White powder, m.p. 122−125 °C. $[\alpha]_D^{25}$ = −39 (*c* = 0.5, $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3453, 1721, 1509, 1370, 1272, 1248, 1161, 1107, 1065, 715 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 0.92 (d, *J* = 7.4 Hz, *i*Bu), 0.94 (d, *J* = 7.4 Hz, *i*Bu), 1.28 (s, 16-H), 1.35 (s, Boc), 1.42 (s, 17-$H_3$), 1.64 (s, 19-$H_3$), 1.89 (s, 18-$H_3$), 2.11 (s, OAc), 2.15 (s, OAc), 2.50 (m, 6a-H), 3.10 (d, *J* = 6.0 Hz, 2′-OH), 3.20 (d, *J* = 3.0 Hz, 7-OH), 3.21 (d, *J* = 11.0 Hz, 3-H), 4.01 (d, *J* = 4.0 Hz, 1-H), 4.10 (s, 2′-H), 4.12 (d, *J* = 8.0 Hz, 3′-H), 4.33 (d, *J* = 8.0 Hz, 20b-H), 4.36 (d, *J* = 8.0 Hz, 20a-H), 4.58 (d, *J* = 12.0 Hz, 13b-H), 4.60 (m, 7-H), 4.60 (d, *J* = 8.0 Hz, NH), 4.97 (d, *J* = 8.0 Hz, 5-H), 5.23 (d, *J* = 12.0 Hz, 13a-H), 5.81 (dd, *J* = 11.0, 4 Hz, 2-H), 6.23 (s, 10-H), 7.45 (BB′-Bz), 7.59 (C-Bz), 8.01 (AA′-Bz). HRMS (70 eV): *m/z* = 817.3880 (calcd. for $C_{42}H_{59}NO_{15}$ 817.3885).

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