Syntheses and Structure−Activity Relationships of Novel Nor-seco Taxoids

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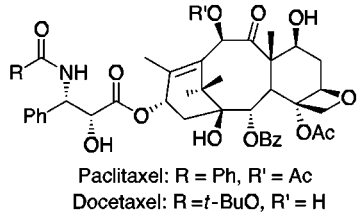
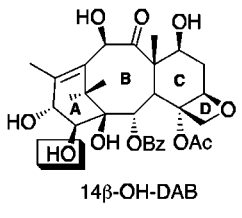
A series of novel nor-seco taxoids (**4a**−**b**, **5a**−**d**, **6**), including either a C-13 ester linkage or a C-13 amide linkage, was synthesized by means of the β-lactam synthon method using the coupling of (3*R*,4*S*)-1-acyl-β-lactams with properly protected nor-seco baccatin III derivatives (**1**, **2**, **3**) as the key step. Nor-seco baccatin III derivatives were prepared through oxidative cleavage of the A ring of 14β-hydroxy-10-deacetylbaccatin III followed by reduction, amination using Mitsunobu conditions, or reductive amination. Nor-seco taxoids with a C-13 ester linkage (**4a**−**b**) or a C-13 *N*-Me amide linkage (**6**) show reduced cytotoxicity against human cancer cell lines as compared with paclitaxel, but still retain a certain level of activity despite the destruction of the taxane A ring. However, none of the analogues with a C-13 *N*-H amide linkage (**5a**−**d**) exhibit appreciable activity (IC_{50} > 1.0 μM). A restrained molecular dynamics study reveals the inability of **5a**−**d** to attain the proposed bioactive conformation, which accounts for the loss of activity.

Taxol (paclitaxel)[1] and Taxotère (docetaxel)[2] are currently considered to be two of the most exciting drugs in cancer chemotherapy.[3−7] Both paclitaxel and docetaxel[8−10] exhibit significant antitumor activity against various cancers which have not been effectively treated by existing chemotherapeutic drugs[11,12] through their unique anti-mitotic mechanism of action.[13] Paclitaxel was approved by FDA for the treatment of advanced ovarian cancer in December 1992 and for the treatment of breast cancer in April 1994. It is also undergoing clinical trials for other cancers. Docetaxel was approved by FDA for the treatment of breast cancer in May 1996 and is currently undergoing phase II and III clinical trials for breast and lung cancers worldwide.[3,12]





The structure−activity relationship (SAR) studies of paclitaxel and docetaxel have revealed the essential roles of the *N*-acylphenylisoserine moiety at the C-13 position, 2-benzoate, 4-acetoxy, and the oxetane ring (D ring) for their strong antitumor activity.[14,15] However, little is known concerning the role of the A ring of the baccatin framework.[14,15] It is very important to clarify the minimum structural requirements for taxoid antitumor activity, e.g., binding ability to the tubulin receptor and cytotoxicity, by looking at the reduced or simplified structure analogues of paclitaxel. Accordingly, as a part of our continuing SAR study of paclitaxel and docetaxel analogues,[16−27] we have studied the role of the A ring by

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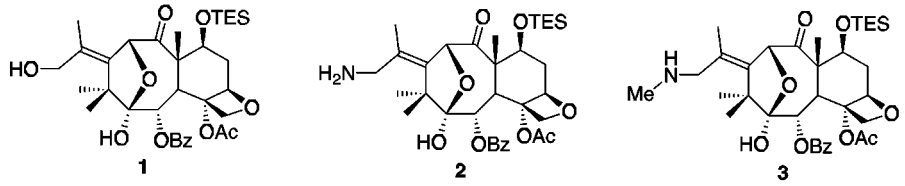
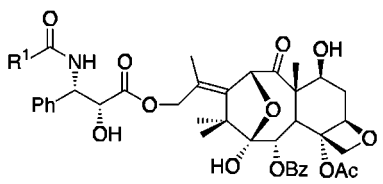
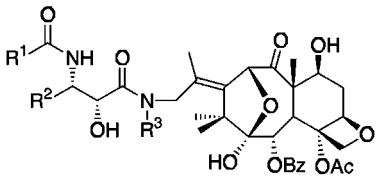
Chart 1



1 **2** **3**



4a: R^1=Ph
4b: R^1=*t*-BuO

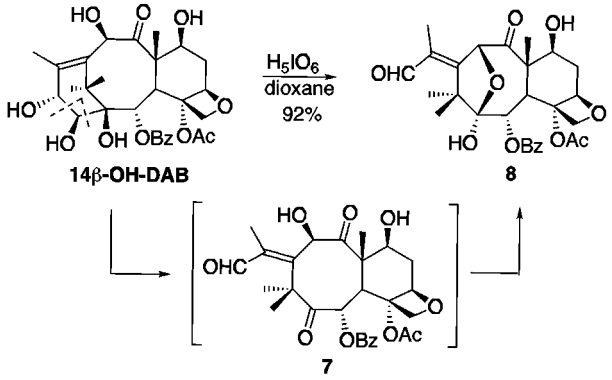


5a: R^1=Ph, R^2=Ph, R^3=H
5b: R^1=*t*-BuO, R^2=Ph, R^3=H
5c: R^1=*t*-BuO, R^2=$(CH_3)_2C$=CH, R^3=H
5d: R^1=*t*-BuO, R^2=$(CH_3)_2CHCH_2$, R^3=H
6: R^1=Ph, R^2=Ph, R^3=CH_3

synthesizing novel nor-seco taxoids in which the A rings are cleaved but the B, C, and D rings are retained.[28]

A novel taxane diterpenoid, 14β-hydroxy-10-deacetylbaccatin III (14β-OH-DAB) was isolated from the needles and other parts of *Taxus wallichiana Zucc.* (Himalayan yew) in 1992.[29] The presence of a cis diol group at the C-1 and C-14 positions of 14β-OH-DAB allows the oxidative cleavage of the A ring with periodic acid to occur, giving the corresponding nor-seco-10-deacetylbaccatin III (**1**) (Chart 1) after the reduction of the resulting aldehyde. Novel nor-seco taxoids **4** were synthesized using the nor-seco-baccatin **1** by means of the β-lactam synthon method.[28] Since it was anticipated that the introduction of an amide linkage at the C-13 position would rigidify the conformation of nor-seco taxoids, two 13-amino-nor-seco-baccatins **2** and **3** were synthesized and coupled with different isoserine precursors to give another series of novel nor-seco taxoids **5** and **6**. The novel nor-seco taxoids thus synthesized were assayed for their cytotoxicity against several human cancer cell lines. We describe here the syntheses and biological activities of the novel nor-seco taxoids **4**, **5**, and **6**.

Scheme 1



14β-OH-DAB **8** **7**

Results and Discussion

A series of novel nor-seco taxoids (**4a**−**b**, **5a**−**d**, **6**) was synthesized from 14β-OH-DAB using highly efficient and practical coupling protocols based on the β-lactam synthon method.[16,30−34] The novel nor-seco baccatin **8** was synthesized in 92% yield through oxidative cleavage of the A ring of 14β-OH-DAB with periodic acid (Scheme 1). It is worthy of note that this oxidative cleavage is realized because of the presence of the hydroxyl group at C-14, i.e., this type of cleavage is impossible for the usual 10-deacetylbaccatin III (DAB). The oxidative cleavage of the A ring gives intermediate **7** bearing a ketone group at C-1, which immediately reacts with the hydroxyl group at C-10 in situ to form the hemiketal **8** (Scheme 1).

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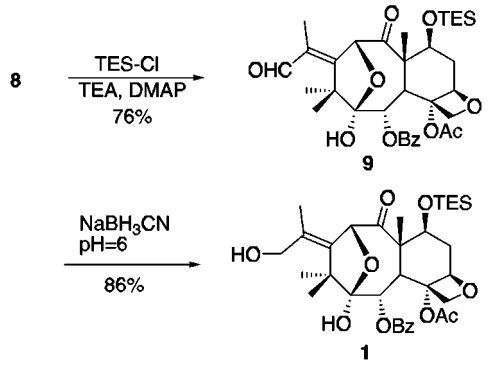
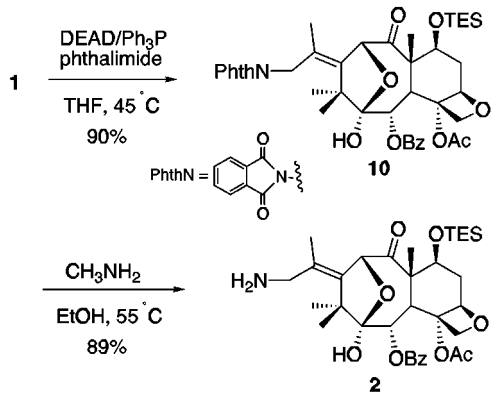
Scheme 2



Scheme 3

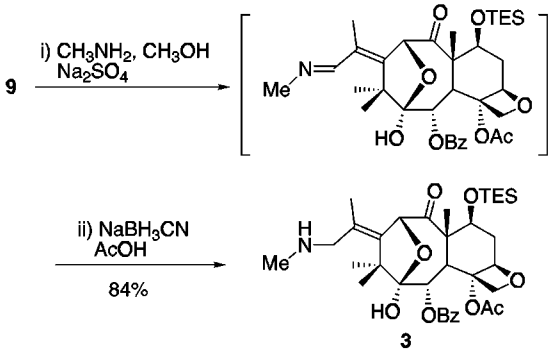


Protection of the C-7 hydroxyl group of **8** as a triethylsilyl (TES) ether gave 7-TES-nor-seco-baccatin **9** in 76% yield (Scheme 2). Reduction of the aldehyde moiety of **9** with sodium cyanoborohydride at pH 6 afforded 7-TES-nor-seco baccatin alcohol **1** in 86% yield (Scheme 2).

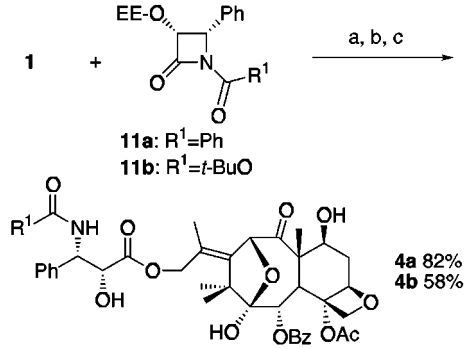
Nor-seco baccatin amine **2** was obtained in two steps from the nor-seco baccatin alcohol **1** in 80% overall yield through the Mitsunobu amination reaction (Scheme 3). Thus, nor-seco baccatin phthalimide **10** was prepared in 90% yield by reacting **1** with triphenylphosphine and diethyl azodicarboxylate (DEAD) in THF at 45 °C. Deprotection of phthalimide **10** using excess methylamine[35] in ethanol at 55 °C afforded desired 7-TES-13-amino-nor-seco baccatin **2** in 89% yield. *N*-methyl-nor-seco baccatin amine **3** was obtained in 84% yield through the reductive amination of nor-seco baccatin aldehyde **9** using methylamine and sodium cyanoborohydride (Scheme 4).

7-TES-nor-seco baccatin alcohol **1**, thus obtained, was coupled with enantiomerically pure *N*-acyl-3-EEO-*β*-lactams **11** (EE = ethoxyethyl)[16,30] using our protocol[30,33] to give novel nor-seco paclitaxel **4a** and nor-seco docetaxel **4b** in fairly good to excellent yields (Scheme 5). It should be noted that it was impossible to remove 7-TES group under the standard acidic conditions (0.5% hydrochloric acid in methanol at room temperature for 36 h).[36] This deprotection was accomplished in excellent yield (= 94%) by using tetra-*n*-butylammonium fluoride (TBAF) in THF at −10 °C for 5 min.

Scheme 4

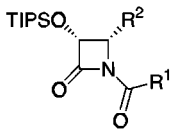


Scheme 5



(a) NaHMDS, THF, -30 °C, 10 min; (b) 0.5 % HCl, 25 °C, 36 h; (c) TBAF, THF, -10 °C, 5 min.

Nor-seco taxoids **13a**−**d** bearing a C-13 amide linkage were synthesized through the ring-opening coupling[37] of *N*-acyl-*β*-lactams **12a**−**d** with nor-seco baccatin amine **2**. (3*R*,4*S*)-*N*-Acyl-3-TIPSO-*β*-lactams (**12a**-**d**, TIPS = triisopropylsilyl) were prepared by the method previously reported from these laboratories.[20,30,31]



12a: R^1=Ph, R^2=Ph
12b: R^1=*t*-BuO, R^2=Ph
12c: R^1=*t*-BuO, R^2=$(CH_3)_2C{=}CH$
12d: R^1=*t*-BuO, R^2=$(CH_3)_2CHCH_2$

The coupling reactions of nor-seco baccatin amine **2** with *N*-acyl-*β*-lactams **12a**−**d**[17,30,33] were carried out under neutral conditions in dichloromethane at 40 °C to give the coupling products **13a**−**d** in 75−89% yields (Scheme 6). Deprotection of the 7-TES and 2′-TIPS groups of **13a**−**d** was carried out using HF/pyridine to give the desired nor-seco taxoids **5a**−**d** in 80−89% yields (Scheme 6).

The attempted ring-opening coupling of 3-TIPSO-*β*-lactam **12a** with *N*-methyl-nor-seco baccatin amine **3** under the standard conditions (vide supra) resulted in low conversion and low yield. It is apparent that this is due to the bulkiness of TIPS group at the C-3 position of *β*-lactam **12a**[37] as well as *N*-Me group of nor-seco baccatin amine **3**. Thus, the TIPS group of **12a** was removed with HF/pyridine to afford 3-OH-*β*-lactam **14a** in nearly quantitative yield. The ring-opening coupling of 3-OH-*β*-lactam **14a** with nor-seco baccatin amine **3** proceeded smoothly under the standard conditions to give the coupling product **15** in 70% yield, which was deprotected

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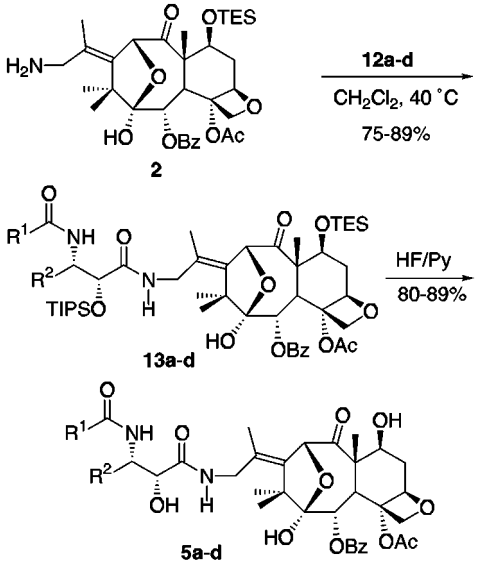
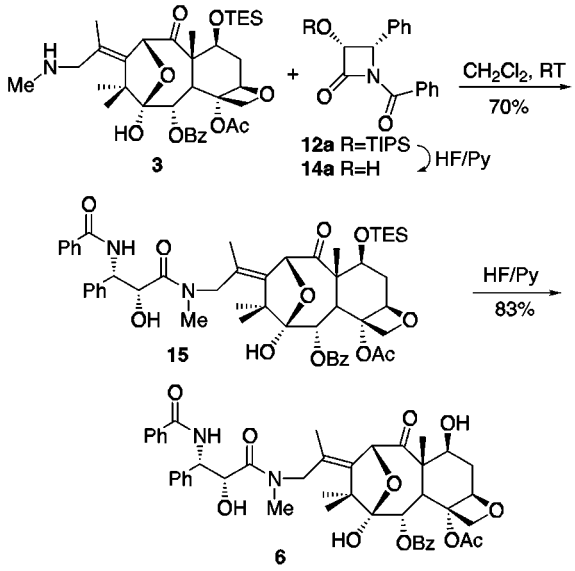
Scheme 6



Scheme 7



using HF/pyridine to afford nor-seco taxoid **6** in 83% yield (Scheme 7).

The in vitro cytotoxicities of the novel nor-seco taxoids thus synthesized were evaluated against several human tumor cell lines, i.e., ovarian (A121), non-small cell lung (A549), colon (HT-29), breast (MCF7) and the drug-resistant breast (MCF7-R) cancer cell lines, using the method developed by Skehan et al.[30] Results are summarized in Table 1. The IC_{50} values of paclitaxel in the same assay are also shown for comparison.

As Table 1 shows, the nor-seco taxoids with a C-13 ester linkage, **4a** and **4b**, possess 0.13−0.08 and 0.17−0.10 μM level IC_{50} values, respectively, which are 20−40 times weaker activities than that of paclitaxel in the same cell line assay, but clearly retain a certain level cytotoxicity. It is worthy of note that **4a** and **4b** exhibit IC_{50} values of 0.47 and 0.36 μM, respectively, against the doxorubicin-resistant human breast cancer (MCF7-R) cell line, i.e., **4a** and **4b** are comparable to paclitaxel. The nor-seco taxoid **6** bearing a *N*-Me amide linkage possesses 0.70−0.20 μM level IC_{50} values, yet still retains a certain level cytotoxicity. In contrast to nor-seco taxoids **4a**, **4b**, and **6**, the nor-seco taxoids with a *N*-H amide linkage, **5a**−**d**, are all virtually inactive (IC_{50} > 1.0 μM).

Table 1. In Vitro Cytotoxicity (IC_{50}, μM)[a] of nor-seco Taxoids

taxoid	A121 (ovarian)	A549 (NSCL)	HT-29 (colon)	MCF-7 (breast)	MCF7-R (breast)
paclitaxel	0.0063	0.0036	0.0036	0.0017	0.300
4a	0.117	0.133	0.134	0.079	0.471
4b	0.131	0.169	0.171	0.101	0.360
5a	>1.0	>1.0	>1.0	>1.0	>1.0
5b	>1.0	>1.0	>1.0	>1.0	>1.0
5c	>1.0	>1.0	>1.0	>1.0	>1.0
5d	>1.0	>1.0	>1.0	>1.0	>1.0
6	0.535	0.708	0.292	0.200	>1.0

[a] The concentration of compound which inhibits 50% (IC_{50}, μM) of the growth of human tumor cell line after 72 h drug exposure.[39]

The results obtained in this SAR study clearly indicate the importance of the A ring for the strong cytotoxicity of taxoids. However, it is also very important to mention that two of these reduced-structure analogues, **4a** and **4b**, retain a certain level of cytotoxicity and their potency against a drug-resistant human breast cancer cell line (MCF7-R) is comparable to that of paclitaxel. Replacement of the C-13 ester linkage with an *N*-H amide linkage is deleterious to cytotoxicity. Similar findings have been reported by Chen et al.[38] for paclitaxel analogues bearing an *N*-H amide linkage. However, the introduction of *N*-Me group to the amide linkage, i.e., nor-seco taxoid **6**, recovers cytotoxicity substantially, which is quite intriguing.

To explain the intriguing structure−activity relationships observed, we carried out molecular modeling studies on the representative analogues **4a** (ester linkage), **5a** (*N*-H amide linkage), and **6** (*N*-Me amide linkage). We conducted a series of restrained molecular dynamics (RMD) simulations in a vacuum (Sybyl 6.04) for these three analogues to investigate their conformational dynamism. For each analogue, three simulations were conducted that maintained the H2′−C2′−C3′−H3′ dihedral angle constant at 180°, 60°, and −60°, respectively. It has been shown that the value of the H2′−C2′−C3′−H3′ dihedral angle is an extremely crucial component in the maintenance of the biologically active conformation of paclitaxel.[40]

This RMD study confirmed the greater dynamism of the phenylisoserine moiety at the C-13 position of the nor-seco taxoids than that of paclitaxel[40] as expected. The cleavage of the taxane A ring allows for free rotation around the C12−C13 bond, resulting in different conformations for the phenylisoserine moiety *mostly not related to potentially bioactive conformations of paclitaxel*. The range of movement of the isoserine moiety is demonstrated in the overlay of the 10 lowest energy structures for **4a**, **5a**, and **6** (Figure 1) obtained from the RMD simulations[40] maintaining the H2′−C2′−C3′−H3′ dihedral at 180° (RMD simulations using 124° dihedral angle gave essentially the same results). We believe this conformational dynamism is responsible for the lack of or low activity of the nor-seco taxoids.

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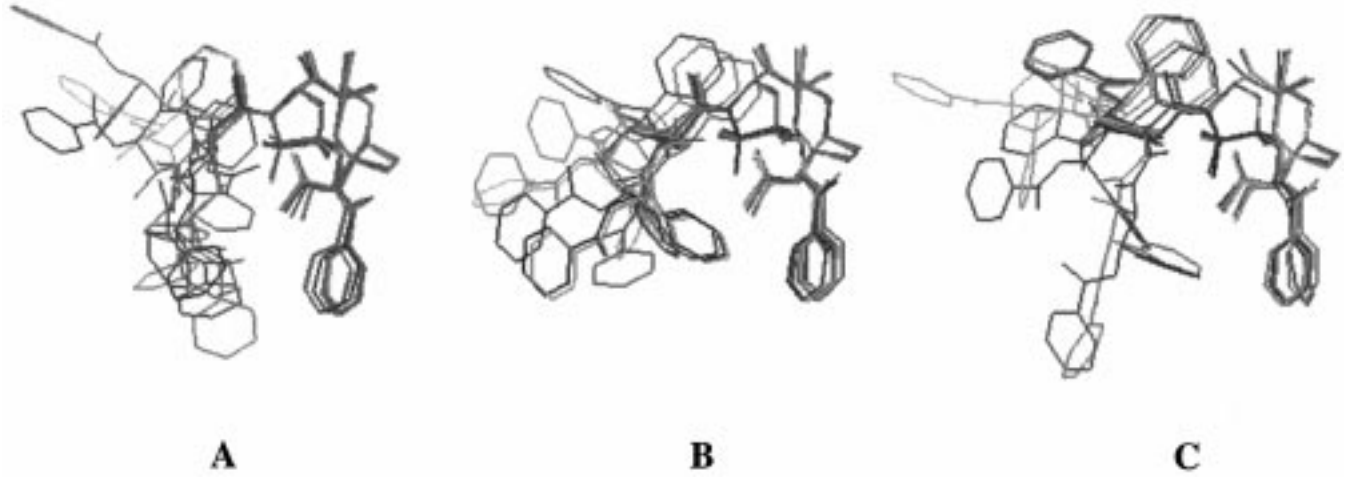

Figure 1. Overlay of 10 lowest energy structures obtained in the RMD study of **4a** (A), **5a** (B), and **6** (C).

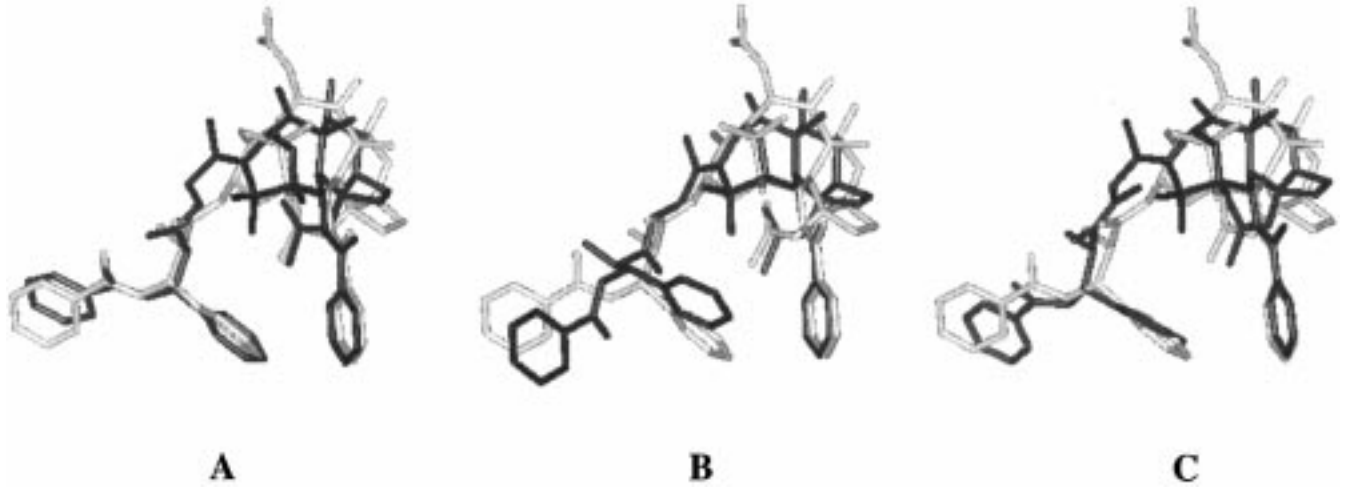

Figure 2. Overlay of hydrophobic clustering structures for **4a** (A), **5a** (B), and **6** (C) (shown in black) with the eclipsed conformer of paclitaxel (gray).[40]

Although the observed loss of biological activity for **5a** can be ascribed to possible biologically unfavorable hydrogen bondings involving the amide hydrogen at the binding site on the microtubules, intrinsic conformational preferences may well dictate biological activity. Accordingly, we have looked into the structural preference of each nor-seco taxoid as compared to the hypothetical bioactive conformations of paclitaxel, i.e., the "hydrophobic clustering conformations".[40] We have recently reported the equilibrium of two hydrophobic clustering conformations (H2′−C2′−C3′−H3′ dihedral angles of 124° and 180°, respectively) for paclitaxel in aqueous media based on our "fluorine-probe approach".[40] Thus, we carried out overlay study of possible hydrophobic clustering conformations of **4a**, **5a**, and **6** selected from the conformations obtained from the RMD study mentioned above, albeit low dynamic population, with that of paclitaxel which is predominant in water[40] (H2′−C2′−C3′−H3′ dihedral angles of 124°). Results are shown in Figure 2.

As Figure 2A indicates, the flexibility of the ester linkage allows **4a** to readily adopt a hydrophobic clustering conformation that overlaps very well with the C-3′ and C-2 phenyl moieties and, to a certain extent, with the C-3′ *N*-benzoyl group of paclitaxel.[42] However, both the amide analogues, **5a** and **6**, are restricted to trans amide conformations that limit the conformational flexibility of the phenylisoserine moiety. The *N*-H amide analogue **5a** is found to have an extremely strong preference for a highly extended phenylisoserine moiety. As Figure 2B clearly shows, the best "hydrophobic clustering" conformer of **5a** has a very poor overlap with that of paclitaxel at its phenylisoserine moiety. In contrast to this, the preferred hydrophobic clustering conformation of the *N*-Me amide analogue **6** overlaps well with that of paclitaxel as shown in Figure 2C. The preference for this conformation for **6** arises from the absence of steric conflict between the three methyl groups at the C13−*N*, C-12, and C-15 positions. This serious steric conflict is clearly observed when **6** is forced to adopt the extended conformation of **5a**. The overlay study using the other hydrophobic conformer of paclitaxel

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(42) In our previous communication,[28] we had proposed a different model for the biologically active conformation for **4a** that was based on the X-ray crystal structure of docetaxel.[2] However, the observation of hydrophobic clustering conformations in aqueous media provides more likely models for biological recognition or binding at the active site.[40,41]

(H2′−C2′−C3′−H3′ dihedral angles of 180°)[40,41] led to essentially the same conclusion. These overlay studies are consistent with the observed dramatic difference in the biological activities of **4a**, **5a**, and **6**.

Conclusions

A series of novel nor-seco taxoids containing an ester, an NH amide, or an NMe amide linkage at the C-13 position have been synthesized. Despite the destruction of the taxane A ring, nor-seco taxoids bearing a C-13 ester linkage or C-13 *N*-Me amide linkage retain a certain level of cytotoxicity against several human cancer cell lines. However, nor-seco taxoids with a C-13 *N*-H amide linkage are found to be inactive (IC_{50} > 1.0 μM). The reduced activity of the nor-seco taxoids can be ascribed to the enhanced conformational flexibility of the phenylisoserine moiety caused by the loss of the constrained taxane A ring. The reduced yet significant activity of nor-seco taxoids **4a** (C-13 ester linkage) and **6** (C-13 *N*-Me amide linkage) is explained by their ability to adopt the hydrophobic clustering conformation of paclitaxel which is proposed to be responsible for its strong cytotoxicity. On the contrary, the low-energy hydrophobic clustering conformation of nor-seco taxoid **5a** (C-13 *N*-H amide linkage) overlaps poorly with that of paclitaxel, which is reflected in the loss of activity.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 250.13 and 62.90 MHz, respectively, using tetramethylsilane as the internal standard. Optical rotations were measured at 589 nm. Column chromatography was carried out on silica gel (230−400 mesh). Elemental analyses were performed at M-H-W Laboratory, Phoenix, AZ. High-resolution mass spectra were obtained from the University of California, Riverside Mass Spectrometry Facility, Riverside, CA.

Materials. The chemicals were purchased from Aldrich Co. and Sigma and purified before use by standard methods. Tetrahydrofuran was freshly distilled under nitrogen from sodium metal and benzophenone. Dichloromethane was also distilled immediately prior to use under nitrogen from calcium hydride. (3*R*,4*S*)-1-Acylazetidin-2-ones (**11a**−**b**, **12a**−**d**, **14a**) were prepared by the methods previously reported from these laboratories.[20,30,31] 14β-Hydroxy-10-deacetylbaccatin III was a gift from Indena, SpA, Italy.

Molecular Modeling. Restrained molecular dynamics (RMD) studies and energy minimizations were carried out using the Tripos force field and Gasteiger−Hückel charges on the Sybyl 6.04 molecular modeling platform (Tripos, Inc.). Three high-temperature dynamics simulations at 900 K were carried out over 100 ps (time step of 1 fs) for each analogue maintaining the H2′−C2′−C3′−H3′ dihedral angle constant at 180°, 60°, and −60°, respectively (force penalty = 0.05 kcal/mol/Å). The dynamics set was sampled every 2 ps, and each structure was subjected to a further 2 ps of RMD at 300 K, followed by minimization using steepest descents and conjugate gradients, maintaining the same constraints. The resultant structures were studied for conformational preferences, including superimposition with our previously described model for paclitaxel based on the ^{19}F and ^{1}H NMR and RMD study of fluorinated analogues.[40]

13-Formyl-14-nor-seco-10-deacetylbaccatin III (8). To a solution of 14β-hydroxy-10-deacetylbaccatin III (950 mg, 1.7 mmol) in dioxane (60 mL) was added a solution of 0.5 N periodic acid in water (8.5 mL, 4.3 mmol). The mixture was stirred for 12 h, neutralized with aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified on a silica gel column using hexane/ethyl acetate (3/2) as the eluant, followed by recrystallization from hexane to give **8** as a white solid (828 mg, 92% yield): mp 190−193 °C; $[\alpha]^{20}_D$ −118.8 (*c* 0.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.67 (s, 3 H), 1.75 (s, 3 H), 1.78 (s, 3 H), 1.93 (ddd, *J* = 14.8, 11.5, 4.2 Hz, 1 H), 2.19 (s, 3 H), 2.47 (ddd, *J* = 14.8, 9.7, 5.9 Hz, 1 H), 3.33 (d, *J* = 11.2 Hz, 1 H), 4.22 (dd, *J* = 11.2, 5.9 Hz, 1 H), 4.27 (d, *J* = 8.4 Hz, 1 H), 4.34 (d, *J* = 8.4 Hz, 1 H), 4.38 (s, 1 H), 4.78 (s, 1 H), 4.80 (dd, *J* = 4.2, 9.7 Hz, 1 H), 5.18 (s, 1 H), 5.90 (d, *J* = 11.2 Hz, 1 H), 7.41 (m, 2 H), 7.68 (m, 1 H), 8.40 (m, 2 H), 10.32 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.1, 13.5, 21.6, 24.2, 29.1, 34.6, 40.8, 48.5, 50.9, 68.7, 74.6, 75.1, 80.3, 83.8, 84.8, 109.2, 128.3, 128.9, 130.3, 132.0, 134.5, 157.3, 168.0, 169.4, 189.1, 211.6. Anal. Calcd for $C_{28}H_{32}O_{10}$: C, 63.63; H, 6.10. Found: C, 63.41; H, 6.13.

7-(Triethylsilyl)-13-formyl-14-nor-seco-10-deacetylbaccatin III (9). To a solution of nor-seco baccatin **8** (936 mg, 1.77 mmol) and 4-(dimethylamino)pyridine (DMAP) (195 mg, 1.60 mmol) in dichloromethane (15 mL) was added dropwise triethylamine (0.8 mL, 5.8 mmol), followed by chlorotriethylsilane (0.9 mL, 5.4 mmol) with stirring at room temperature. The mixture was stirred for 20 h, quenched with water, and extracted with chloroform. The combined organic extracts were dried on anhydrous magnesium sulfate and concentrated in vacuo to give an oily residue. The crude product was purified on a silica gel column using petroleum ether followed by hexane/ethyl acetate (7/3) as the eluant, followed by recrystallization from hexane to give **9** as a white solid (865 mg, 76% yield): mp 154−155 °C; $[\alpha]^{20}_D$ −44.4 (*c* 0.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.75 (m, 6 H), 0.94 (m, 9 H), 1.23 (s, 3 H), 1.70 (s, 3 H), 1.72 (s, 3 H), 1.77 (s, 3 H), 1.95 (ddd, *J* = 14.7, 11.5, 4.4 Hz, 1 H), 2.13 (s, 3 H), 2.46 (ddd, *J* = 14.7, 9.5, 5.8 Hz, 1 H), 3.33 (d, *J* = 11.3 Hz, 1 H), 4.16 (m, 1 H), 4.18 (d, *J* = 8.4 Hz, 1 H), 4.48 (d, *J* = 8.4 Hz, 1 H), 4.72 (s, 1 H), 4.78 (dd, *J* = 9.5, 4.4 Hz, 1 H), 5.15 (s, 1 H), 5.87 (d, *J* = 11.3 Hz, 1 H), 7.50 (m, 2 H), 7.61 (m, 1 H), 8.03 (m, 2 H), 10.31 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 5.8, 6.9, 13.0, 21.7, 24.5, 30.1, 34.8, 41.0, 49.6, 51.0, 68.8, 74.4, 75.5, 80.5, 83.9, 85.0, 109.7, 128.6, 129.6, 129.8, 131.6, 133.5, 157.3, 164.9, 169.6, 189.2, 211.8. Anal. Calcd for $C_{34}H_{46}O_{10}Si$: C, 63.53; H, 7.21. Found: C, 63.56; H, 7.28.

7-(Triethylsilyl)-13-hydroxy-14-nor-seco-10-deacetylbaccatin III (1). To a solution of nor-seco baccatin **9** (88 mg, 0.137 mmol) in methanol (6 mL) was added a 0.19 M solution of sodium cyanoborohydride in methanol (3 mL, 0.57 mmol), and the mixture was stirred at room temperature for 20 min. The pH of the mixture was maintained at pH 6 with 1 N hydrochloric acid. Then, a saturated aqueous solution of ammonium chloride was added to quench the reaction and the reaction mixture was extracted with chloroform. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified on a silica gel column using hexane/ethyl

acetate (1/1) as the eluant to give **1** as a white solid (76 mg, 86% yield): mp 143−144 °C; $[\alpha]^{20}_D$ −42.9 (*c* 0.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.70 (m, 6 H), 0.87 (m, 9 H), 0.85 (s, 3 H), 1.00 (s, 3 H), 1.52 (s, 3 H), 1.73 (s, 3 H), 1.97 (ddd, J = 14.6, 11.4, 4.5 Hz, 1 H), 2.23 (s, 3 H), 2.46 (ddd, J = 14.6, 9.6, 6.0 Hz, 1 H), 3.79 (d, J = 12.0 Hz, 1 H), 3.87 (d, J = 11.2 Hz, 1 H), 4.13 (dd, J = 11.4, 6.0 Hz, 1 H) (H7), 4.19 (d, J = 8.4 Hz, 1 H), 4.48 (d, J = 8.4 Hz, 1 H), 4.61 (d, J = 12.0 Hz, 1 H), 4.77 (dd, J = 9.6, 4.5 Hz, 1 H), 4.95 (s, 1 H), 5.80 (d, J = 11.2 Hz, 1 H), 7.39 (m, 2 H), 7.62 (m, 1 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 5.8, 6.9, 13.9, 19.3, 22.0, 22.1, 28.2, 34.9, 40.0, 48.3, 50.7, 62.3, 68.8, 74.5, 75.7, 81.4, 84.2, 84.6, 109.1, 128.5, 129.7, 130.4, 133.4, 138.0, 165.0, 171.9, 212.9. Anal. Calcd for $C_{34}H_{48}O_{10}Si$: C, 63.33; H, 7.50. Found: C, 63.13; H, 7.49.

7-(Triethylsilyl)-13-amino-14-nor-seco-10-deacetylbaccatin III (2). To a solution of nor-seco baccatin **1** (130 mg, 0.20 mmol), phthalimide (50 mg, 0.34 mmol), and triphenylphosphine (91 mg, 0.35 mmol) in 13 mL of anhydrous THF was added dropwise a solution of diethyl azodicaboxylate (DEAD) (60 μL, 0.38 mmol) in 1.0 mL THF, and the mixture was stirred at 45 °C for 20 h. The solvent was removed in vacuo, and the reaction mixture was purified on a silica gel column using hexane/ethyl acetate (2/1) as the eluant to give nor-seco baccatin phthalimide **10** as a white solid (141 mg, 90.4% yield). To a solution of **10** (141 mg, 0.18 mmol) in ethanol (12 mL) was added an aqueous solution of methylamine (40% w/w, 0.25 mL, excess), and the mixture was stirred at 55 °C for 22 h. Then the solvent was removed in vacuo, and the residue was purified on a silica gel column using methanol/dichloromethane (3/97) as the eluant to give **2** as a white solid (104 mg, 88.7% yield): mp 73−75 °C; $[\alpha]^{20}_D$ −46.4 (*c* 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.67 (m, 6 H), 0.83 (m, 9 H), 1.01 (s, 3 H), 1.52 (s, 3 H), 1.67 (s, 3 H), 1.73 (s, 3 H), 1.95 (ddd, J = 14.7, 11.3, 4.3 Hz, 1 H), 2.20 (s, 3 H), 2.46 (ddd, J = 14.7, 9.6, 6.0 Hz, 1 H), 3.00 (d, J = 13.8 Hz, 1 H), 3.68 (d, J = 11.2 Hz, 1 H), 3.77 (d, J = 13.8, 1 H), 4.07−4.24 (m, 2 H), 4.47 (d, J = 8.1 Hz, 1 H), 4.79 (dd, J = 9.5, 4.0 Hz, 1 H), 4.93 (s, 1 H), 5.79 (d, J = 11.2 Hz, 1 H), 7.46 (m, 2 H), 7.60 (m, 1 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 5.8, 6.9, 13.8, 19.3, 22.0, 22.2, 27.9, 34.9, 40.3, 43.5, 48.0, 50.6, 69.1, 74.5, 75.6, 80.9, 84.0, 84.6, 109.2, 128.5, 129.8, 133.3, 136.0, 165.0, 170.8, 213.3. Anal. Calcd for $C_{34}H_{49}NO_9Si$: C, 63.43; H, 7.67; N, 2.18. Found: C, 63.51; H, 7.80; N, 2.24.

7-(Triethylsilyl)-13-(*N*-methylamino)-14-nor-seco-10-deacetylbaccatin III (3). To a solution of nor-seco baccatin **9** (30 mg, 0.467 mmol) in dry methanol (2 mL) was added dropwise a 2.0 M solution of methylamine in THF (0.25 mL) in the presence of anhydrous sodium sulfate. After the mixture was stirred for 15 min, sodium cyanoborohydride (8.8 mg, 0.14 mmol) was added quickly followed by the addition of 0.1 mL of glacial acetic acid, and the mixture was stirred at room temperature for 9 h. The solvent was removed under reduced pressure, and water was added to the reaction mixture. The pH of the solution was adjusted to pH 13 with solid sodium hydroxide, and the mixture was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified on a silica gel column using methanol/dichloromethane (5/95) as the eluant to give **3** as a white solid (26 mg, 84% yield): mp 67−68 °C; $[\alpha]^{20}_D$ −34.2 (*c* 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.65−0.76 (m, 6 H), 0.80−0.89 (m, 9 H), 1.02 (s, 3 H), 1.52 (s, 3 H), 1.68 (s, 3 H), 1.73 (s, 3 H), 1.92 (ddd, J = 14.7, 11.2, 4.1 Hz, 1 H), 2.17 (s, 3 H), 2.39−2.52 (m, 1 H), 2.45 (s, 3H), 3.05 (d, J = 12.1 Hz, 1 H), 3.55 (d, J = 12.8 Hz, 1 H), 3.59 (d, J = 11.2 Hz, 1 H), 4.12−4.19 (m, 2 H), 4.46 (d, J = 8.5 Hz, 1 H), 4.80 (dd, J = 9.5, 3.9 Hz, 1 H), 4.95 (s, 1 H), 5.79 (d, J = 11.3 Hz, 1 H), 7.45 (m, 2 H), 7.60 (m, 1 H), 8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 5.8, 6.7, 13.7, 20.0, 21.7, 22.1, 27.6, 34.9, 36.3, 40.5, 48.0, 50.5, 53.2, 69.1, 74.7, 75.4, 80.5, 83.9, 84.7, 109.2, 128.4, 129.7, 129.9, 130.6, 133.2, 137.0, 165.0, 169.9, 213.4. Anal. Calcd for $C_{35}H_{51}O_9SiN$: C, 63.90; H, 7.81; N, 2.13. Found: C, 63.98; H, 7.97; N, 2.19.

14-Nor-seco-10-deacetylbaccatin III 13-[*N*-Acyl-(2′*R*,3′*S*)-3′-phenylisoserinate] (4a and 4b). A typical procedure is described for the synthesis of 14-nor-seco-10-deacetylbaccatin III 13-[*N*-benzoyl-(2′*R*,3′*S*)-3′-phenylisoserinate] (**4a**). To a solution of 7-TES-nor-seco-baccatin alcohol **1** (30 mg, 0.046 mmol) and of 3-EEO-1-benzoyl-β-lactam **11a** (31 mg, 0.09 mmol) in THF (1 mL) was added a 1.0 M solution of sodium hexamethyldisilazide in THF (0.046 mL, 4.6 mmol) at −30 °C over a period of 10 min. TLC analysis of the reaction mixture revealed that **1** had been completely consumed. The reaction mixture was poured into a saturated aqueous ammonium chloride solution to quench the reaction. The reaction mixture was extracted with ether and then with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give an oily residue. The residue (66 mg) was dissolved in THF (1.5 mL), and 0.5 N hydrochloric acid (1.5 mL) was added at room temperature with stirring. After 36 h, ethyl acetate was added to the reaction mixture and washed with saturated sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give a white solid. The crude product was purified on a silica gel column using ethyl acetate/hexane (1/4) as the eluant to afford 7-TES-**4a** as a white solid (37 mg, 87% yield for two steps): mp 105−106 °C; $[\alpha]^{20}_D$ −61.6 (*c* 1.72, CH_2Cl_2); ^{1} H NMR ($CDCl_3$) δ 0.68 (m, 9 H), 0.76 (q, J = 7.0 Hz, 6 H), 0.95 (s, 3 H), 1.42 (s, 3 H), 1.44 (s, 3 H), 1.66 (s, 3 H), 1.88 (ddd, J = 14.8, 11.1, 3.8 Hz, 1 H), 2.09 (s, 3 H), 2.40 (ddd, J = 14.8, 9.4, 6.0 Hz, 1 H), 3.43 (d, J = 11.2 Hz, 1 H), 4.01 (dd, J = 6.0, 11.1 Hz, 1 H), 4.09 (d, J = 8.4 Hz, 1 H), 4.40 (d, J = 8.4 Hz, 1 H), 4.58 (d, J = 11.5 Hz, 1 H), 4.63 (d, J = 1.7 Hz, 1 H), 4.71 (dd, J = 9.4, 3.8 Hz, 1 H), 4.88 (s, 1 H), 4.89 (d, J = 11.5 Hz, 1 H), 5.72 (m, 1 H), 5.73 (d, J = 11.1 Hz, 1 H), 7.14 (d, J = 8.9 Hz, 1 H), 7.18∼7.46 (m, 10 H), 7.53 (t, J = 7.2 Hz, 1 H), 7.75 (d, J = 7.2 Hz, 2 H), 7.94 (d, J = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 5.8, 6.9, 13.8, 19.1, 21.9, 22.1, 28.4, 34.9, 40.5, 48.3, 50.7, 55.0, 64.8, 69.1, 74.1, 74.3, 75.5, 80.9, 83.8, 84.6, 109.3, 126.9, 127.0, 127.2, 127.9, 128.5, 128.7, 128.9, 129.8, 131.8, 133.4, 138.6, 141.3, 164.9, 166.6, 170.8, 172.2, 212.9. Anal. Calcd for $C_{50}H_{61}O_{13}NSi$: C, 65.84; H, 6.74; N, 1.54. Found: C, 66.01; H, 6.90; N, 1.49.

A solution of 7-TES-**4a** (149 mg, 0.16 mmol) in THF (5 mL) was added a 1.0 M solution of tetra-*n*-butylammonium fluoride in THF (0.2 mL) at −10 °C for 5 min under nitrogen. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was submitted to a short column chromatography on silica gel using ethyl acetate/hexane (1/4) as the eluant to give **4a** as a white solid (120.3 mg, 94% yield): mp 141−142 °C; $[\alpha]^{20}_D$ −80.2

(*c* 0.76, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.51 (s, 3 H), 1.53 (s, 3 H), 1.74 (s, 3 H), 1.94 (d, J = 3.7, 11.2, 15.0 Hz, 1 H), 2.24 (s, 3 H), 2.49 (ddd, J = 15.0, 9.6, 6.1 Hz, 1 H), 3.52 (d, J = 11.0 Hz, 1 H), 4.15 (dd, J = 11.2, 6.1 Hz, 1 H), 4.25 (d, J = 8.3 Hz, 1 H), 4.29 (d, J = 8.3 Hz, 1 H), 4.71(d, J = 11.0 Hz, 1 H), 4.73 (d, J = 1.7 Hz, 1 H), 4.83 (dd, J = 9.6, 3.7 Hz, 1 H), 4.95 (d, J = 11.0 Hz, 1 H), 4.98 (s, 1 H), 5.78 (dd, J = 8.9, 1.7 Hz, 1 H), 5.83 (d, J = 11.0 Hz, 1 H), 7.20 (d, J = 8.9 Hz, 1 H), 7.31∼7.55 (m, 10 H), 7.66 (dd, J = 7.6, 7.2 Hz, 1 H), 7.82 (d, J = 7.2 Hz, 2 H), 8.12 (d, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 19.0, 21.6, 21.8, 29.7, 34.7, 40.3, 47.2, 50.5, 54.9, 64.8, 69.1, 73.9, 74.5, 75.0, 80.6, 83.7, 84.4, 108.6, 125.8, 127.0, 128.0, 128.7, 130.2, 131.8, 133.9, 134.3, 138.6, 141.3, 166.6, 167.9, 170.6, 172.3, 212.7. Anal. Calcd for $C_{44}H_{47}O_{13}N$: C, 66.24; H, 5.94; N, 1.76. Found: C, 66.12; H, 6.09; N, 1.60.

In a similar manner, **4b** was obtained from nor-seco baccatin **1** and β-lactam **11b via** 7-TES-**4b**.

7-TES-4b: colorless oil; $[\alpha]^{20}_D$ −43.3 (*c* 1.22, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.73 (m, 9 H), 0.82 (m, 6 H), 1.05 (s, 3 H), 1.42 (s, 9 H), 1.53 (s, 3 H), 1.61 (s, 3 H), 1.75 (s, 3 H), 1.95 (m, 1 H), 2.15 (s, 3 H), 2.49 (m, 1 H), 3.52 (d, J = 11.2 Hz, 1 H), 3.90 (bs, 1 H), 4.12 (m, 1 H), 4.16 (d, J = 8.3 Hz, 1 H), 4.47 (d, J = 8.3 Hz, 1 H), 4.54 (bs, 1 H), 4.74−4.91 (m, 3 H), 4.99 (s, 1 H), 5.25 (bd, J = 9.5 Hz, 1 H), 5.53 (d, J = 9.5 Hz, 1 H), 5.81 (d, J = 11.2 Hz, 1 H), 7.28−7.49 (m, 7 H), 7.60 (m, 1 H), 8.02 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 5.8, 6.9, 13.7, 19.0, 21.7, 22.1, 28.3, 29.7, 34.9, 40.5, 48.3, 50.7, 56.3, 64.7, 69.1, 74.2, 74.5, 75.5, 80.8, 83.8, 84.6, 109.3, 125.4, 126.8, 127.7, 128.5, 128.6, 130.0, 133.3, 141.1, 155.1, 164.9, 170.5, 172.3, 213.0. Anal. Calcd for $C_{48}H_{65}NO_{14}Si$: C, 63.49; H, 7.21; N, 1.54. Found: C, 63.38, H, 7.31; N, 1.58.

4b: white solid, mp 119−121 °C; $[\alpha]^{20}_D$ −66.7 (*c* 0.27, $CHCl_3$); ($CDCl_3$) δ ^1H NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.41 (s, 9 H), 1.51 (s, 3 H), 1.62 (s, 3 H), 1.74 (s, 3 H), 1.93 (m, 1 H), 2.20 (s, 3 H), 2.50 (m, 1 H), 3.52 (d, J = 11.1 Hz, 1 H), 3.80 (bs, 1 H), 4.13−4.23 (m, 2 H), 4.22 (d, J = 7.7 Hz, 1 H), 4.29 (d, J = 8.2 Hz, 1 H), 4.54 (s, 1 H), 4.82 (m, 3 H), 5.02 (m, 2 H), 5.25 (m, 1 H), 5.52 (d, J = 9.4 Hz, 1 H), 5.85 (d, J = 11.1 Hz, 1 H), 7.28−7.42 (m, 5 H), 7.49 (m, 2 H), 7.65 (m, 1 H), 8.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 19.0, 21.7, 27.3, 28.3, 32.8, 34.7, 40.3, 47.2, 50.5, 56.3, 64.8, 69.0, 74.1, 75.0, 76.9, 78.1, 79.8, 80.5, 83.8, 84.5, 108.8, 126.1, 126.7, 127.8, 128.6, 128.7, 130.2, 134.2, 141.0, 155.1, 167.9, 170.3, 170.9, 212.8. Anal. Calcd for $C_{42}H_{51}NO_{14}$: C, 63.55; H, 6.48; N, 1.76. Found: C, 63.59; H, 6.77; N, 1.64.

General Procedure for the Synthesis of 14-Nor-seco-10-deacetylbaccatin III 13-[*N*-Acyl-(2′*R*,3′*S*)-isoserinamide] (5a−d). A mixture of nor-seco baccatin amine **2** (0.047−0.067 mmol) and β-lactam **12** (0.097−0.140 mmol, 2.0 equiv) in 3 mL of dichloromethane was stirred at 40 °C for 20−60 h. Then the solvent was removed in vacuo, and the residue was purified on a silica gel column using dichloromethane followed by methanol/dichloromethane (3/97) as the eluant to afford **13** as a white solid (75−89% yields). To a solution of **13** in 4 mL of pyridine/acetonitrile (1/1) was added dropwise HF/pyridine (70/30, 0.50 mL) at 0 °C, and the mixture was allowed to warm to room temperature. Then, the mixture was stirred for 27−48 h at 40 °C. The reaction was quenched with aqueous saturated sodium carbonate solution, and the reaction mixture was extracted with ethyl acetate. The combined extracts were washed with aqueous saturated copper sulfate solution and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified on a silica gel column using methanol/dichloromethane (3/97) as the eluant to afford **5** as a white solid (80−91% yields).

14-Nor-seco-10-deacetylbaccatin III 13-[*N*-benzoyl-(2′*R*,3′*S*)-3′-phenylisoserinamide] (5a): mp 168−170 °C; $[\alpha]^{20}_D$ −130.8 (*c* 0.13, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.09 (s, 3 H), 1.28 (s, 9 H), 1.44 (s, 3 H), 1.69 (s, 3 H), 1.93 (ddd, J = 14.6, 11.4, 4.0 Hz, 1 H), 2.27 (s, 3 H), 2.45 (ddd, J = 14.6, 9.5, 6.0 Hz, 1 H), 3.62 (d, J = 11.0 Hz, 1 H), 3.93−4.02 (m, 3 H), 4.21 (d, J = 8.2 Hz, 1 H), 4.29 (d, J = 8.2 Hz, 1 H), 4.62 (s, 1 H), 4.78 (dd, J = 9.4, 4.1 Hz, 1 H), 4.87 (s, 1 H), 5.71 (d, J = 6.1 Hz, 1 H), 5.80 (d, J = 11.1 Hz, 1 H), 6.88 (s, 1 H), 7.26−7.30 (m, 3 H), 7.40−7.53 (m, 7 H), 7.65 (m, 1 H), 7.88 (m, 2 H), 8.10 (m, 2 H), 8.35 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 18.8, 21.6, 21.9, 26.7, 34.7, 39.7, 40.3, 46.9, 50.4, 55.9, 68.8, 73.3, 74.4, 75.1, 80.8, 83.9, 84.4, 108.5, 127.1, 127.2, 127.5, 127.7, 127.9, 128.4, 128.5, 128.7, 130.2, 131.9, 133.7, 134.2, 137.3, 138.5, 167.0, 167.6, 171.2, 172.5, 212.7. Anal. Calcd for $C_{44}H_{48}N_2O_{12}$: C, 66.32; H, 6.07; N, 3.52. Found: C, 66.19; H, 6.25; N, 3.32.

14-Nor-seco-10-deacetylbaccatin III 13-[*N*-(*tert*-butoxycarbonyl)-(2′*R*,3′*S*)-3′-phenylisoserinamide] (5b): mp 162−164 °C; $[\alpha]^{20}_D$ −94.4 (*c* 0.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H), 1.41−1.49 (m, 15 H), 1.71 (s, 3 H), 1.93 (ddd, J = 14.5, 11.4, 4.0 Hz, 1 H), 2.27 (s, 3 H), 2.45 (ddd, J = 14.6, 9.7, 5.9 Hz, 1 H), 3.63 (d, J = 11.0 Hz, 1H), 3.98−4.16 (m, 4 H), 4.22 (d, J = 8.2 Hz, 1 H), 4.29 (d, J = 8.2 Hz, 1 H), 4.47 (s, 1 H), 4.78 (dd, J = 9.5, 3.9 Hz, 1 H), 4.94 (s, 1 H), 4.98 (br s, 1 H), 5.14 (br d, J = 6.3 Hz, 1 H), 5.82 (d, J = 11.0 Hz, 1 H), 6.05 (br d, J = 7.6 Hz, 1 H), 6.68 (br s, 1 H), 7.31−34 (m, 5 H), 7.49 (m, 2 H), 7.65 (m, 1 H), 8.11 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.2, 21.5, 22.0, 26.8, 28.3, 34.7, 39.8, 40.5, 46.9, 50.5, 56.7, 69.0, 74.4, 75.1, 79.9, 81.0, 83.9, 84.4, 108.6, 126.8, 126.9, 127.7, 128.5, 128.7, 130.2, 134.2, 138.5, 155.5, 167.7, 171.5, 171.5, 212.7. Anal. Calcd for $C_{42}H_{52}N_2O_{13}$: C, 63.62; H, 6.61; N, 3.53. Found: C, 63.49; H, 6.60; N, 3.38.

14-Nor-seco-10-deacetylbaccatin III 13-[(*N*-*tert*-butoxycarbonyl)-(2′*R*,3′*S*)-3′-(2-methyl-1-propenyl)-isoserinamide] (5c): mp 140−142 °C; $[\alpha]^{20}_D$ −96.2 (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.41 (s, 9 H), 1.47 (s, 3 H), 1.50 (s, 3 H), 1.61 (s, 3 H), 1.72−1.76 (m, 9 H), 1.94 (ddd, J = 14.7, 11.1, 4.4 Hz, 1 H), 2.29 (s, 3 H), 2.44 (ddd, J = 15.2, 9.6, 5.9 Hz, 1 H), 3.70 (d, J = 11.0 Hz, 1 H), 4.09−4.24 (m, 6 H), 4.31 (d, J = 8.2 Hz, 1 H), 4.63 (br s, 1 H), 4.80 (dd, J = 4.9, 9.5 Hz, 1 H), 4.91−4.97 (m, 2 H), 5.22−5.29 (m, 2 H), 5.46 (d, J = 8.2 Hz, 1 H), 5.83 (d, J = 11.0 Hz, 1 H), 6.95 (br s, 1 H), 7.52 (m, 2 H), 7.65 (m, 1 H), 8.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 18.4, 19.1, 21.6, 21.9, 25.8, 26.7, 28.0, 28.3, 34.7, 39.8, 40.4, 47.0, 48.1, 50.5, 51.8, 56.6, 68.9, 74.5, 74.9, 75.2, 79.9, 80.8, 83.9, 84.5, 108.7, 116.7, 120.5, 127.9, 128.5, 128.6, 128.7, 129.7, 130.2, 134.2, 137.5, 138.4, 156.4, 167.7, 171.3, 172.5, 213.0. Anal. Calcd for $C_{40}H_{54}N_2O_{13}$: C, 62.32; H, 7.06; N, 3.63. Found: C, 62.13; H, 6.89; N, 3.47.

14-Nor-seco-10-deacetylbaccatin III 13-[*N*-(*tert*-butoxycarbonyl)-(2′*R*,3′*S*)-3′-(2-methylpropyl)isoserinamide] (5d): mp 146−148 °C; $[\alpha]^{20}_D$ −95.0 (*c* 0.20, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 (d, J = 2.4 Hz, 3 H), 0.96 (d, J = 2.4 Hz, 3 H), 1.15 (s, 3 H), 1.41 (s, 9 H), 1.50 (s, 3 H), 1.61 (s, 3 H), 1.73 (s, 3 H), 1.95 (m, 1 H), 2.32 (s,

3 H), 2.46 (m, 1 H), 3.74 (d, J = 11.0 Hz, 1 H), 3.92 (br s, 1 H), 4.13 (m, 3 H), 4.23 (d, J = 8.2 Hz, 1 H), 4.31 (d, J = 8.1 Hz, 1 H), 4.82 (dd, J = 9.5, 4.9 Hz, 1 H), 4.98 (s, 1 H), 5.07 (bs, 1 H), 5.84 (d, J = 11.1 Hz, 1 H), 6.99 (br s, 1 H), 7.50 (m, 2 H), 7.66 (m, 1 H), 8.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.0, 21.5, 22.0, 22.1, 23.0, 24.9, 26.7, 28.2, 34.7, 39.2, 39.7, 40.5, 47.0, 50.5, 52.0, 68.9, 74.5, 74.6, 74.7, 75.2, 80.0, 80.8, 84.0, 84.5, 108.7, 127.8, 128.6, 128.7, 130.2, 134.2, 138.3, 157.0, 167.7, 171.2, 173.2, 213.0. Anal. Calcd for $C_{40}H_{56}N_2O_{13}$: C, 62.16; H, 7.30; N, 3.62. Found: C, 62.30; H, 7.46; N, 3.40.

14-Nor-seco-10-deacetylbaccatin III 13-(*N*-Methyl)-13-[*N*-benzoyl-(2′*R*,3′*S*)-3′-phenylisoserinamide] (6). A solution of nor-seco baccatin amine **3** (27.0 mg, 0.041 mmol) and β-lactam **14a** (15.5 mg, 0.058 mmol) in 1.5 mL of dichloromethane was stirred for 24 h at room temperature. Then the solvent was removed in vacuo, and the residue was purified on a silica gel column using hexane/ethyl acetate (1/1) as the eluant to afford **15a** as a white solid (26.5 mg, 70%). To a solution of **15a** (26.0 mg, 0.028 mmol) in 3 mL of pyridine/acetonitrile (1/1) was added dropwise HF/pyridine (70/30, 0.25 mL) at 0 °C, and the mixture was allowed to warm to room temperature. Then the mixture was stirred at 40 °C for 18 h. The reaction was quenched with aqueous saturated sodium carbonate solution, the mixture was extracted with ethyl acetate, and the combined extracts were washed with aqueous saturated copper sulfate solution and water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was purified on a silica gel column using hexane/ethyl acetate (1/2) as the eluant to afford **6** as a white solid (19.0 mg, 83% yield): mp 158−160 °C; $[\alpha]^{20}_D$ −57.5 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.52 (s, 3 H), 1.55 (s, 3 H), 1.75 (s, 3 H), 1.93 (m, 1 H), 2.25 (s, 3 H), 2.46 (m, 1 H), 3.07 (s, 3 H), 3.43 (d, J = 11.2 Hz, 1 H), 3.96 (d, J = 14.9 Hz, 1 H), 4.16−4.26 (m, 2 H), 4.22 (d, J = 8.8 Hz, 1 H), 4.34 (d, J = 8.2 Hz, 1 H), 4.43 (d, J = 5.2 Hz, 1 H), 4.64 (d, J = 14.8 Hz, 1 H), 4.83 (dd, J = 9.7, 4.5 Hz, 1 H), 4.92 (d, J = 3.6 Hz, 1 H), 5.05 (s, 1 H), 5.06 (s, 1 H), 5.68 (d, J = 9.1 Hz, 1 H), 5.88 (d, J = 11.2 Hz, 1 H), 6.95 (d, J = 9.1 Hz, 1 H), 7.32−7.52 (m, 10 H), 7.67 (m, 1 H), 7.75 (m, 2 H), 8.14 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.1, 17.7, 21.7, 21.9, 26.5, 33.8, 34.7, 40.4, 47.0, 48.7, 50.4, 53.1, 69.3, 70.7, 74.8, 75.1, 80.6, 83.7, 84.5, 87.5, 108.8, 126.9, 127.0, 127.9, 128.5, 128.6, 128.67, 128.73, 128.8, 130.3, 131.8, 134.3, 139.0, 139.1, 167.3, 167.9, 169.7, 170.9, 172.1, 213.4; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{45}H_{50}N_2O_{12}\cdot H^+$: 811.3442, found 811.3430.

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