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New Taxane Derivatives: Synthesis of Baccatin[14,1-*d*]furan-2-one Nucleus and Its Condensation with the Norstatine Side Chain

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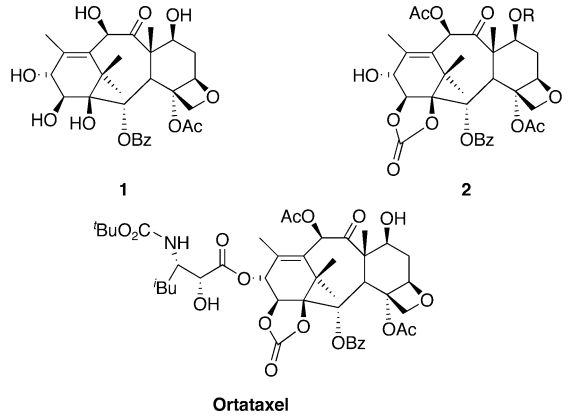
New taxanes **15** and **18**, containing the unsaturated and saturated baccatin[14,1-*d*]furan-2-one nucleus, respectively, were prepared starting from the readily available 13-oxo-7-Tes-baccatin III (**3**). Sequential formation of the enolate of **3** and reaction with ethyl glyoxylate gave the 13-oxo-7-Tes-baccatin[14,1-*d*]-3,4-dehydrofuran-2-one **4**. The reduction of **4** can result in the formation of a mixture of compounds corresponding to 13-hydroxy alcohol **5** and 13-enol derivative **6**. Both **5** and **6** were transformed into 13-oxo-7-Tes-baccatin[14,1-*d*]furan-2-one **8** by treatment with a base. Further reduction of **8** gave 13-hydroxy compound **9**. Esterification of **6** and **9** with *N*,*O*-protected norstatine **12**, followed by deprotection, gave the new promising anticancer taxanes **15** and **18**, respectively.

Introduction

Paclitaxel (Taxol), a complex natural diterpene extracted from *Taxus brevifolia*, is one of the most efficient anticancer agents for the treatment of ovarian and breast cancer. A major limitation is the development of multidrug resistance (MDR) during the therapy.[1]

For this reason, recent research is targeted toward discovery of more effective and less toxic analogues of paclitaxel by modifying its basic structure. In fact, it is well established from structure−activity studies of several research groups that changes to the "southern hemisphere", comprising the C-14 and C-1 to C-5 positions, exert a major effect on Taxol's activity.[2] These studies were supported by the discovery of a potent "second-generation" of taxoid anticancer agents, which have been prepared[3] from the scarcely available 14β-hydroxy-10-deacetylbaccatin III **1** (Chart 1), isolated from the needles of *Taxus wallichiana Zucc*.[4] The presence of the 14β-OH functionality in a form of 1,14-carbonate

CHART 1. Baccatin Derivatives and Ortataxel



moiety displays improved pharmacological properties such as a remarkably better bioavailability than paclitaxel and docetaxel after oral administration and a wide activity spectrum against various cancer types (human ovarian, non-small-cell-lung, colon, and breast cancer cell lines). One of these new taxanes, ortataxel (Chart 1) has been selected for preclinical development.[5]

We have recently developed a semisynthetic protocol for the preparation of 14β-OH-baccatin III 1,14 carbonates **2** (Chart 1). The key step of this synthesis was the

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(1) (a) Verweij, J.; Clavel, M.; Chevalier, B. *Ann. Oncol.* **1994**, *5*, 495−505. (b) Casazza, A. M.; Fairchild, C. R. In *Drug Resistance Cancer Treatment and Research*; Freidreich, E. J., Series Ed.; Hait, W. N., Ed.; Kluwer Academic Publishers: New York, 1996; Chapter 6, pp 149−171. (c) Horwitz, S. B. Taxol: Mechanism of Action and Resistance. In *Stony Brook Symposium on Taxol and Taxotère*; May 14−15, 1993; The State University of New York at Stony Brook: Stony Brook, NY, 1993; Abstracts 23−24. (d) Gottesmann, M. M.; Pastan, I. *Annu. Rev. Biochem.* **1993**, *62*, 385−427. (e) Rose, W. C.; Clark, J. L.; Lee, F. Y.; Casazza, A. M. *Cancer Chemother. Pharmacol.* **1997**, *39*, 446.

(2) See,for example: Kingston, D. J. I. *J. Nat. Prod.* **2000**, *63*, 726−734 and references therein.

(3) (a) Ojima, I.; Slater, J. C.; Kuduk, S. D.; Takeuchi, C. S.; Gimi, R. I.; Sun, C.-M.; Park, Y. H.; Pera, P.; Veith, J. M.; Bernacki, R. J. *J. Med. Chem.* **1997**, *40*, 267−278. (b) Ojima, I.; Fenoglio, I.; Park, Y. H.; Pera, P.; Bernacki, R. J. *Bioorg. Med. Chem. Lett.* **1994**, *37*, 1408. (c) Ojima, I.; Park, Y. H.; Sun, C.-M.; Fenoglio, I.; Appendino, G.; Pera, P.; Bernacki, R. J. *J. Med Chem.* **1994**, *37*, 1408. (d) Distefano, M.; Scambia, G.; Ferlini, C.; Gaggini, C.; DeVincenzo, R.; Riva, A.; Bombardelli, E.; Ojima, I.; Fattorossi, A.; Panici, P. B.; Mancuso, S. *Int. J. Cancer* **1997**, *72*, 844−850.

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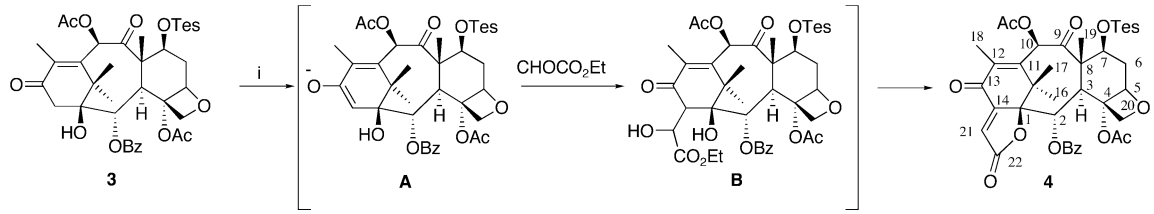
SCHEME 1. Synthesis of Baccatin[14,1-*d*]dehydrofuran-2-one Nucleus[a]



[a] Reagents and conditions: (i) THF, −60 °C, *t*-BuOK.

selective *β*-hydroxylation of the enolates of protected 13-oxobaccatins with oxaziridines, followed by 1,14-carbonylation and reduction of the 13-oxo group.[6] It is worth noting that 13-oxobaccatins are prepared in high yields from 10-deacetylbaccatin III, a readily available compound from natural sources. The simplicity of the enolate route for the stereoselective insertion of the OH group at C-14 prompted us to test this methodology with other electrophilic reagents to access to novel antitumor taxoids.

Since bioisosters are known in many cases to improve the efficacy of a drug, new promising anticancer agents were designed and developed in our laboratory. Our project focused on the synthesis of compounds **15** and **18**, containing the unsaturated and saturated baccatin[14,1-*d*]furan-2-one nucleus, respectively, which differ from ortataxel for the presence of a carbon atom linked to C-14 instead of the oxygen atom. For their preparation the 13-oxo-7-Tes-baccatin III **3** and ethyl glyoxylate were used as the starting materials.

Results and Discussion

Previous studies showed that the 13-oxo compound **3** is the key starting material for the functionalization of the C-14 position via its enolate,[6,7] which was efficiently obtained using potassium *tert*-butoxide as the base in the polar mixed solvent THF/DMPU at −60 °C.[6] In the present case, the reaction of the enolate of **3** with ethyl glyoxylate (2 equiv) was performed using THF as the solvent and selectively gave the 13-oxo-7-Tes-baccatin-[14,1-*d*]-3,4-dehydrofuran-2-one **4** in 79% yield (Scheme 1). For its formation it is assumed that the aldol reaction occurred between the enolate **A** and the aldehyde group of glyoxylate, giving intermediate **B**, followed by a sequential lactonization reaction between the ester function and the hydroxy group at C-1 and water elimination.

The reduction of the 13-keto function of **4** was studied in order to obtain both the 13-hydroxy unsaturated lactone **5** and the saturated analogue **9** (Scheme 2). Bu_4NBH_4 in methanol was selected as the reducing agent since this hydride gave the best α-diasterocontrol in the reduction of isosteric 14*β*-OH 1,14-carbonates.[6] Instead, the target 13α-OH epimer of 7-Tes-baccatin-[14,1-*d*]-3,4-dehydrofuran-2-one **5** was obtained as the minor product (33%) of a mixture with the enol **6** (66%) (Scheme 2). The last compound was formed by 1,4-addition of the hydride ion to the α,*β*-unsaturated carbonyl group of **4**. Other reducing agents such as $Bu_4NBH_4/CeCl_3$ and DIBAL-H failed to reduce the 13-oxo group, while $NaBH_4$ in EtOH, $NaBH_4/CeCl_3$, and $NaBH_4$/CuCl only gave compound **6.** This enol was also obtained by catalytic hydrogenation in the presence of Pd/C in quantitative yield, so this last protocol must be considered the best one to prepare this compound. These results clearly showed that the double bond is more reactive than the keto group, probably for steric reasons.

The enol derivative **6** is stable in a solid state but was quantitatively transformed into hydroperoxide **7** on standing in solution (toluene/THF, 70 °C, 8 h; $CHCl_3$, 25 °C, 24 h) (Scheme 2). This air-induced hydroperoxidation is typical for compounds bearing a stable enol group.[8a] It is worth noting that an identical air-induced hydroperoxidation of the enolic function also occurred in 12,-13-isobaccatin III, a baccatin III analogue of **6**.[8b]

Attempts to carry out a direct reduction of the alcohol **5**, or the enol **6** to the saturated analogue **9** probing several reducing agents, failed.[9] Instead, this target was efficiently achieved by inducing with a base (DMAP in CH_2Cl_2) a tautomerization process between the enol **6** and the keto compound **8** which was then reduced to **9** (Scheme 2). Very important, the tautomerization of **6** must be performed in an inert medium since the presence of air associated to a basic medium favored a competitive oxidation of **6** into **4**[10] through the hydroperoxide **7** (Scheme 2). An independent experiment confirmed the quantitative conversion of pure **7** into **4** in the presence of DMAP (Scheme 2). Despite our attempts to avoid the

(4) Appendino, G.; Gariboldi, P.; Gabetta, B.; Pace, R.; Bombardelli, E.; Viterbo, D. *J. Chem. Soc., Perkins Trans. 1* **1992**, 2925−29296.

(5) (a) Nicoletti, M. I.; Colombo, T. Rossi, C.; Monardo, C.; Stura, S.; Zucchetti, M.; Riva, A.; Morazzoni, P.; Donati, M. B.; Bombardelli, E.; D'Incalci, M.; Giavazzi, R. *Cancer Res.* **2000**, *60*, 842−846. (b) Polizzi, D.; Pratesi, G.; Monestiroli, S.; Tortoreto, M.; Zunino, F.; Bombardelli, E.; Riva, A.; Morazzoni, P.; Colombo, T.; D'Incalci, M.; Zucchetti, M. *Clin. Cancer Res.* **2000**, *6*, 2070−2074. (c) Polizzi, D.; Pratesi, G.; Tortoreto, M.; Supino, R.; Riva, A.; Bombardelli, E.; Zunino, F. *Cancer Res.* **1999**, *59*, 1036−1040.

(6) Baldelli, E.; Battaglia, A.; Bombardelli, E.; Carenzi, G.; Fontana, G.; Gambini, A.; Gelmi, M. L.; Guerini, A.; Pocar, D. *J. Org. Chem.* **2003**, *68*, 9773−9779.

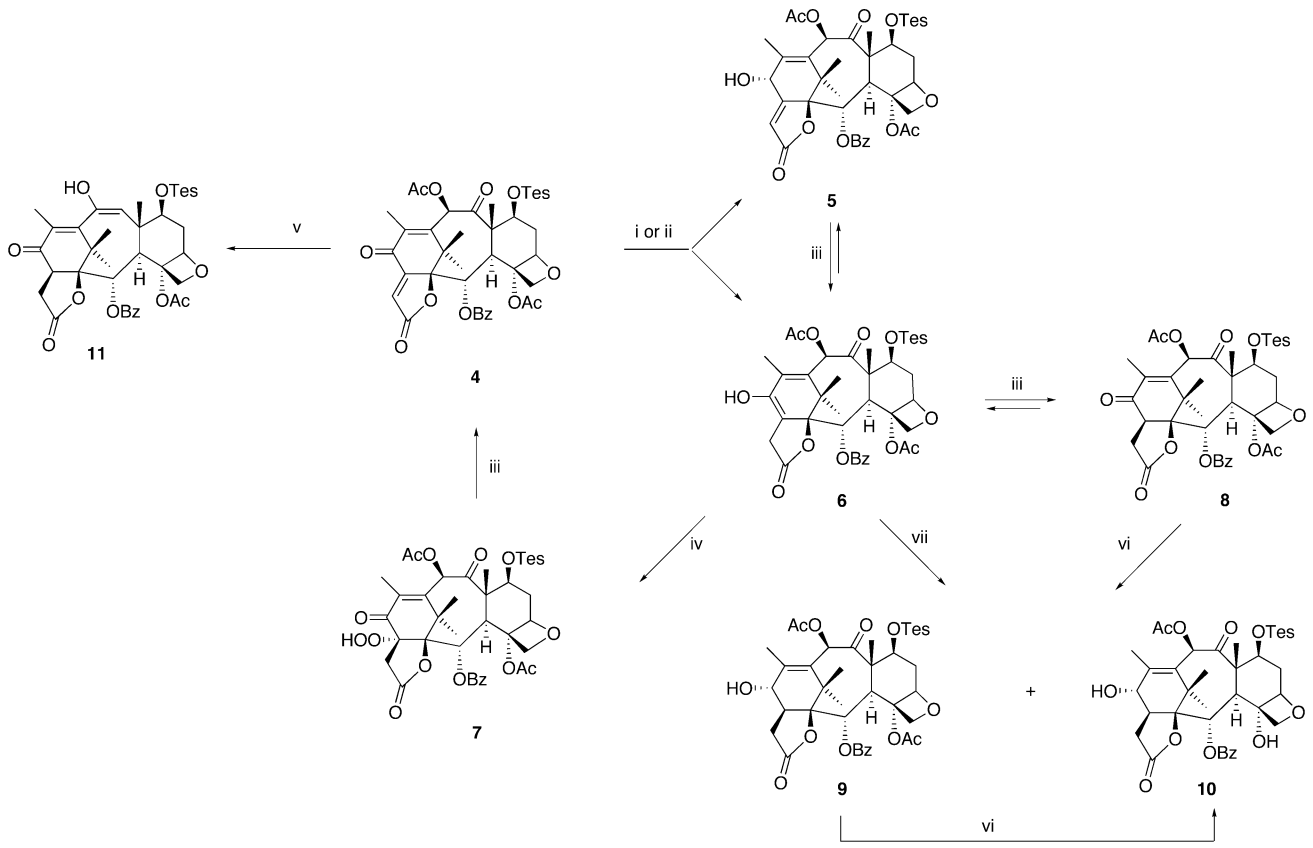
(7) Fang, W. S.; Fang, Q. C.; Liang, X. T. *Chinese Chem. Lett.* **2001**, *12*, 675−678.

(8) (a) Hayakawa, K.; Ueyama, K.; Kanematsu, K. *J. Org. Chem.* **1985**, *50*, 1963−1969. (b) Kelly, R. C.; Wicnienski, N. A.; Gebhard, I.; Qualls, S. J.; Han, F.; Dobrowolski, P. J.; Nidy, E. G.; Johnson, R. A. *J. Am. Chem. Soc.* **1996**, *118*, 919−920.

(9) The alcohol **5** was hydrogenated both with Pd/C and Pt_2O as the catalysts operating at room temperature both at 1 atm and under pressure, but the starting material was recovered. When **6** was treated both with (*i*-PrO)$_3$Al in *i*-PrOH at 60 °C and $NaBH_4$ in EtOH (−20 to 25 °C), the unreacted starting material was recovered.

(10) When **6** was treated in the presence of air with a base such as (dimethylamino)pyridine (DMAP) or *N*-methylimidazole or di*iso*propylethylamine (DIPEA) in a solvent such as CH_2Cl_2, toluene/THF, toluene/CH_2Cl_2 both at room temperature and reflux, a mixture of the keto compound **8** and the unsaturated starting ketone **4** was obtained in a different ratio (Scheme 2). The oxidized compound **4** was the major one in most cases i.e., when different amounts of one of the above bases (from 0.2 to 1 eq.) and a mixture of toluene/THF were used (**4/8** = 4−4.5:1). Instead, performing the reaction in CH_2Cl_2 and using DMAP (1 equiv), operating at 25 °C for 2 h, compounds **8** and **4** were obtained in a 4:1 ratio.

SCHEME 2. Oxidoreduction Reactions[a]



[a] Reagents and conditions: (i) **5/6** (1:2): Bu_4NBH_4, MeOH, −10 °C; (ii) **6**: H_2, Pd/C, AcOEt; (iii) CH_2Cl_2, DMAP, 25 °C; (iv) O_2, $CHCl_3$, 25 °C; (v) $NaBH_4$, DMAP, EtOH/CH_2Cl_2; (vi) $NaBH_4$, EtOH, from 0 to 25 °C; (vii) CH_2Cl_2, DMAP, 25 °C, then (vi).

presence of air in the reaction medium, trace amounts of **4** were always formed. The best result obtained was a 16:1 mixture of **8**/**4** operating in CH_2Cl_2 and using DMAP (1 equiv) at 25 °C for 2 h.

Derivative **5** showed the same reactivity of **6** under basic conditions, giving a mixture of compounds **4** and **8** (^{1}H NMR analysis) (Scheme 2).

The formation of compound **8** from **5** may be accounted by a prototropic allylic shift, giving intermediate **6**, followed by a base-induced anionotropic rearrangement.[11] Noteworthy, compounds **5** and **6** can equilibrate in basic medium, and in the absence of other reactants (see below) the equilibrium is in favor of **6** and then transformed into **8**.

Compound **8** was then reduced to the 13α-hydroxy derivative **9** (Scheme 2). Bu_4NBH_4 did not work, while a mixture of the expected alcohol **9** and the 4,13-dihydroxy derivative **10** (4:1 ratio by ^{1}H NMR analysis) was obtained using $NaBH_4$ in EtOH. Compound **9** was isolated in 70% yield after chromatography. As confirmed by an independent experiment, compound **10** is formed by a competitive C4-*O* deacetylation of **9** when reacted with $NaBH_4$ in EtOH (48 h). The same behavior was observed using MeOH as the solvent at low temperature. The reductive 4-*O* deacetylation was previously observed.[6]

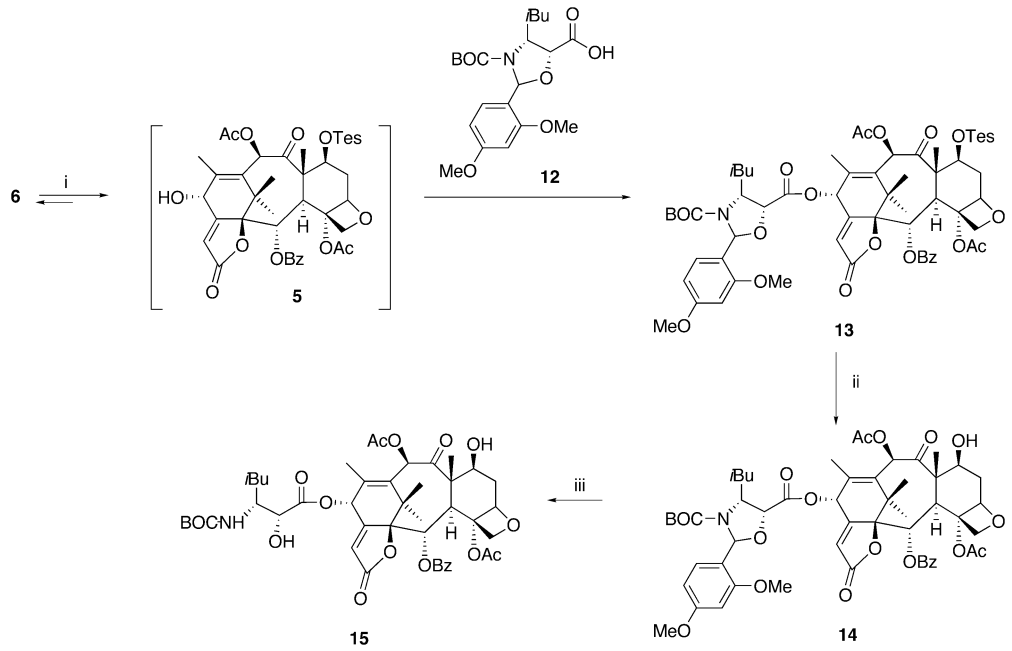
The reduction of the keto function, starting from both **4** and **8**, occurred with high stereocontrol. Unlike the reduction of 13-oxobaccatin III 1,14-carbonate,[6] which gave a mixture of 13α- (major stereomer) and 13*β*-hydroxybaccatin III derivatives, only the single 13α-hydroxy epimers (i.e., **5** from **4** and **9/10** from **8**) were isolated. A favored approach of the hydride ion from the less hindered *β*-face of the C-13 keto group of the folded structure of the taxane skeleton, or the double bond of the lactone ring, well accounts for such selectivity.[6,12] In the present case, the presence of the furanone ring increased the steric demand, thus allowing a high steric control in the reduction process. Furthermore, the α-OH isomers are probably the more thermodinamically stable compounds, as evinced when an equilibration occurred between **6** and **5** (see below, Scheme 3).

To increase the yield of the 13-hydroxy compound **9**, a "one-pot reaction" was attempted both starting from **6** and **4**. After the DMAP-induced tautomerization of the enol **6** into **8** (traces of the oxidized compound **4** were present), the reaction mixture was directly reduced with $NaBH_4$ (8 equiv) at 25 °C in EtOH. The α-diastereomer **9** was formed as the major product (71%) besides a minor amount of compound **10** (14%). The whole protocol was more feasible, and yields of **9** increased. When the same protocol was carried out in the presence of air, we noticed that the ^{1}H NMR spectrum revealed consistent amounts

(11) Di Giacomo, M.; Leggeri, P.; Azzolina, O.; Pirillo, D.; Traverso, G. *J. Chem. Res., Synop.* **1990**, 16−17.

(12) Wigfield, D. C.; Phelpss, D. J. *Can. J. Chem.* **1972**, *50*, 388−394.

SCHEME 3. Synthesis of Taxane Derivative 15[a]



[a] Reagents and conditions: (i) DCC, DMAP, CH_2Cl_2, 25 °C; (ii) PyHF, MeCN/Py, 25 °C; (iii) AcCl/MeOH cat., CH_2Cl_2.

of a new compound **11** (**9/11** = 1.25:1) which derived from **4** (see below).

In fact, the same compound **11** was the sole reaction product when **4** was reduced with the couple $NaBH_4$/DMAP (8 equiv/1 equiv) at 0 °C (Scheme 2). The reaction was monitored by ^{1}H NMR. After 2 h, the starting material **4** disappeared and the ^{1}H NMR spectrum showed the presence of the enol **6** and traces of the new compound **11**. Prolonging the reaction time (18 h) to favor the complete transformation of **6**, the ^{1}H NMR spectrum showed only the presence of **11** (74% after column chromatography). The same results (TLC, ^{1}H NMR analyses) were observed when starting from pure **6** by reduction with a mixture of $NaBH_4$/DMAP (8 equiv/1 equiv). In all cases neither TLC nor ^{1}H NMR analyses showed the presence of **9**. On the basis of the above observations, it must be concluded that compound **4** was reduced to **6**, which was transformed into **11**. The structure of compound **11** stemmed from their ^{1}H and ^{13}C NMR spectra which showed the presence of the 13-keto group, the [14,1-*d*]furan-2-one ring, the enol group at C-9-C-10, and the absence of the 10-acetoxy group. The reduction of acyloins to ketones[13] is a known procedure, but to our knowledge, this protocol was for the first time applied to taxane chemistry.

Both compounds **6** and **9** were esterified with the suitable *N*,*O*-protected norstatinic acid **12**. The esterification of **6** with acid **12** was carried out under standard conditions,[14] i.e., dicyclohexylcarbodiimide (DCC, 1.2 equiv) and DMAP (0.4 equiv), in a mixture of toluene/CH_2Cl_2 (2:1) at 70 °C. The reaction resulted in the formation of a mixture of **4** (15%), ketone **8** (10%), and the taxoid derivative **13** (57%) (Scheme 3). The DMAP-promoted formation of compounds **4** and **8** from the reagent **6** (Scheme 2) was avoided with a slight modification of esterification protocol. When compound **6** (1 equiv) was reacted with **12** (1.5 equiv) in high concentration in CH_2Cl_2, in the presence of DCC (2 equiv) and DMAP (0.1 equiv) and operating at room temperature under argon, compound **13** was isolated in 88% yield.

Clearly, compound **13** derived from the condensation of **12** with **5** which is formed from enol **6** via a 1,3-sigmatropic proton shift induced by the base. As reported above, this process is reversible: in fact, **5** is transformed into **8** via enol **6** in the presence of a base. In the present case, the equilibrium is shifted toward compound **5** that is removed during the esterification with the amino acid **12** (Scheme 3).

The esterification of baccatin derivative **9** with **12** using the new protocol gave the taxoid derivative **16** in 94% yield (Scheme 4).

Both compounds **13** and **16** were desilylated with pyridinium hydrogen fluoride in MeCN/pyridine solvents at room temperature. Compounds **14** (Scheme 3) and **17** (Scheme 4) were isolated in 75 and 87% yield, respectively. The *N*,*O*-deprotection of the oxazolidine ring of the side chain of **14** and **17** was carried out in CH_2Cl_2 with catalytic HCl, obtained by methanolysis of a MeOH solution of acetyl chloride. The final compounds **15** (Scheme 3) and **18** (Scheme 4) were obtained in 85 and 70% yield, respectively.

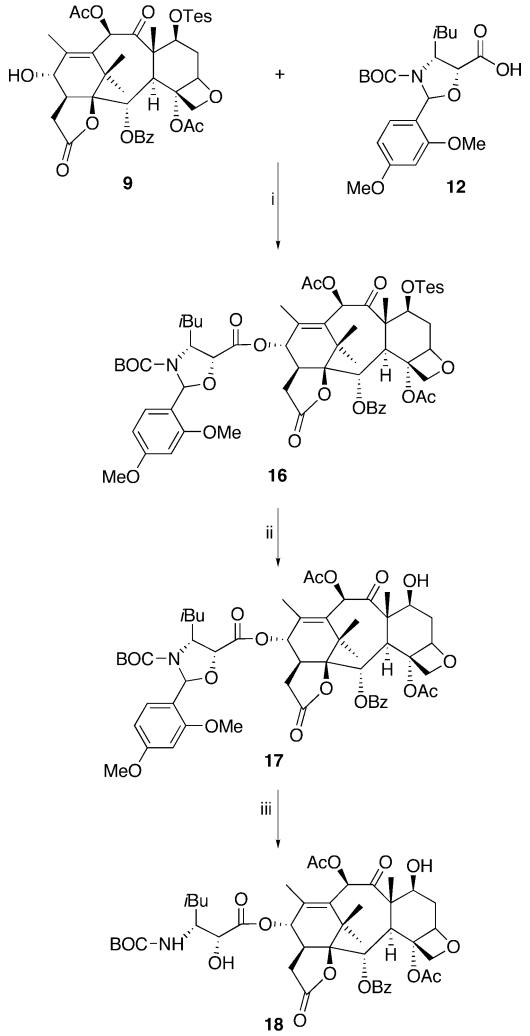
Conclusions

In conclusion, the synthesis of two new taxoid derivatives **15** and **18**, containing the baccatin[14,1-*d*]dehydrofuran-2-one and -furan-2-one nucleus, respectively, was performed starting from the readily available 13-oxo-7-

(13) (a) Ueki, M.; Okamura, A.; Yamaguchi, J. *Tetrahedron Lett.* **1995**, *36*, 7467−7470 and references therein. (b) He Y.; Pan, X.; Zhao, H.; Wang, S. *Synthetic Comm.* **1989**, *19*, 3051−3054. (c) Hurnaus, R.; Reiffen, M.; Sauter, R.; Grell, W.; Rupprecht, E. GWXXB DE 3718638 A1 19881222. *Chem. Abstr.* **1989**, *111*, 77643.

(14) Pontiroli, A.; Bombardelli, E. PCT Int. Appl. 20020444161; *Chem Abstr.* **2002**, *137*, 6295.

SCHEME 4. Synthesis of Taxane Derivative 18[a]



[a] Reagents and conditions: (i) DCC, DMAP, CH_2Cl_2, 25 °C; (ii) PyHF, MeCN/Py, 25 °C; (iii) AcCl/MeOH cat., CH_2Cl_2.

Tes-baccatin III **3**. The protocol followed for the preparation of the above nucleus consists of two (compound **15**) or three (compound **18**) steps, i.e., (i) condensation of **3** with ethyl glyoxylate (compound **4**), (ii) reduction of the double bond (intermediate **6**), and (iii) reduction of the keto group of **6** to **9**. Both **6** and **9** were successfully condensed with *N*,*O*-protected isoserinic acid **12** giving compounds **13** and **16**, respectively, transformed into the final products **15** (45% overall yield from **3**) and **18** (32% overall yield from **3**) after deprotection.

Experimental Section

7-TES-13-oxobaccatin[14,1-*d*]-3,4-dehydrofuran-2-one (4). A solution of 13-oxo-7-TES-baccatin **3** (600 mg, 0.86 mmol) in anhydrous THF (15 mL) was cooled to −70 °C and stirred under nitrogen. Potassium *tert*-butoxide (2.16 mL, 1 M in THF, 2.16 mmol) was added dropwise and the solution stirred at −65 °C for 45 min. Then ethyl glyoxylate (0.36 mL, 50% in toluene, 1.29 mmol) was added and the reaction monitored by TLC: after 2 h, the conversion was not complete, so a further amount of ethyl glyoxylate (0.12 mL, 0.43 mmol) was added. After 1 h (total reaction time: 3 h), the reaction mixture was quenched with anhydrous citric acid and warmed to room temperature, and then it was immediately purified by column chromatography (silica, EtOAc/cyclohexane = 1:9−2:8) to give lactone **4** (503 mg, 79%) as a yellow solid: R_f = 0.55 (silica, EtOAc/cyclohexane = 1:1); mp 252−253 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ +72 (*c* 1, $CHCl_3$); IR ($CDCl_3$) ν_{max} 1771, 1728, 1661, 1221; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (d, 2H, J = 8.4 Hz), 7.43−7.62 (m, 3H), 6.87 (s, 1H), 6.66 (s, 1H), 6.16 (d, 1H, J = 6.9 Hz), 4.88 (d, 1H, J = 8.8 Hz), 4.50 (dd, 1H, J_1 = 6.6, Hz, J_2 = 3.6 Hz), 4.22 (d, 1H, J = 8.8 Hz), 4.15 (d, 1H, J = 8.8 Hz), 3.98 (d, 1H, J = 6.9 Hz), 2.49−2.64 (m, 1H), 2.39 (s, 3H), 2.27 (s, 3H), 2.14 (s, 3H), 1.84−1.98 (m, 1H), 1.75 (s, 3H), 1.45 (s, 3H), 1.27 (s, 3H), 0.95 (t, 9H, J = 8.4 Hz), 0.56−0.68 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 199.4, 182.9, 171.0, 169.5, 168.5, 165.2, 158.7, 156.3, 143.1, 134.7, 130.5, 129.4, 128.7, 127.4, 94.3, 84.4, 77.3, 77.1, 76.4, 72.8, 68.6, 60.8, 47.3, 45.2, 37.9, 32.9, 22.3, 21.4, 20.8, 14.6, 10.3, 7.4, 5.3. Anal. Calcd for $C_{39}H_{48}O_{12}Si$: C, 63.57; H, 6.57. Found: C, 63.49; H, 6.66.

7-TES-13,14-dehydrobaccatin[14,1-*d*]furan-2-one (6). Compound **4** (90 mg, 0.12 mmol) was dissolved in EtOAc (10 mL) and hydrogenated with Pd/C as the catalyst (90 mg, 10%) for 45 min at room temperature and 1 atm. After removal of Pd/C by filtration over Celite and evaporation of the solvent, the residue was purified by column chromatography (EtOAc/cyclohexane = 1:4 to 1:1) to give enol derivative **6** (85 mg, 93%) as a white solid: R_f = 0.3 (silica, EtOAc/cyclohexane = 1:1); mp 235−236 °C (EtOAc/*n*-hexane); $[\alpha]^{20}_D$ −15 (*c* 0.6, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3432, 1771, 1743, 1695, 1222; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, 2H, J = 6.9 Hz), 7.44−7.62 (m, 3H), 6.43 (s, 1H), 6.10 (d, 1H, J = 6.6 Hz), 4.98 (d, 1H, J = 5.9 Hz), 4.44 (dd, 1H, J_1 = 6.6 Hz, J_2 = 3.6 Hz), 4.35 (d, 1H, J = 8.4 Hz), 4.19 (d, 1H, J = 8.4 Hz), 3.76 (d, 1H, J = 7.0 Hz), 3.35 (d, 1H, J = 22.0 Hz), 3.19 (d, 1H, J = 21.6 Hz), 2.49−2.64 (m, 1H), 2.23 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.84−1.98 (m, 1H), 1.74 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H), 0.94 (t, 9H, J = 8.1 Hz), 0.56−0.68 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.5, 175.0, 170.1, 169.6, 164.9, 148.7, 136.8, 134.9, 133.8, 129.6, 128.8, 128.7, 102.2, 92.4, 84.1, 80.8, 76.1, 75.9, 72.2, 70.4, 58.4, 45.0, 39.6, 37.3, 32.0, 28.1, 21.3, 20.9, 19.6, 13.5, 10.0, 6.7, 5.3. Anal. Calcd for $C_{39}H_{50}O_{12}Si$: C, 63.39; H, 6.82. Found: C, 63.44; H, 6.76.

7-TES-baccatin[14,1-*d*]-3,4-dehydrofuran-2-one (5) and (6). A solution of Bu_4NBH_4 (180 mg, 0.7 mmol) in MeOH (10 mL) was cooled to −30 °C. Then compound **4** (200 mg, 0.28 mmol) was dissolved in THF (1 mL) and added dropwise. After 30 min. the reaction mixture was quenched with citric acid (180 mg) and warmed to room temperature. After addition of water (10 mL), it was extracted with EtOAc (2 × 10 mL) and the organic layers were washed with water (5 mL), dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (silica, EtOAc/cyclohexane = 1:4 to 1:2) giving two fractions containing **6** (103 mg, 52%) and **5** (52 mg, 26%) as white solids. **5**: R_f = 0.25 (silica, EtOAc/cyclohexane = 1:1); mp 235 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −23 (*c* 0.7, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3455, 1768, 1740, 1668, 1223; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, 2H, J = 6.9 Hz), 7.40−7.63 (m, 3H), 6.47 (s, 1H), 6.25 (s, 1H), 6.12 (d, 1H), 5.14 (m, 1H), 4.92 (d, 1H, J = 8.1 Hz), 4.55 (dd, 1H, J_1= 7.0 Hz, J_2 = 3.6 Hz), 4.27 (d, 1H, J = 8.0 Hz), 4.27(d, 1H, J = 8.0 Hz), 4.16 (d, 1H, J = 8.0 Hz), 2.49−2.56 (m, 1H), 2.28 (s, 3H), 2.22 (s, 3H), 2.13 (s, 3H), 1.84−1.97 (m, 1H), 1.80 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H), 0.90−0.99 (t, 9H, J = 8.1 Hz), 0.58−0.65 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.1, 171.0, 170.3, 169.2, 165.4, 165.0, 140.0, 134.2, 133.7, 129.8, 128.8, 128.6, 122.8, 93.7, 84.3, 80.4, 75.8, 75.5, 72.3, 69.8, 66.8, 59.1, 48.5, 40.8, 37.1, 29.2, 22.7, 21.0, 20.8, 15.7, 10.1, 6.7, 5.2. Anal. Calcd for $C_{39}H_{50}O_{12}Si$: C, 63.39; H, 6.82. Found: C, 63.46; H, 6.74.

7-TES-14-hydroperoxy-13-oxobaccatin[14,1-*d*]furan-2-one (7). Enol **6** (50 mg, 0.07 mmol) was dissolved in $CHCl_3$ (3 mL) and stirred for 18 h, and then the solvent was evaporated to give compound **7** (50 mg, 100%): R_f = 0.4 (silica, EtOAc/cyclohexane = 1:1); mp 152−155 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −28 (*c* 0.8, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3425, 1790, 1724, 1226; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.96 (d, 2H, J = 7.4

Hz), 7.47−7.65 (m, 3H), 6.55 (s, 1H), 6.33 (d, 1H, J = 6.6 Hz), 4.84 (d, 1H, J = 8.6 Hz), 4.54 (dd, 1H, J_1 = 6.6 Hz, J_2 = 3.7 Hz), 4.38 (d, 1H, J = 8.3 Hz), 4.30 (d, 1H, J = 8.2 Hz), 4.15 (d, 1H, J = 6.5 Hz), 3.55 (d, 1H, J = 20.0 Hz), 2.96 (d, 1H, J = 20.0 Hz), 2.49−2.59 (m, 1H), 2.26 (s, 3 H), 2.22 (s, 3H), 2.21 (s, 3H), 1.84−1.98 (m, 1H), 1.81 (s, 3H), 1.38 (s, 3H), 1.09 (s, 3H), 0.94 (t, 9H, J = 8.4 Hz), 0.55−0.63 (m, 6H); ^{13}C (300 MHz, $CDCl_3$) δ 199.8, 193.6, 172.1, 171.5, 169.1, 165.5, 149.2, 139.3, 134.5, 129.9, 129.5, 128.8, 93.5, 91.9, 86.0, 81.3, 76.9, 74.6, 72.6, 70.1, 60.2, 45.2, 43.7, 37.7, 37.4, 33.8, 22.6, 21.1, 21.0, 13.8, 10.1, 7.1, 5.6; MS m/z 770. Anal. Calcd for $C_{39}H_{50}O_{14}Si$: C, 60.76; H, 6.54. Found: C, 60.49; H, 6.68.

7-TES-13-oxobaccatin[14,1-*d*]furan-2-one (8). Enol **6** (200 mg, 0.27 mmol) was dissolved in outgassed dry CH_2Cl_2 (10 mL) under argon, and *p*-(dimethylamino)pyridine (33 mg, 0.27 mmol) was added. The reaction mixture was stirred for 4 h, and then it was quenched with saturated NH_4Cl solution (15 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (EtOAc/cyclohexane = 1:9−1:4) to afford compound **4** (10 mg) and compound **8** (180 mg, 90%) as a white solid: R_f = 0.5 (silica, EtOAc/cyclohexane = 1:1); mp 256 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ +3 (*c* 0.25, $CHCl_3$); IR ($CDCl_3$) ν_{max} 1790, 1731, 1687, 1223; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (d, 2H, J = 7.4 Hz), 7.45−7.62 (m, 3H), 6.54 (s, 1H), 6.06 (d, 1H, J = 6.8 Hz), 4.95 (d, 1H, J = 8.3 Hz), 4.50 (dd, 1H, J_1 = 6.6 Hz, J_2 = 4.0 Hz), 4.34 (d, 1H, J = 8.4 Hz), 4.23 (d, 1H, J = 8.4 Hz), 3.91 (d, 1H, J = 6.7 Hz), 3.34 (t, 1H, J = 10.1 Hz), 2.90 (d, 2H), 2.49−2.64 (m, 1H), 2.23 (s, 3H), 2.22 (s, 3H), 2.16 (s, 3H), 1.84−1.98 (m, 1H), 1.74 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H), 0.94 (t, 9H, J = 8.4 Hz), 0.56−0.64 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 199.9, 198.7, 172.9, 170.2, 169.2, 164.8, 149.9, 140.1, 134.5, 130.2, 129.4, 128.7, 89.3, 84.3, 81.2, 76.3, 75.4, 72.4, 70.8, 59.3, 46.0, 45.7, 42.7, 37.3, 33.1, 32.5, 22.0, 21.1, 19.9, 14.3, 10.3, 7.1, 5.6. Anal. Calcd for $C_{39}H_{50}O_{12}Si$: C, 63.39; H, 6.82. Found: C, 63.48; H, 6.77.

7-TES-baccatin[14,1-*d*]furan-2-one (9). (i) A solution of $NaBH_4$ (108 mg, 2.88 mmol) in EtOH (10 mL) was cooled to 0 °C. Then compound **8** (264 mg, 0.36 mmol) was dissolved in THF (2 mL) and added dropwise. The reaction mixture was raised to room temperature and stirred for 4 h, and then acetone (2 mL) and finally NH_4Cl saturated solution (10 mL) were added. The organic phase was evaporated, and after addition of water (10 mL) the residue was extracted with CH_2Cl_2 (2 × 10 mL) and the organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (EtOAc/cyclohexane = 1:4−1:3) to give **9** (185 mg, 70%) as a white solid. A second fraction was isolated containing the corresponding 4-deacetyl derivative **10**. (ii) Compound **6** (200 mg, 0.27 mmol) was dissolved in outgassed dry CH_2Cl_2 (4 mL) under argon, and *p*-(dimethylamino)pyridine (33 mg, 0.27 mmol) was added. The reaction mixture was stirred for 4 h, and then it was added to a solution of $NaBH_4$ (81 mg, 2.16 mmol) in EtOH (8 mL) and the reaction stirred, quenched, extracted, and purified as described in method i to obtain **9** (141 mg, 71%): R_f = 0.2 (silica, EtOAc/cyclohexane = 1:1); mp 246 °C (Et_2O/*n*-pentane); $[\alpha]^{20}_D$ −34 (*c* 0.7, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3469, 1791, 1743, 1705, 1228; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, 2H, J = 7.3 Hz), 7.44−7.62 (m, 3H), 6.45 (s, 1H), 6.01 (d, 1H, J = 7.4 Hz), 4.97 (d, 1H, J = 8.1 Hz), 4.67 (m, 1H), 4.50 (dd, 1H, J_1 = 6.9 Hz, J_2 = 3.7 Hz), 4.30 (d, 1H, J = 8.1 Hz), 4.23 (d, 1H, J = 8.4 Hz), 3.86 (d, 1H, J = 7.3 Hz), 2.94−3.07 (m, 2H), 2.47−2.59 (m, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 1.79−1.98 (m, 1H), 1.74 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H), 0.95 (t, 9H, J = 8.1 Hz), 0.58−0.66 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.6, 174.6, 170.8, 169.7, 165.1, 153.0 144.0, 134.2, 132.8, 130.0, 129.1, 91.4, 84.5, 81.1, 76.6, 75.7, 75.6, 72.5, 72.2, 58.9, 46.8, 42.5, 42.3, 37.5, 36.8, 30.0, 26.7, 22.8, 22.3, 21.2, 15.1, 10.5, 7.1, 5.6. Anal. Calcd for $C_{39}H_{52}O_{12}Si$: C, 63.22; H, 7.07. Found: C, 63.37; H, 6.99.

Synthesis of 11. A solution of $NaBH_4$ (45 mg, 1.13 mmol) in EtOH (6 mL) was cooled to 0 °C under argon. Then compound **4** (104 mg, 0.14 mmol) and DMAP (16 mg, 0.14 mmol) were dissolved in CH_2Cl_2 (1.5 mL) and added dropwise. The reaction mixture was raised to room temperature and stirred for 18 h, and then acetone (1 mL) and finally NH_4Cl saturated solution (5 mL) were added. Organic solvents were evaporated, and after addition of water (5 mL) the residue was extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (EtOAc/cyclohexane = 1:4−3:7) to give **11** (70 mg, 74%) as a white solid: R_f = 0.3 (silica, EtOAc/cyclohexane = 1:1); mp 238 °C (Et_2O); $[\alpha]^{20}_D$ +105 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, CD_3COCD_3) δ 8.00 (d, 2H, J = 7.2 Hz), 7.69 (s, 1H, exch.), 7.49−7.66 (m, 3H), 6.10 (s, 1H), 5.83 (d, 1H, J = 5.0 Hz), 4.90 (d, 1H, J = 8.3 Hz), 4.41 (dd, 1H, J_1 = 7.1 Hz, J_2 = 3.3 Hz), 4.25 (d 1H, J = 4.9 Hz,), 4.11 (d, 1H, J = 8.2 Hz), 4.11 (d, 1H, J = 8.1 Hz), 2.99−3.05 (m, 3H, 14-H), 2.35−2.55 (m, 1H), 2.26 (s, 3H), 1.98 (s, 3H), 1.62−1.81 (m, 1H), 1.58 (s, 3H), 1.23 (s, 3H), 0.96 (t, 9H, J = 8.1 Hz), 0.89 (s, 3H), 0.55−0.66 (m, 6H); ^{13}C NMR (300 MHz, CD_3COCD_3) δ 210.7, 171.4, 170.8, 164.7, 159.2, 142.3, 134.0, 130.2, 129.4, 129.0, 111.7, 90.1, 84.6, 80.7, 76.9, 73.5, 68.4, 57.3, 49.3, 40.3, 40.2, 39.2, 37.8, 28.5, 22.7, 22.3, 20.2, 15.3, 8.8, 6.5, 5.3; MS m/z 680. Anal. Calcd for $C_{37}H_{48}O_{10}Si$: C, 65.27; H, 7.11. Found: C, 65.38; H, 6.99.

General Procedure for the Synthesis of 13-[*N*-Boc-*N*,*O*-(2,4-dimethoxybenziliden)-*β*-isobutylisoserinoyl]-7-TES-baccatin[14,1-*d*]-3,4-dehydrofuran-2-one (13) and 13-[*N*-Boc-*N*,*O*-(2,4-dimethoxybenziliden)-*β*-isobutylisoserinoyl]-7-TES-baccatin[14,1-*d*]furan-2-one (16). (i) Generation of Free Acid 12 from Its Sodium Salt. To a solution of the sodium salt of **12** (72 mg, 0.168 mmol) in water (5 mL) was added CH_2Cl_2 (3 mL). A solution of $NaHSO_4$ (2 M, 0.15 mL) was added dropwise until pH 3.0. After being stirred for a few minutes, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 mL). The combined organic layers were washed with water (5 mL) and with brine (5 mL), dried over Na_2SO_4, and evaporated to give free acid **12** (68 mg, 100%) as a white solid. **(ii) Coupling of 6 or 9 with Protected Side Chain 12.** To a solution of compounds **6** or **9** (0.1 mmol) in CH_2Cl_2 (1.2 mL) under argon were added in sequence compound **12** (free acid) (61 mg, 0.15 mmol) dissolved in CH_2Cl_2 (0.5 mL), *N*,*N*-(dimethylamino)pyridine (DMAP) (1.2 mg, 0.01 mmol), and dicyclohexylcarbodiimmide (DCC) (41 mg, 0.2 mmol). The reaction mixture was stirred for 1.5 h, and then it was cooled until precipitation of dicyclohexylurea (DCU) was complete. The precipitate (DCU) was filtered and washed with toluene (2 × 2 mL), and then the filtrate was diluted with CH_2Cl_2 (5 mL) and washed first with a saturated solution of $NaHCO_3$ (5 mL) and then with HCl (0.4 M, 5 mL) to remove DMAP, and finally with a saturated solution of $NaHCO_3$ (5 mL). The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (EtOAc/cyclohexane = 1:9−1:4) to afford compound **13** (99 mg, 88%) or **16** (106 mg, 94%) as a white solid. **13**: R_f = 0.55 (silica, EtOAc/cyclohexane = 1:1); mp 150−153 °C (*i*-Pr_2O/*n*-pentane); $[\alpha]^{20}_D$ +44 (*c* 0.25, $CHCl_3$); IR ($CDCl_3$) ν_{max} 1788, 1741, 1699, 1265, 1224; ^{1}H NMR (200 MHz, $CDCl_3$) relevant resonances at δ 7.97 (d, 2H, J = 7.0 Hz), 7.42−7.60 (m, 3H), 7.19−7.25 (m, 1H), 6.68 (s, 1H), 6.46−6.54 (m, 2H), 6.03 (s, 1H), 5.98 (d, 1H, J = 5.1 Hz), 5.81 (s, 1H), 4.91 (d, 1H, J = 7.0 Hz), 4.40−4.47 (m, 1H), 4.28 (s, 2H), 3.95 (d, 1H, J = 5.5 Hz), 3.89 (s, 3H), 3.85 (s, 3H), 2.81 (s, 1H), 2.49−2.64 (m, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 2.08 (s, 3H), 1.84−1.98 (m, 1H), 1.69 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H), 1.03−1.13 (m, 9H), 0.94 (t, 9H, J = 7.7 Hz), 0.54−0.62 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.5, 170.6, 170.2, 168.8, 164.5, 161.7, 159.1, 155.7, 139.0, 138.5, 133.9, 130.0, 129.6, 129.0, 128.7, 128.3, 127.8, 118.8, 104.3, 98.6, 90.0, 87.0, 84.3, 81.3, 80.8, 79.5, 75.0, 73.6, 72.9, 72.1, 67.7, 60.1, 58.9, 56.9, 55.4, 50.9, 50.1, 45.4, 43.7, 39.3, 38.3, 37.4, 29.7, 29.1, 28.2, 26.9, 25.5, 22.8, 22.6, 22.5, 21.1, 19.8, 15.9, 9.5, 6.8, 5.6. Anal. Calcd for $C_{60}H_{79}NO_{18}Si$: C, 63.75; H, 7.04. Found: C, 63.67; H, 6.99.

16: R_f = 0.5 (silica, EtOAc/cyclohexane = 1:1); mp 193 °C (*i*-Pr_2O); $[\alpha]^{20}_D$ −28 (*c* 1, $CHCl_3$); IR ($CDCl_3$) ν_{max} 1786, 1738, 1698, 1260, 1231; ^{1}H NMR (200 MHz, $CDCl_3$) relevant resonances at δ 8.00 (d, 2H, *J* = 7.3 Hz), 7.42−7.61 (m, 3H), 7.23−7.27 (m, 1H), 6.57 (s, 1H), 6.46−6.54 (m, 2H), 6.20 (d, 1H), 6.05 (d, 1H, *J* = 7.3 Hz), 4.96 (d, 1H, *J* = 7.7 Hz), 4.42 (m, 1H), 4.32 (d, 1H, *J* = 8.4 Hz), 4.24 (d, 1H, *J* = 8.4 Hz), 3.95 (d, 1H, *J* = 5.5 Hz), 3.90 (s, 3H), 3.85 (s, 3H), 2.99 (d, 1H), 2.68−2.75 (m, 2H), 2.49−2.64 (m, 1H), 2.31 (s, 3H), 2.21 (s, 3H), 2.06 (s, 3H), 1.84−1.98 (m, 1H), 1.62 (s, 9H), 1.36 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 0.94 (t, 9H, *J* = 7.7 Hz), 0.54−0.62 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.9, 173.4, 171.3, 170.0, 164.8, 161.8, 159.3, 153.3, 140.0, 134.1, 133.9, 129.8, 129.0, 128.9, 128.1, 119.2, 104.5, 98.7, 91.7, 87.0, 84.3, 81.0, 80.9, 80.1, 77.0, 76.2, 74.7, 72.2, 72.1, 58.7, 58.6, 57.9, 55.6, 50.3, 49.3, 46.4, 43.9, 42.6, 40.1, 37.3, 34.1, 29.9, 28.5, 28.4, 26.4, 25.5, 25.1, 24.8, 23.0, 22.4, 22.1, 20.9, 14.7, 10.5, 6.9, 5.5. Anal. Calcd for $C_{60}H_{81}NO_{18}Si$: C, 63.64; H, 7.21. Found: C, 63.60; H, 7.09.

General Procedure for the Synthesis of 13-[*N*-Boc-*N*,*O*-(2,4-dimethoxybenziliden)-β-isobutylisoserinoyl]baccatin[14,1-*d*]-3,4-dehydrofuran-2-one (14) and 13-[*N*-Boc-*N*,*O*-(2,4-dimethoxybenziliden)-β-isobutylisoserinoyl]-baccatin[14,1-*d*]furan-2-one (17). A solution of **13** or **16** (0.09 mmol) in acetonitrile (3 mL) and pyridine (3 mL) was cooled to 0 °C. HF−pyridine (0.5 mL) was slowly added under stirring, and then the reaction mixture was raised to room temperature and stirred for 24 h. Then it was poured into ice−water (10 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was washed with $NaHSO_4$ 2 M until pH 2 and then with $NaHCO_3$ 5% (5 mL) and finally with brine (5 mL), and then it was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (EtOAc/cyclohexane = 1:3−1:2) to afford compounds **14** (71 mg, 80%) or **17** (80 mg, 87%) as white solids. **14**: R_f = 0.3 (silica, EtOAc/cyclohexane = 1:1); mp 154−158 °C (*i*-Pr_2O−*n*-pentane); $[\alpha]^{20}_D$ +82 (*c* 0.9, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3435, 1781, 1738, 1697, 1231; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* = 7.5 Hz), 7.43−7.59 (m, 3H), 7.22−7.27 (m, 1H), 6.66 (s, 1H), 6.51−6.54 (m, 2H), 5.99 (d, 1H, *J* = 5.5 Hz), 5.84 (s, 1H), 5.57 (s, 1H), 5.05−5.13 (m, 1H), 4.90 (d, 1H, *J* = 7.0 Hz), 4.70 (s, 1H), 4.42 (m, 1H), 4.32 (d,, 1H *J* = 8.8 Hz), 4.28 (d, 1H, *J* = 8.8 Hz), 3.89 (s, 3H), 3.86 (d, 1H, *J* = 5.5 Hz), 3.84 (s, 3H), 3.03 (s, 1H), 2.49−2.64 (m, 1H), 2.34 (s, 3H), 2.27 (s, 3H), 1.88 (s, 3H), 1.84−1.98 (m, 1H), 1.69 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.6, 172.2, 171.2, 170.1, 169.0, 164.9, 162.1, 159.4, 155.6, 153.5, 139.2, 137.6, 134.3, 130.3, 129.3, 129.1, 128.5, 127.9, 119.0, 114.2, 104.6, 98.9, 90.5, 87.2, 84.7, 81.6, 81.2, 79.8, 76.8, 72.0, 68.3, 59.2, 58.4, 57.5, 55.9, 55.8, 44.0, 39.4, 38.1, 35.8, 30.0, 29.3, 28.5, 25.8, 23.2, 22.9, 22.8, 21.3, 20.8, 16.3, 9.5. Anal. Calcd for $C_{54}H_{65}NO_{18}$: C, 63.83; H, 6.45. Found: C, 63.69; H, 6.59.

17: R_f = 0.25 (silica, EtOAc/cyclohexane = 1:1); mp 149−155 °C (*i*-Pr_2O−*n*-pentane); $[\alpha]^{20}_D$ −35 (*c* 0.6, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3441, 1785, 1741, 1685, 1228; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* = 7.3 Hz), 7.43−7.62 (m, 3H), 7.22−7.28 (m, 1H), 6.51−6.58 (m, 2H), 6.23 (d, 1H), 6.04 (d, 1H, *J* = 7.3 Hz), 4.99 (d, 1H, *J* = 7.0 Hz), 4.48−4.54 (m, 2H), 4.33 (d, 1H, *J* = 8.8 Hz), 4.25 (d, 1H, *J* = 8.8 Hz), 3.90 (s, 3H), 3.85 (s, 3H), 3.84 (d, 1H), 3.00 (m, 1H), 2.56−2.76 (m, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.03 (s, 3H), 1.84−1.98 (m, 1H), 1.73 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.26 (s, 9H), 1.07−1.13 (m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.1, 173.3, 171.4, 170.2, 164.8, 161.8, 159.3, 153.3, 142.2, 134.2, 133.1, 129.8, 129.1, 128.8, 127.9, 119.1, 104.4, 98.7, 91.8, 87.0, 84.6, 81.2, 80.9, 79.8, 76.8, 76.2, 75.3, 72.2, 72.0, 68.3, 58.8, 58.7, 55.7, 55.6, 45.2, 42.5, 40.4, 35.8, 35.0, 34.1, 28.4, 26.6, 25.7, 25.1, 23.2, 23.1, 22.5, 22.1, 21.0, 15.2, 10.0. Anal. Calcd for $C_{54}H_{67}NO_{18}$: C, 63.70; H, 6.63. Found: C, 63.59; H, 6.69.

General Procedure for the Synthesis of 13-(*N*-Boc-β-isobutylisoserinoyl)baccatin[14,1-*d*]-3,4-dehydrofuran-2-one (15) and 13-(*N*-Boc-β-isobutylisoserinoyl)baccatin-[14,1-*d*]furan-2-one (18). Compound **14** or **17** (0.08 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. Acetyl chloride solution in MeOH (0.01 M, 1 mL) was added dropwise. The reaction mixture was stirred at room temperature and monitored by TLC. After 24 h, it was quenched with saturated NH_4Cl solution (5 mL), and the organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (EtOAc/cyclohexane = 1:3−1:2) to afford compound **15** (54 mg, 85%) or **18** (45 mg, 70%) as a white solid. **15**: R_f = 0.2 (silica, EtOAc/cyclohexane = 1:1); mp. 149−154 °C (CH_2Cl_2/*i*-Pr_2O); $[\alpha]^{20}_D$ +58 (*c* 0.9, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3514, 3305, 1791, 1758, 1733, 1710, 1695, 1239; ^{1}HNMR (200 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* = 7.4 Hz), 7.42−7.60 (m, 3H), 6.16 (s, 1H), 5.99 (d, 1H, *J* = 5.5 Hz), 5.57 (s, 1H), 4.90 (dd, *J* = 3.7, 6.2 Hz, 1H), 4.77 (d, 1H, *J* = 10.2 Hz), 4.30−4.47 (m, 4H), 3.81 (d, 1H, *J* = 5.5 Hz), 3.00 (s, 1H), 2.49−2.61 (m, 1H), 2.45 (s, 3H), 2.27 (s, 3H), 1.84−1.97 (m, 1H), 1.83 (s, 3H), 1.69 (s, 3H), 1.44 (s, 9H), 1.27 (s, 3H), 1.24 (s, 3H), 1.07 (m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.4, 172.0, 171.6, 171.3, 170.0, 164.8, 156.1, 154.8, 139.7, 136.3, 134.0, 130.3, 128.9, 128.4, 115.5, 90.1, 84.6, 81.2, 81.0, 77.8, 76.7, 73.3, 71.9, 68.1, 58.3, 57.4, 51.2, 42.3, 39.1, 38.1, 35.7, 29.9, 29.1, 28.5, 25.0, 23.4, 23.3, 22.4, 21.2, 20.6, 16.4, 9.3. Anal. Calcd for $C_{45}H_{57}NO_{16}$: C, 62.27; H, 6.62. Found: C, 62.19; H, 6.70. **18:** R_f = 0.15 (silica, EtOAc/cyclohexane = 1:1); mp. 181 °C (*i*-Pr_2O−*n*-pentane); $[\alpha]^{20}_D$ −36.11 (*c* 4.32, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3510, 3302, 1790, 1756, 1732, 1710, 1698, 1241; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, 2H, *J* = 7.4 Hz), 7.47−7.63 (m, 3H), 6.27 (s, 1H), 6.12 (d, 1H), 6.00 (d, 1H, *J* = 7.3 Hz), 4.96 (d, 1H, *J* = 7.4 Hz), 4.60 (d, 1H, *J* = 9.9 Hz), 4.38 (dd, 1H, J_1 = 10.6 Hz, J_2 = 7.3 Hz), 4.27 (s, 2H), 4.20 (s, 1H), 4.15 (d, 1H, *J* = 7.0 Hz), 4.11 (d, 1H, *J* = 7.0 Hz), 3.79 (d, 1H, *J* = 7.0 Hz), 2.99−3.18 (m, 3H), 2.48−2.64 (m, 2H), 2.41 (s, 3H), 2.24 (s, 3H), 2.04 (s, 3H), 1.84−1.97 (m, 1H), 1.89 (s, 3H), 1.72 (s, 3H), 1.32 (s, 9H), 1.25 (s, 3H), 1.22 (s, 3H), 0.95−1.01 (m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.0, 174.0, 173.9, 171.3, 170.2, 164.9, 155.9, 142.1, 134.0, 133.1, 139.9, 129.1, 128.8, 91.4, 84.5, 81.2, 80.4, 78.1, 75.4, 73.0, 72.2, 72.1, 60.6, 58.7, 51.4, 45.2, 42.6, 42.1, 39.8, 35.7, 28.5, 26.6, 25.0, 23.8, 23.5, 22.8, 22.2, 21.0, 15.0, 10.0. Anal. Calcd for $C_{45}H_{69}NO_{16}$: C, 62.13; H, 6.84. Found: C, 62.00; H, 6.89.

Supporting Information Available: General techniques and spectroscopic data for compounds **4**−**9** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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