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Selective synthesis of 14β-amino taxanes

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Dedicated to Professor J. Ojima on the occasion of his 60th birthday

Abstract—The base induced deprotonation of H-14 of 7-triethylsilyl- (7-TES-) and 7-*tert*-butoxycarbonyl- (7-BOC-) protected 13-oxo-baccatins gave the corresponding enolates, which were selectively aminated with electrophilic nitrogen donors, such as azodicarboxylates and tosyl azide. In particular, tosyl azide gave the corresponding 7-BOC- and 7-TES-13-oxo-14β-azido-baccatin III. Alternatively, the last compound was prepared via NaN_3 induced azidation of the 13-silyl enol ether of 7-TES-13-oxo-baccatin III under oxidative (cerium ammonium nitrate) conditions. The 13-silyl enol ether was obtained in a multistep process by DBU induced silylation of 7-TES-13-oxo-baccatin III. The 7-TES-13-oxo-14β-azido-baccatin III was used as a key intermediate for the synthesis of a new family of antitumour taxanes containing amino based functional groups at the C-14 position, such as: 14β-azido, 14β-amino, 14β-amino 1, 14-carbamate, 14β-amino 1, 14-thiocarbamate, and 14β-amino *N-tert*-butoxycarbonyl-1,14-carbamate.

1. Introduction

7-TES-13-oxo-baccatin III (**1**, Fig. 1)[1] is an intermediate of choice for studies on taxane chemistry, being used for the synthesis of 12, 13-dihydro-10-DAB III,[2] the 13-epi-7-TES-baccatin III,[3] the enol ester 12, 13-isobaccatin III,[4] and their 12, 13-isotaxanes analogues.[5] In addition, the 13-oxo group activates the functionalization of the C-14 atom via enolate chemistry. For example, the base induced hydroxylation with oxaziridines of the potassium enolate of **1** and its

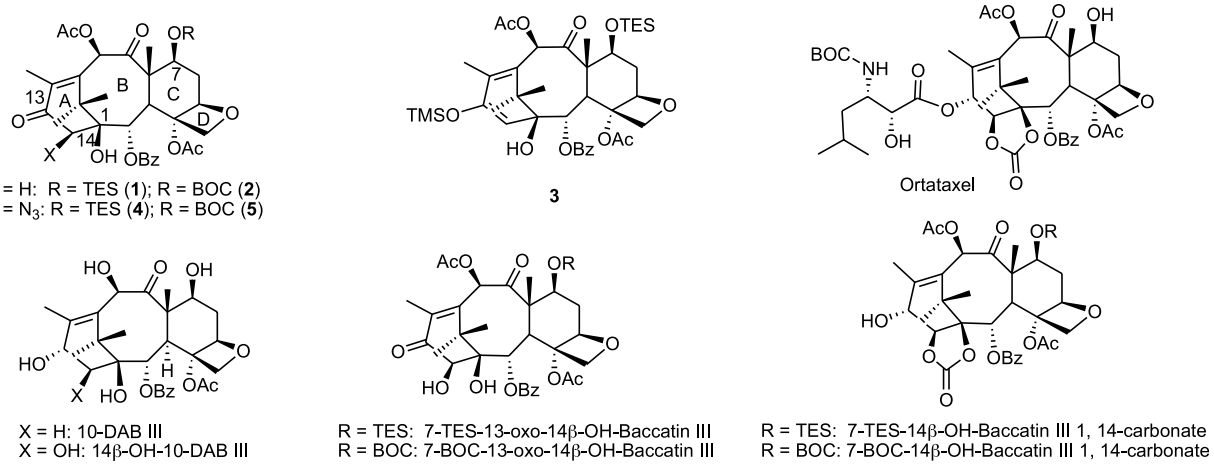

Figure 1. Baccatin III derivatives and Ortataxel.

Keywords: 14β-Amino taxanes; 10-DAB III; Silyl enol ethers; Electrophilic amination; 13-Oxo-baccatins.
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7-BOC analogue **2** gave 7-TES- and 7-BOC-13-oxo-14β-OH-baccatin III (Fig. 1).[6] The enolate of **1** was employed for the synthesis of the 13-OTMS enol ether **3**, which was converted into 7-TES-13-oxo-14β-OH-baccatin III by *m*CPBA oxidation.[7] A part from these results, the enolate chemistry was no longer explored since 13-oxobaccatins display a remarkable tendency to skeleton rearrangements when treated with bases such as NaH, pyridine, and DBU.[8a–d] Even so, the inherent potentiality of this chemistry opens new perspectives for innovative functionalizations of the C-14 position. For example, we performed the reduction of the 13-oxo group of 7-TES- and 7-BOC-13-oxo-14β-OH-baccatin III 1, 14-carbonate to afford the corresponding 14β-OH-baccatin III derivatives (Fig. 1), which are suitable intermediates of potent anticancer taxanes bearing 1,14 carbonate as masked 14β-OH group. These taxanes, which have been so far synthesized from the natural occurring 14β-OH-10-DAB III, a scarcely available chemical feedstock (Fig. 1),[9] display cytotoxic activity in cell lines, which express multi-drug resistance (MDR). The lead compound, Ortataxel, is now in phase II clinical trial.[10] We envisioned that the 'enolate chemistry' could be useful for the synthesis of new antitumor taxanes isosters of 14β-OH carbonates. The main support to this project was the observation that SAR studies have established that changes to the 'southern hemisphere', comprising C-14, exert a strong effect on taxol's activity.[11] Our efforts produced other potent antitumor taxanes, which bear an unsaturated and saturated baccatin[14, 1-*d*]-furan-2-one nucleus via aldol addition of ethyl glyoxylate to the enolate of **1**.[12]

Here, we wish to report our studies on the electrophilic amination of the enolates of 13-oxobaccatins **1** and **2**, and the 13-silyl enol ether **3**, to afford a new class of antitumor taxanes. It is worth noting that the insertion of the nitrogen functionality at the C-14 position can afford two epimers, since the new substituent may be located on the lower face of the baccatin skeleton (α-face), or the upper β-face. These α/β descriptors are defined observing the molecule with the methyl group at C-8 placed in the 'northern hemisphere' and pointing toward the observer.[13] To obtain isosteres of Ortataxel, only β-selective amination procedures, and a selective reduction of the C-13 oxo group to afford 13α-OH epimers, must be developed since the antitumor activity of the resulting taxane is related to the stereochemistry of the 13 and 14 positions of the precursor 14β-OH-10-DAB III.

2. Results and discussion

2.1. Amination studies of 13-oxobaccatins 1 and 2

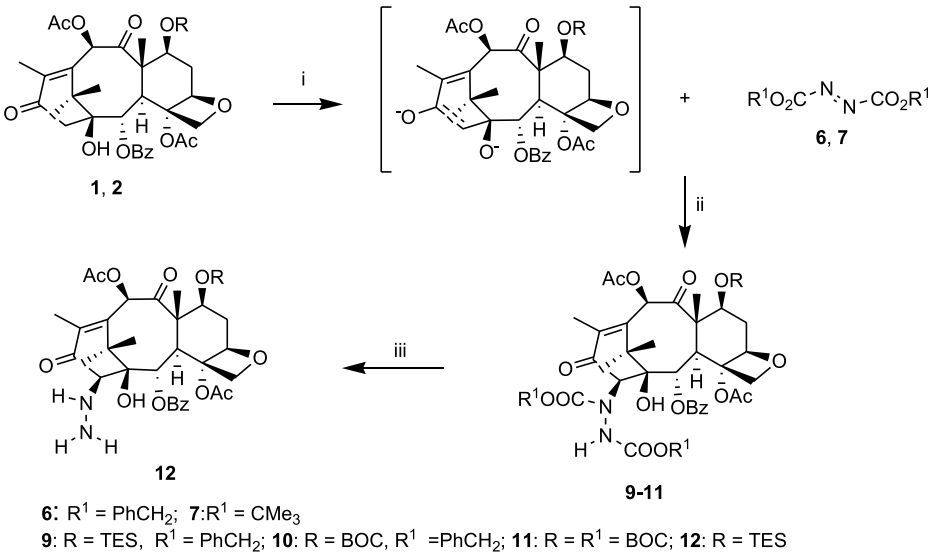
Our synthesis of the target 14β-amino substituted taxanes starts from the natural synthon 10-DAB III. This economically available reagent can be transformed into suitable 7-protected 13-oxobaccatins III according to standard protocols.[14] Namely, the 7-TES derivative **1** was obtained by sequential silylation and acetylation of the C-7 and C-10 hydroxy groups followed by MnO_2 oxidation of the 13-OH, while the 7-BOC analogue **2** was prepared by ozonolysis of 10-DAB III followed by acetylation and carbonylation of the C-10 and C-7 hydroxy groups. The treatment of **1** and **2** with metallic bases at low temperatures (−78 °C) afforded relatively stable enolates. Alternatively, base induced silylation affords 13-silyl enol ethers via a multistep process. The selective amination of both the enolates of **1** and **2** (protocol A) and the 13-silyl enol ethers (protocol B) afforded the key intermediates 13-oxo-14β-azido-baccatins **4** and **5** (Fig. 1).

2.1.1. Protocol A. Amination of the enolates of 1 and 2. Among the variety of bases available for the synthesis of the enolates of **1** and **2**, potassium *tert*-butoxide (^{t}BuOK) in a 4:1 mixed solvent THF/DMPU at −72 °C turned out to be the best one. The enolate is stable for several hours in a range of temperatures (−70/−40 °C) even in the presence of the polar additive DMPU (10–25%). Dibenzyl- and di-*tert*-butyl-azodicarboxylate (**6** and **7**, respectively),[15] and tosyl azide (**8**)[16] were selected as amination reagents.

(i) *Reaction of* **1** *and* **2** *with azodicarboxylates*. The amination of enolates **1** and **2** with azodicarboxylates **6** and **7** provided 14-hydrazino baccatins, as possible precursors of the corresponding 14-amino taxanes. In particular, the addition of dibenzyl-azodicarboxylate **6** to the enolates of **1** and **2** afforded the 14-*N*,*N*′-di(benzyl-oxycarbonyl)-hydrazino derivatives **9** (76%) and **10** (65%), respectively, as single β-epimer (Scheme 1). Similarly, the stereoselective addition of di-*tert*-butyl-azodicarboxylate **7** to the enolate of **2** gave the β-isomer of the *N*,*N*′-di(*tert*-butyloxycarbonyl)hydrazino derivative **11** in 72% yield. The stereochemistry of the C-14 stereogenic center of compounds **9**–**11** was assessed by qualitative homonuclear NOE experiments. An enhancement of the H-14 proton (7–9%) upon irradiation of the H-3 proton clearly indicated a β-face selectivity of the reaction. As expected, no effect was observed upon irradiation of the vicinal H-2. Thus, the hydrazino group is placed on the β-face of the taxane skeleton. The chemoselective reduction of the 13-oxo group of compounds **9**–**11** with sodium or alkyl boron hydrides, according to the methodology developed for the reduction of 13-oxo-14β-OH-baccatins 1, 14-carbonates,[6] failed.

Next, the conversion of compounds **9**–**11** into the corresponding 13-oxo-14β-amino baccatins was in vain attempted. In fact, the deprotection of the BOC groups of **11** with formic acid, or TFA in MeOH, yielded several products derived from rearrangements of the taxane skeleton whose structures were no further investigated. Instead, the debenzylation of **9** with 10% Pd/C, followed by one-pot thermal decarbonylation, successfully gave the *N*,*N*′-unsubstituted hydrazino derivative **12**, which, however, was thermally unstable and rapidly decomposed in solution or in a neat state. In conclusion, all intermediates **9**–**12** were not workable to achieve our targets.

(ii) *Reaction of* **1** *and* **2** *with tosyl azide* **8**. It is well known that azides are useful reagents for synthesis of α-azido ketones.[17] Among the electrophilic azides usually employed for ketone enolates (phenylsulfonyl-, tosyl-, and the encumbered 2,4,6-triisopropylbenzenesulfonyl azide[18]) we selected the less sterically demanding tosyl azide **8**. Since this azide may serve both for diazo or azide transfer reactions,[19] the parameters of the quenching step must be carefully evaluated. The reaction of the enolate of **1** with **8**, performed at −78 °C in a THF/DMPU=4:1 mixed solvent,



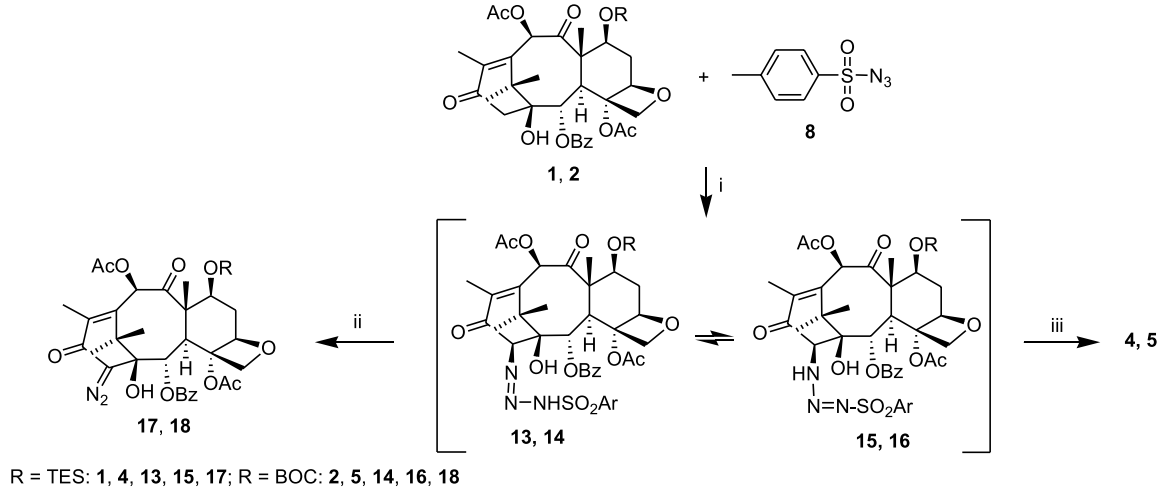
Scheme 1. Reagents and conditions: (i) ^{t}BuOK, 4:1 THF/DMPU, −70 °C; (ii) −50 °C, then saturated NH_4Cl; (iii) H_2, 10% Pd/C.

proceeded through transient intermediates, probably a mixture of two tautomeric triazenes **13** and **15**, which quickly converted into products derived from diazo and azide transfer reactions (Scheme 2).[20] For this reason, we attempted to optimize the azido transfer reaction. As soon as the reagent **1** disappeared, the quenching with saturated aqueous NH_4Cl solution selectively transformed the mixture of **13** and **15** into the 14-azido derivative **4** (92%, Fig. 1) as a single β-epimer. Instead, a clean diazo transfer reaction occurred when the reaction was quenched with an excess of acetic acid, which afforded the 7-TES-13-oxo-14-diazo-baccatin III (**17**) (82% yield). The 7-BOC derivative **2** behaved identically. When the reaction was quenched with NH_4Cl the triazenes **14** and **16** were transformed into the azido derivative **5** (85%), while quenching with acetic acid yielded the diazo derivative **18** in 72%. The β-stereochemistry of the C-14 stereogenic center of **4** and **5** was assessed by NOE experiments. An enhancement of the H-14 proton (9–11%) was observed upon irradiation of the H-3 proton. The β-selectivity of all amination reactions, similar to that observed in the hydroxylation of these enolates,[6] can be explained by the folded terpenoid structure, which precludes an approach to the sterically demanding electrophile from the more hindered α-face of the A ring, thus promoting the formation of the 14β epimers.

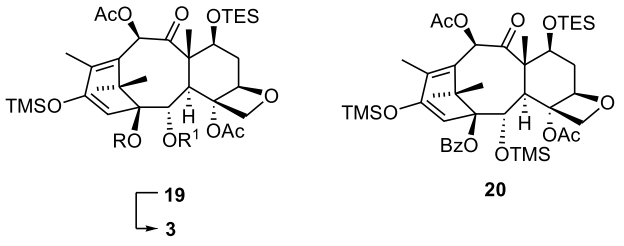
2.2. Silylation of 13-oxobaccatin III (1) and amination of the silyl enol ethers under oxidative conditions

It has been reported that the reaction of **1** with TMSCl and DBU gave a mixture of silylated compounds consisting of the major product 1, 13-bis-OTMS enol ether **19**, traces of the target 13-OTMS enol ether **3** and the rearranged taxane **20** (Scheme 3). Selective solvolysis of the 1-OTMS group of **19** gave the enol ether **3** in good yield.[7]

Surprisingly, when we repeated the silylation reaction of **1** we obtained a mixture of products different from that reported in the literature. We were unable to explain these differences due to a lack of information about the experimental procedures and analytical data products. For this reason, we have revisited the silylation of **1** employing a variety of silylating agents (TMSCl, TESCl, TIPSCl, and BSA), bases and solvents. From these studies the correct



Scheme 2. Reagents and conditions: (i) ^{t}BuOK, 4:1 THF/DMPU; (ii) CH_3COOH (**17**, **18**); (iii) NH_4Cl (**4**, **5**).



3: R = H, R^1 = Bz; **19**: R = OTMS, R^1 = Bz;

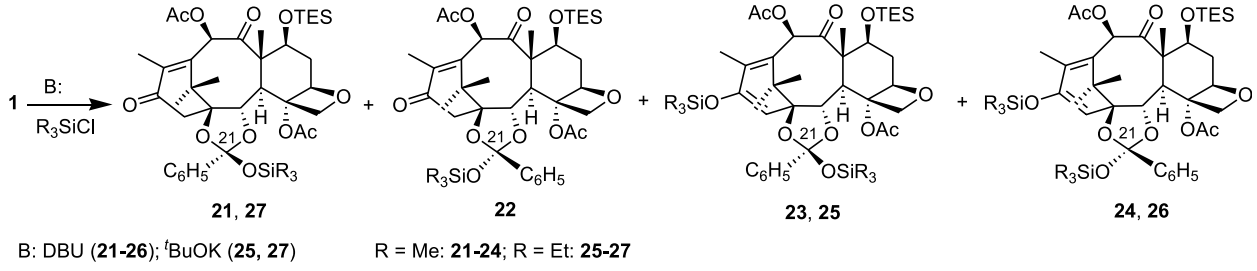
Scheme 3.

structures of the intermediates involved in these reactions were assessed and the best reaction conditions to selectively obtain 13-silyl enol ethers were found.

2.2.1. Silylation studies. (i) *Silylation of* **1** *with* Me_3SiCl *and DBU*. The reaction of **1** (1.0 equiv) with TMSCl (2.5 equiv) and DBU (2.0 equiv) in CH_2Cl_2 under reflux provided, after a few hours, a complex mixture of 13-oxobaccatins consisting of two *ortho* esters **21** and **22** and minor amounts of their corresponding 13-OTMS enol ethers **23** and **24**, and traces of the 13-OTMS enol ether **3** (Scheme 4).[21] Compounds having a structure consistent with those of the 1-OTMS enol ether **19** and the rearranged taxane **20** were not detected.

The *ortho* esters are formed by DBU induced hydrogen abstraction of 1-OH of **1**. The nucleophilic attack of the resulting 1-oxyanion to the carbonyl of the 2-benzoyl group affords an epimeric mixture of cyclic 1,2-benzylidene oxyanions (*ortho* esters), which are quenched by the silylating agent. The stereochemical assessments of *ortho* esters **21**, **22**, the 13-enol derivative **3**, and the 13-enol *ortho* esters **23** and **24** was based on ^1H and ^{13}C NMR spectroscopic evidences (see Appendix A of Section 4). In particular, we established that the OTMS group of the C-21 carbon atom of the *ortho* ester has β orientation in compounds **21** and **23** and α orientation in compounds **22** and **24**.[13] No significant selectivity was found in the formation of these epimers (see Table 1), while the relative ratio between the 13-oxo *ortho* esters and their 13-OTMS enol ethers depended on the relative **1**/TMSCl ratio. Polar solvents, like CH_3CN, increased the reactivity but did not affect the products distribution. Instead, this distribution was altered by chromatography on silica gel due to a partial desilylation of the *ortho* esters, which reverted to the starting reagent **1** and the silyl enol ether **3** (entry 1). The best conversion of **1** into 13-OTMS *ortho* esters **23** and **24**, valuable precursors of the enol ether **3**, was obtained with a large excess of base and silylating agent according to standard silylation protocols (entry 2).[22] These compounds were quantitatively isolated by chromatography on alumina.

(ii) *Silylation of* **1** *with TESCl and DBU or* ^{t}*BuOK*. The DBU induced silylation of **1** with the more sterically demanding triethylsilyl chloride only occurred in the very polar solvent CH_3CN and required strong excesses of base and silylating agent. The epimeric pair of 13, 21-bis-OTES *ortho* esters **25** (21 β-OTES) and **26** (21α-OTES) was obtained in 93% yield (entry 3). A different product distribution was found when we performed the silylation of **1** in the presence of ^{t}BuOK as the base. The reaction was run at −75 °C with 2.5 equiv of base. Sequential addition of 2.0 equiv of TESCl at this temperature stereoselectively gave the 21β-epimers of 13-oxo-21-OTES *ortho* ester **27**, as the major product (80%, entry 4), and its 13, 21-bis-OTES *ortho* ester **25** as the minor (20%). Only **25** was obtained with a large excess of TESCl. This compound was isolated



Scheme 4.

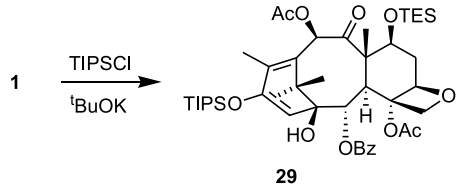
Table 1. Product distribution of the silylation of **1** (1.0 equiv) with TMSCl, TESCl, TIPSCl, and BSA

Entry	Reaction conditions eq:eq:eq	A[a]	B[b]	C[c]	Overall yield %
1	**1**/TMSCl/DBU 1.0:2.5:2.0 (CH_2Cl_2)	**21/22**=0.94[d] (1.14)[e]	**23/24**=1.1[d] (1.6)[e]	**3** (≤5%)[d,e]	**21**+**22**+**23**+**24**=87[d]
2	**1**/TMSCl/DBU 1.0:7.0:6.0 (CH_2Cl_2)	—	**23/24**=1.4[f]	**3** (≤5%)	**23**+**24**=92[f]
3	**1**/TESCl/DBU 1.0:6.0:7.0 (CH_3CN)	—	**25/26**=1.2	—	**25**+**26**=93[f]
4	**1**/TESCl/^{t}BuOK 1.0:1.7:2.5 (THF)	**27** (80%)[f]	**25** (20%)[f]	—	**25**+**27**=100
5	**1**/TESCl/^{t}BuOK 1.0:6.0:5.0 (THF)		**25**	—	**25**=94
6	**1**/TIPSCl/^{t}BuOK 1.0:5.0:6.0	—	—	**29** (55%)	**29**+**1**=86
7	**1**/BSA 1.0:2.5 (CD_3CN)	**21/22**=1.5	—	**3** (33%)[f]	**21**+**22**+**3**=53[f]
8	**1**/BSA/DMAP 1.0:2.5:0.2 (CD_3CN)	**21/22**=1.5	**23/24**=4		**21**+**22**+**23**+**24**=100[f]

[a] A: 13-oxo 21-*ortho* esters.
[b] B: 13-silyl enol 21-*ortho* esters.
[c] C: 13-Silyl enol ethers.
[d] Product distribution and overall yield after chromatography on silica.
[e] Product distribution as determined by ^1H NMR.
[f] Product distribution and overall yield after chromatography on alumina.

in 94% yield after chromatography on Al_2O_3 (entry 5).[23] Although we failed to directly obtain the 13-silyl enol ether **28** through this route we successfully achieved a total chemoselectivity in the formation of the precursors 13-OTES *ortho* esters **25** and **26**.

(iii) *Silylation of* **1** *with TIPSCl and* ^{t}*BuOK*. The reaction of the enolate of **1** with 5.0 equiv of TIPSCl at −78 °C required ^{t}BuOK as base and a polar mixed solvent (THF/DMPU, 4:1). The 13-OTIPS-enol ether derivative **29** was obtained in 55% yield along with unreacted **1** (entry 6 and Scheme 5). This result gave evidence that sterically demanding silylating agents, such as TIPSCl, favor the enolization pathway instead of the formation of products derived from the 21-oxyanion.

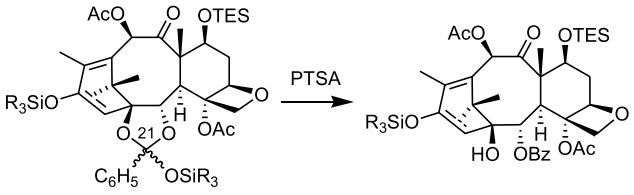


Scheme 5.

(iv) *Silylation of* **1** *with N, O bis(trimethylsilyl)acetamide* (*BSA*). The silylation of **1** with 2.5 equiv of BSA in CD_3CN gave the silyl enol ether **3** as the major product (33%) and the 13-oxo-*ortho* esters **21** and **22** (20%) (entry 7). Only *ortho* esters **21/22**=1.5 (65% yield) and **23/24**=4 (35%) were obtained when the same reaction was performed in the presence of the base DMAP (0.2 equiv, entry 8).

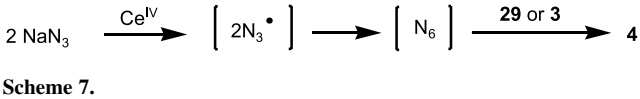
In conclusion, ^{1}H NMR experiments clearly showed that the DBU induced silylation of **1** with a slight excess of TMSCl (1.5–2.0 equiv) initially gave α/β epimeric mixtures of the 13-oxo *ortho* esters **21** and **22** and traces of the 13- OTMS silyl enol ether **3**. Sequential silylation of **21** and **22** furnished the 13, 21-bis-silylated *ortho* esters **23** and **24**. Hence, variable mixtures of compounds **21–24** were obtained, along with trace amounts of **3**, depending on the reagents' stoichiometry. Only the potent BSA directly afforded moderate amounts of the silyl enol ether **3** as the major product, but in a non-basic medium (entry 7). The 13, 21-bis-silyl enol *ortho* esters **23–26** were obtained in very high yield (92–94%, entries 2, 3, and 5 of Table 1) when an excess of base and silylating agent was used. The folded terpenoid structure of the taxane skeleton favors an attack to the less hindered C-21β oxyanion only when the sterically demanding TES-Cl and TIPSCl are the electrophilic partners. Moreover, both the nature of the base, and the temperature play a key role on the chemo and diastereoselectivity at the C-21 position. For example, face discrimination was observed in the ^{t}BuOK induced reaction of **1** with TESCl, which afforded only the β-epimers **25** and **27** at low temperatures (entries 4 and 5, Table 1). This discrimination did not occur when this reaction was done in refluxing CH_2Cl_2 with DBU as the base (entry 3).

2.2.2. Solvolysis of the *ortho* esters enolates 23–26. While we failed to directly synthesize the 13-silyl enol ethers **3** and **28** in good yield by silylation of the enolate of **1**, we achieved this target by performing a study of chemoselective solvolysis of the silyl group at the C-21 carbon atom of the 13, 21-bis-OTMS-silyl enol *ortho* esters **23–26**. The desilylation of mixtures of **23/24** (or **25/26**), performed according to the reported procedure (1.0 M HCl),[7] afforded non-reproducible mixtures of silyl enol ethers **3** or **28** and the reagent **1**. Moreover, the β-epimers **23** and **25** were desilylated more rapidly than the α-epimers **24** and **26**, thus favouring an uncontrolled formation of **1**. This selectivity was again the result of the folded structure of the baccatin skeleton, since the 21-OTMS substituent of the α-epimers is more embedded of the β-epimers and, for this reason, less prone toward solvolysis. When we carried out solvolysis studies at different pH values we found that the priority of the desilylation at the C-13 and C-21 positions reversed with the pH of the medium. In fact, the desilylation of **23** and **24** in a basic medium, such as a mixture of DBU/water, afforded the 13-oxo *ortho* esters **21** and **22**, which in turn were hydrolyzed to **1**. This was the reason why the reactions of **1** with Me_3SiCl, reported in section i, required an excess of Me_3SiCl with respect to DBU for their quantitative conversion into **23** and **24** (entry 2). By contrast, the reaction of **1** with TESCl gave **25** and **26** although it was carried out with an excess of DBU, since the TES substituent is three order more stable toward base-catalysed hydrolysis.[24] Harsh desilylation agents, such as TBAF and CsF_2, gave random mixtures of product of solvolysis at C-13, C-21, C-7, and contaminants. These attempts suggested that the selective C-21 desilylation could be carried out only in a very mild acidic medium, that is, with catalytic PTSA (8%) in CH_2Cl_2 at 20 °C. When **23/24**=1.4, or **25/26**=1.25 mixtures were desilylated under these conditions, the enol ethers **3** (95%) and **28** (93%) were exclusively obtained (Scheme 6).

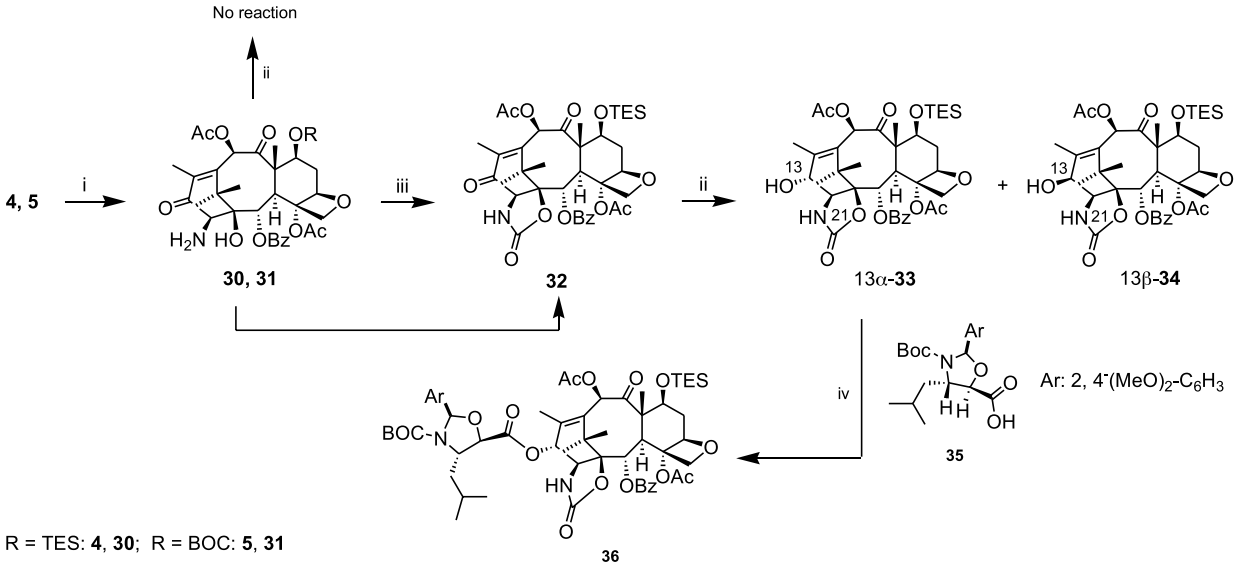


Scheme 6.

2.2.3. Protocol B. CAN induced azidation of the silyl enol ethers 3 and 29. Synthesis of 7-TES-13-oxo-14β-azido-baccatin III (4). The azidation of silyl enol ethers with NaN_3 represents an interesting protocol of α-amination of ketones. This protocol is based on the oxidation of sodium azide by cerium-(IV) ammonium nitrate to give dinitrogen, a very potent aminating agent.[25] This reagent has been successfully experimented mainly with silyl enol ethers bearing a sterically encumbered TIPS substituent, such as **29**.[26] The azidation of **29** in CH_3CN occurred in 1 day under forced conditions, such as a large excess of NaN_3 (11.0 equiv) and CAN (7.0 equiv), the target **4** being obtained in moderate



Scheme 7.



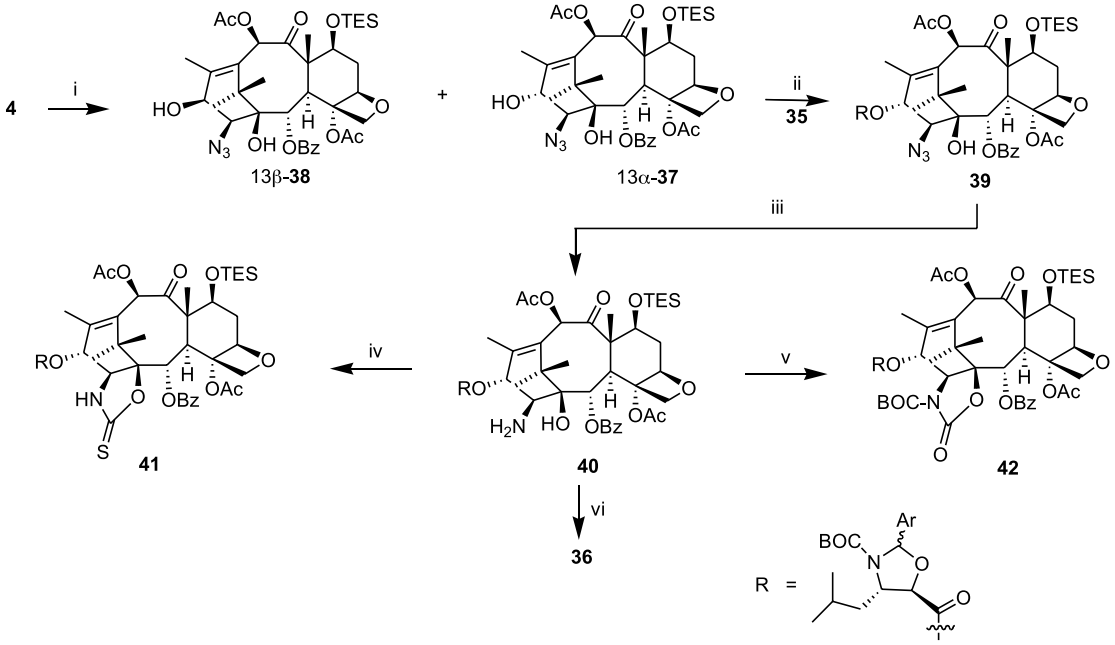
Scheme 8. Reagents and conditions: (i) PPh_3/H_2O; (ii) $NaBH_4$/EtOH; (iii) $COCl_2$/Py; (iv) DCC/DMAP/PTSA.

amounts (55%) (Scheme 7). For this reason, we also probed the less sterically demanding compound **3** even if the OTMS silyl enol ethers are usually prone toward a concurrent hydrolysis due to the acidic CAN medium. Gratifying, compound **4** was obtained in 95% yield after 1 h at 20 °C when **3** was reacted with only 4.0 equiv of NaN_3 and 3.0 equiv of CAN.

2.3. Synthesis of 14β-amino taxanes

The reduction of the azido group of **4** and **5** was carried out via the iminophosporane method with PPh_3 in 9:1 CH_3CN/H_2O to give the 7-TES-13-oxo-14β-amino-baccatin III (**30**) in 88% yield, and its 7-BOC analogue **31** in 77% (Scheme 8). The attempted reduction of the 13-oxo group of **30** and **31** with sodium or alkyl boron hydrides failed, probably due to a condensation of the hydride reagents with the 14-NH_2 group.[27] For this reason, the 14-NH_2 and the 1-OH groups of **30** were transformed into the 1, 14-carbamate group of compound **32** by treatment with phosgene in pyridine (86% yield). Next, **32** was reduced by $NaBH_4$ in EtOH affording the 13α-epimer of 7-TES-14β-amino baccatin III 1,14-carbamate (13α-**33**) in 56% and its 13β-OH epimer (13β-**34**, 35%).[28] *N*-Boc-norstatinic acid **35**, protected as *N*,*O*-(2,4-dimethoxy-benzylidene) derivative,[29] was selected as the partner of 13α-**33** since this amino acid was also present in Ortataxel. The esterification was carried out with *N*,*N*′-dicyclohexyl-carbodiimide (DCC), 4-dimethyl-amino-pyridine (DMAP) and catalytic *p*-toluenesulfonic acid,[30] affording the fully protected taxane **36**.

Next, we reasoned that a 14β-azido taxane, with the amino



Scheme 9. Reagents and conditions: (i) $NaBH_4$, ETOH; (ii) DCC/DMAP/PTSA; (iii) H_2/Pd-C; (iv) $(2\text{-Piridyl})_2C{=}S$; (v) BOC_2O/Et_3N/DMAP; (vi) $COCl_2$/Py.

acid appendant and the terpenoid skeleton fully protected, might be a key intermediate for synthesis of other taxanes bearing the 14β-amino function. Hence, the 13-oxo group of **4** was reduced by sodium or alkylammonium borohydrides to afford a mixture of 7-TES-14β-azido-baccatin III (13α-**37**), as the major product, and its 13β-OH epimer (13β-**38**) (Scheme 9). Best yield of 13α-**37** (76%) were obtained with $NaBH_4$ in EtOH (α/β=91:9).

The stereochemistry at C-13 of 13α-**37**, assessed by NOE experiments, was the same as the natural synthons DAB III and 14β-OH-DAB, as required for pharmacologically active taxanes. A 7% enhancement of the H-13 proton was observed upon irradiation of the H-2 proton, while no effect was noticed upon irradiation of H-14. This suggests that H-13 and H-2 are located on the same β-face. An oppostite trend was found for the epimer 13β-**38**: a NOE effect of 9% was observed for the H-13 proton upon irradiation of H-14, since the two protons are located on the same α-face. The esterification of 13α-**37** with the acid **35**, following the standard protocol, gave the fully protected 14β-azido taxane **39** in 80% yield. Catalytic hydrogenation (10% Pd/C) of the azido group of **39** gave the 14β-amino analogue **40** in 90% yield. The 1β-OH and 14β-NH_2 groups of **40** were subjected to further elaborations that allowed the synthesis of other taxanes. Thiocarbonylation of **40** with di-2-pyridyl-thionocarbonate in CH_3CN gave the 1,14-thiocarbamate derivative **41** in 73% yield, while the carbonylation of the 14β-amino derivative **37** with excess of BOC_2O, Et_3N and DMAP gave the *N*-BOC-1, 14-carbamate derivative **42** in 69%. It is worth noting that the taxane 1, 14 carbamate **36** was obtained in 74% yield by an independent route by carbonylation of the amino derivative **40** with $COCl_2$/pyridine.

Finally, the sequential desilylation of the 7-OTES group of **36**, **39**–**42** with HF/pyridine, followed by *N*, *O*-deprotection of the isoserine moiety with acetyl chloride in MeOH, gave the target taxoids: 13-*N*-BOC-β-isobutylisoserinoyl-14β-amino-baccatin III 14,1-carbamate (**43**), 13-(*N*-BOC-β-isobutylisoserinoyl)-14β-azido-baccatin III (**44**), 13-(*N*-BOC-β-isobutyl-isoserinoyl)-14β-amino-baccatin III (**45**), 13-(*N*-BOC-β-isobutylisoserinoyl)-14β-amino-baccatin III 14,1-thiocarbamate (**46**), 13-(*N*-BOC-β-isobutyl-isoserinoyl)-14β-*t*-butoxycarbamoyl-baccatin III 14,1-carbamate (**47**) (Scheme 10).

3. Conclusions

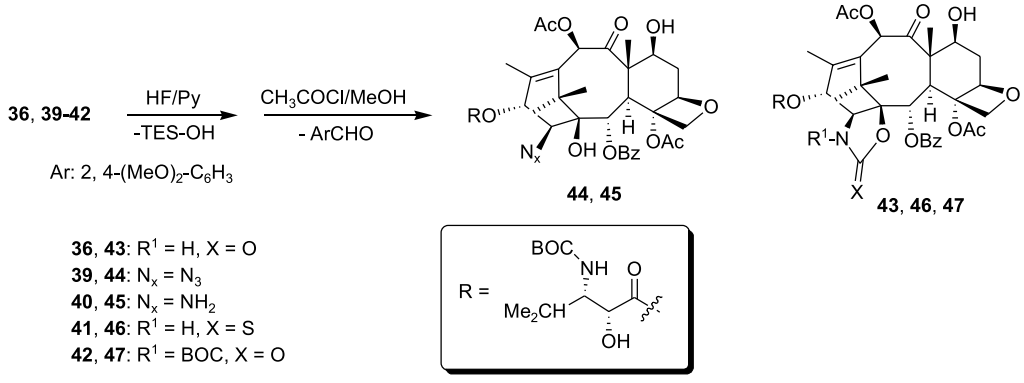
A preliminary optimization of the synthesis of silyl enol ethers has been carried out. We have clearly identified an high yield protocol for the conversion of **1** into 13,21-bis-silylated enol ethers *ortho* esters **23**–**26** using an excess of silylating agent and base. The lability of the silyl substituent at C-21 provides a way for an high recovery of the 13-silyl enol ethers **3** and **28** only when a suitable reagent, PTSA, is adopted for the chemoselective desilylation at C-21 of the α/β-epimeric mixtures. The use of alumina instead of silica for chromatographic purification was required to prevent uncontrolled desilylation of the intermediates. Instead, the 13-OTIPS enol ether **29** was obtained in an one step process but in a moderate amounts.

Moreover, we have developed useful protocols for the synthesis of 14β-nitrogen functionalized taxanes. These compounds were synthesized starting from the commercially available 10-DAB III. Key steps of this protocol were the azidation of the enolates of 13-oxo-baccatins **1** and **2** with tosyl azide, or the azidation of the 13-silyl enol ethers **3** and **29** with NaN_3 under oxidative conditions. Both amination protocols occurred with total β-stereoselectivity regardless of the type of aminating agent (azodicarboxylates, tosyl azide, NaN_3) to afford the key intermediate 14β-azido derivatives **4** and **5**. This selectivity was induced by the folded structure of the taxane skeleton, which favors the approach of the aminating agent from the less hindered β-face. In particular, we have prepared the fully protected 14β-azido taxane **39** from compound **4** using standard procedures. This compound was the key intermediate for the synthesis of a new family of 14β-amino taxanes (**43**–**47**) whose study of antitumor in vitro and in vivo activity is actively under way.[31]

4. Experimental

4.1. General techniques

Solvents were purified and dried prior to use. Reactions were monitored by thin-layer chromatography on 0.25mm E. Merck silica gel plates (60 F254) using UV light as a visualizing agent or a 7% ethanolic phosphomolibdic acid as developing agent. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with Me_4Si or $CHCl_3$ (in



Scheme 10.

$CDCl_3$) as internal reference. Infrared Spectra were recorded on a Fourier transform IR spectrometer, and values are reported in cm^{-1} units. Positive Ion mass spectra were obtained by direct infusion of 1.2 mM solutions in 0.02 M ammonium acetate/MeOH, 20/80 at an ion trap mass spectrometer Thermoquest LCQ-duo (Finnigam USA) equipped with an ESI ionization source.

4.1.1. 7-TES-13-oxo-14-(*N*,*N*′-bis-(benzyloxycarbonyl) hydrazino)-baccatin III (9). A solution of **1** (0.45 g, 0.64 mmol) in THF (12.0 mL) and DMPU (2.5 mL) was cooled to −72 °C and stirred under nitrogen. ^{t}BuOK (1.61 mL, 1.61 mmol, 1.0 M in THF) was added dropwise and the solution stirred at −65 °C for 45 min. Then compound **6** (0.28 g, 0.82 mmol) was added and the reaction monitored by TLC. After 2 h the conversion was not complete, so a further amount of **6** (0.07 g, 0.2 mmol) was added. After 1 h (total reaction time: 3 h) the reaction was quenched with acetic acid (0.15 mL, 40% in THF) and warmed to room temperature. After dilution with brine (10.0 mL) the mixture was extracted with EtOAc and the organic layer washed with brine (10.0 mL), dried and evaporated. The residue was purified by chromatography (SiO_2, CH_2Cl_2/EtOAc, 1.0:0.2) to obtain 0.49 g (0.49 mmol, 76%) of **9** as a white solid. IR (KBr, cm^{-1}): 3394, 2993, 2920, 1725, 1342, 1212; $[\alpha]_D^{20}$ +53.6 (*c* 0.12, $CHCl_3$); MS (*m*/*z*) ESI: 998 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.27–8.32 (m, 2H, arom), 7.19–7.55 (m, 13H, arom), 6.87 (s, 1H, NH), 6.53 (s, 1H, H-10), 5.99 (d, 1H, H-2, J= 6.6 Hz), 5.63 (s, 1H, H-14), 5.16 (d, 2H, J=4.8 Hz, CH_2Ph), 5.04 (d, 2H, J=4.8 Hz, CH_2Ph), 4.88 (d, 1H, H-5, J= 4.0 Hz), 4.51 (dd, 1H, H-7, J=6.6, 4.0 Hz), 4.34–4.36 (m, 2H, H-20), 4.01 (d, 1H, H-3, J=6.6 Hz), 2.42–2.61 (m, 1H, Hα-6), 2.23 (s, 3H, Me), 2.22 (s, 3H, Me), 2.15 (s, 3H, Me), 1.84–1.98 (m, 1H, Hβ-6), 1.74 (s, 3H, Me), 1.29 (s, 3H, Me), 1.28 (s, 3H, Me), 0.90–0.98 (m, 9H, 3 Me), 0.58–0.66 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 200.1, 196.7, 171.9, 169.3, 166.3, 158.1, 157.1, 138.0, 135.5, 135.2, 133.6, 131.3, 129.5, 129.0, 128.9, 128.7, 128.5, 127.7, 84.6, 81.3, 75.8, 75.3, 74.0, 72.5, 69.6, 68.9, 66.3, 59.6, 46.0, 43.7, 37.6, 34.8, 22.2, 21.1, 20.2, 14.2, 10.2, 7.1, 5.6. Anal. Calcd $C_{53}H_{64}N_2O_{15}Si$: C, 63.84; H, 6.47; N, 2.81. Found: C, 63.70; H, 6.51; N, 2.67.

4.1.2. 7-BOC-13-oxo-14β-[*N*,*N*′-bis-(benzyloxycarbonyl) hydrazino]-baccatin III (10). ^{t}BuOK (0.16 g, 1.47 mmol) was suspended, under nitrogen and stirring, in 3.0 mL of anhydrous THF at −72 °C. 7-BOC-13-oxo-baccatin III **2** (0.37 g, 0.54 mmol) in 2.5 mL of THF and 1.8 mL of DMPU was added. After 15 min, 0.32 g (1.19 mmol) of **6**, dissolved in 3.0 mL of THF and 0.2 mL of DMPU was added at −68 °C. Temperature was raised to −50 °C, and after 8 h the reaction mixture was quenched by addition of 2.0 mL (0.03 mmol) of acetic acid, diluted with 10.0 mL of ethyl ether, and extracted with 10.0 mL of saturated solution of NH_4Cl. The organic phases was washed with water, dried, filtered, and evaporated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/EtOAc, 1.3:1.0) afforded 0.35 g (0.35 mmol, 65%) of **10** as a white solid. IR (KBr, cm^{-1}): 3397, 2983, 2930, 1728, 1393, 1252; $[\alpha]_D^{20}$ +58.4 (*c* 0.42, CH_2Cl_2); MS (*m*/*z*) ESI: 984 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24–8.37 (m, 2H, arom), 7.50–7.55 (m, 1H, arom), 7.34–7.40 (m, 2H, arom), 7.15–7.30 (m, 10H, arom), 6.89 (s, 1H, NH), 6.56 (s, 1H, H-10), 5.97 (d, 1H, H-2, J=6.2 Hz), 5.62 (s, 1H, H-14), 5.18 (d, 1H, CH_2Ph, J=12.5 Hz), 5.34–5.38 (m, 1H, H-7), 5.12 (d, 1H, CH_2Ph, J=12.5 Hz), 5.06 (d, 1H, CH_2Ph, J= 12.5 Hz), 4.99 (d, 1H, CH_2Ph, J=12.5 Hz), 4.92 (dd, 1H, H-5, J=2.5, 9.5 Hz), 4.37 (d, 2H, H-20, J=8.6 Hz), 4.14 (d, 1H, H-3, J=6.2 Hz), 2.59 (ddd, 1H, Hα-6, J=7.2, 9.5, 14.3 Hz), 2.19 (s, 3H, Me), 2.18 (s, 3H, Me), 2.13 (s, 3H, Me), 1.97 (ddd, 1H, Hβ-6, J=2.5, 10.9, 14.3 Hz), 1.82 (s, 3H, Me), 1. 47 (s, 9H, 3 Me), 1.23 (s, 3H, Me), 0.86 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.2, 196.4, 171.7, 168.4, 166.2, 158.0, 157.0, 153.3, 152.6, 138.4, 135.3, 135.0, 133.6, 131.1, 129.2, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 127.5, 84.2, 83.3, 80.9, 76.8, 75.8, 75.2, 74.4, 73.6, 69.5, 68.8, 66.1, 57.2, 45.9, 43.5, 33.6, 27.9, 22.0, 21.0, 20.1, 14.4, 10.9. Anal. Calcd for $C_{52}H_{58}N_2O_{17}$: C, 63.53; H, 5.95; N, 2.85. Found: C, 63.50; H, 6.02; N, 2.77.

4.1.3. 7-BOC-13-oxo-14β-[*N*,*N*′-bis-(*tert*-butoxycarbonyl)hydrazino]-baccatin III (11). ^{t}BuOK (0.16 g, 1.47 mmol) was suspended, under nitrogen and stirring, in 3.0 mL of anhydrous THF at −72 °C. Compound **2** (0.37 g, 0.54 mmol) in 2.5 mL of THF and 1.8 mL of DMPU was added to the mixture. Compound **7** (0.27 g, 1.19 mmol), dissolved in 3.0 mL of THF and 0.2 mL of DMPU, was added after 15 min at −68 °C. After 1 h the reaction was quenched by addition of 2.0 mL (0.03 mmol) of acetic acid, diluted with ethyl ether and extracted with a saturated aqueous solution of NH_4Cl. The organic phase was washed with water, dried, filtered and evaporated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/ EtOAc, 1.2:1.0) afforded 0.36 g (0.38 mmol, 72%) of **11** as a solid. IR (KBr, cm^{-1}): 3408, 2980, 2933, 1728, 1682, 1369, 1255, 1155; $[\alpha]_D^{20}$ +57.0 (*c* 0.75, CH_2Cl_2); MS (*m*/*z*) ESI: 916 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27–8.30 (m, 2H, arom), 7.50–7.55 (m, 1H, arom), 7.38–7.42 (m, 2H, arom), 6.58 (s, 1H, N–H), 6.53 (s, 1H, H-10), 5.97 (d, 1H, H-2, J=6.4 Hz), 5.58 (s, 1H, H-14), 5.41 (dd, 1H, H-7, J=6.9, 10.7 Hz), 4.90 (dd, 1H, H-5, J=2.6, 9.7 Hz), 4.35 (d, 1H, H-20, J=8.4 Hz), 4.23 (d, 1H, H-20, J=8.4 Hz), 4.15 (d, 1H, H-3, J=6.4 Hz), 2.59 (ddd, 1H, Hα-6, J=6.9, 9.7, 14.3 Hz), 2.21 (s, 3H, Me), 2.18 (s, 3H, Me), 2.17 (s, 3H, Me), 1.97 (ddd, 1H, Hβ-6, J=2.6, 10.7, 14.3 Hz), 1.82 (s, 3H, Me), 1.46 (s, 9H, 3 Me), 1.40 (s, 9H, 3 Me), 1.35 (s, 9H, 3 Me), 1.26 (s, 3H, Me), 1.00 (s, 3H, Me); ^{13}C NMR ($CDCl_3$,100 MHz) δ 200.4, 196.9, 171.7, 168.4, 166.2, 157.3, 155.8, 153.2, 152.6, 138.5, 133.3, 131.2, 129.4, 128.4, 84.2, 83.3, 83.2, 82.7, 80.9, 76.8, 76.1, 75.0, 74.5, 73.4, 65.1, 57.3, 45.9, 43.6, 34.6, 33.7, 28.2, 28.1, 27.9, 21.9, 21.0, 20.1, 14.3, 10.9. Anal. Calcd $C_{46}H_{62}N_2O_{17}$: C, 60.38; H, 6.83; N, 3.06. Found: C, 60.30; H, 6.71; N, 3.14.

4.1.4. 7-TES-13-oxo-14β-hydrazino-baccatin III (12). A solution of **9** (0.50 g, 0.50 mmol) in EtOAc (45.0 mL) was hydrogenated under balloon pressure with 10% Pd/C as catalyst (0.05 g) for 45 min. The catalyst was filtered off through celite, the solvent was evaporated under reduced pressure without heating to obtain 0.35 g of **12** (0.48 mmol, 96%). This compound was unstable in various conditions (chromatographic column) and solvents ($CDCl_3$). (**12**): IR (KBr, cm^{-1}): 3340, 2980, 1734, 1252; ^{1}H NMR ($CDCl_3$, 200 MHz) relevant resonances at δ 8.19–8.23 (m, 2H, arom), 7.41–7.61 (m, 3H, arom), 6.54 (s, 1H, H-10), 5.85 (d,

1H, H-2, $J=6.6$ Hz), 5.37 (s, 1H), 5.18 (s, 1H), 4.92 (d, 1H, H-5, $J=8.1$ Hz), 4.51 (m, 1H, H-7), 4.29 (s, 2H, H-20), 3.92 (d, 1H, H-3, $J=7.0$ Hz), 2.47–2.62 (m, 1H, Hα-6), 2.25 (s, 3H, Me), 2.23 (s, 3H, Me), 2.06 (s, 3H, Me), 1.84–1.98 (m, 1H, Hβ-6), 1.74 (s, 3H, Me), 1.31 (s, 3H, Me), 1.28 (s, 3H, Me), 0.90–0.98 (m, 9H, 3 Me).

4.1.5. 7-TES-13-oxo-14-diazo-baccatin III (17). 0.8 mL of a 1.0 M solution of ^{t}BuOK in THF was added under stirring at −72 °C to a solution of 0.22 g (0.32 mmol) of **1** in 3.5 mL of THF and 1.0 mL of DMPU. Tosyl azide (0.11 g, 0.58 mmol), dissolved in 0.9 mL of THF was added after 15 min. The temperature was raised to −50 °C and the reaction was quenched after 1 h by addition of 0.8 mL of acetic acid. The reaction temperature was raised at 20 °C and the mixture left for 12 h. The reaction mixture was extracted with Et_2O and the organic phase was dried, filtered and evaporated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/EtOAc, 2.1:1.0) afforded 0.19 g of **17** as a white solid (0.26 mmol, 82%). IR (KBr, cm^{-1}): 3358, 3261, 2957, 2877, 2097, 1727, 1628, 1369, 1306, 1161; $[\alpha]_D^{20}$ +66.0 (*c* 0.9, CH_2Cl_2); MS (*m/z*) ESI: 726 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10–8.20 (m, 2H, arom), 7.59–7.62 (m, 1H, arom), 7.42–7.50 (m, 2H, arom), 6.50 (s, 1H, H-10), 5.84 (d, 1H, H-2, $J=7.2$ Hz), 4.92 (dd, 1H, H-5, $J=2.2$, 9.7 Hz), 4.47 (dd, 1H, H-7, $J=6.7$, 10.7 Hz), 4.33 (d, 1H, H-20, $J=8.2$ Hz), 4.07 (d, 1H, H-20, $J=8.2$ Hz), 3.89 (d, 1H, H-3, $J=7.2$ Hz), 2.53 (ddd, 1H, Hα-6, $J=6.7$, 9.7, 14.2 Hz), 2.21 (s, 3H, Me), 2.20 (s, 3H, Me), 2.16 (s, 3H, Me), 1.85 (ddd, 1H, Hβ-6, $J=2.2$, 10.7, 14.2 Hz), 1.65 (s, 3H, Me), 1.28 (s, 3H, Me), 1.26 (s, 3H, Me), 0.89–92 (m, 9H, 3 Me), 0.54–0.58 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.6, 183.9, 170.3, 168.9, 167.0, 146.4, 140.4, 134.3, 130.4, 130.2, 129.0, 84.2, 80.6, 79.5, 76.5, 76.0, 74.0, 72.3, 69.6, 59.1, 45.9, 43.0, 37.4, 33.1, 22.0, 21.2, 18.9, 14.4, 10.4, 7.2, 5.7. Anal. Calcd $C_{37}H_{48}N_2O_{11}Si$: C, 61.31; H, 6.67; N, 3.86. Found: C, 61.39; H, 6.75; N, 3.92.

4.1.6. 7-BOC-13-oxo-14-diazo-baccatin III (18). A solution of **2** (0.15 g, 0.22 mmol) in THF (0.7 mL) and DMPU (0.4 mL) was added under nitrogen and stirring to a suspension of ^{t}BuOK (0.06 g, 0.57 mmol) in anhydrous THF (0.7 mL) at −72 °C. After 15 min, a solution of tosyl azide (0.08 g, 0.39 mmol) in 0.5 mL of THF was added. The temperature was raised to −50 °C and the reaction was quenched after 2 h by addition of 1.0 mL of acetic acid. Work-up of the reaction mixture was performed as described for compound **17**. Chromatography of the crude residue (SiO_2, *n*-hexane/EtOAc, 1.7:1.0) yielded 0.11 g of compound **18** (0.16 mmol, 72%) as a white solid. IR (KBr, cm^{-1}): 3359, 2957, 2878, 2097, 1726, 1630, 1305; $[\alpha]_D^{20}$ +72.6 (*c* 0.3, CH_2Cl_2); MS (*m/z*) ESI: 712 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17–8.22 (m, 2H, arom), 7.62–7.68 (m, 1H, arom), 7.48–7.54 (m, 2H, arom), 6.50 (s, 1H, H-10), 5.85 (d, 1H, H-2, $J=7.2$ Hz), 5.41 (dd, 1H, H-7, $J=6.8$, 10.8 Hz), 4.95 (dd, 1H, H-5, $J=1.5$, 8.0 Hz), 4.36 (d, 1H, H-20, $J=8.4$ Hz), 4.08 (d, 1H, H-20, $J=8.4$ Hz), 4.04 (d, 1H, H-3, $J=7.2$ Hz), 2.63 (ddd, 1H, Hα-6, $J=6.8$, 8.0, 14.0 Hz), 2.22 (s, 3H, Me), 2.19 (s, 3H, Me), 2.18 (s, 3H, Me), 1.92 (ddd, 1H, Hβ-6, $J=1.5$, 8.0, 14.0 Hz), 1.77 (s, 3H, Me), 1.48 (s, 9H, 3Me), 1.31 (s, 3H, Me), 1.23 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.9, 184.1, 170.4, 168.3, 167.3, 152.5, 145.7, 141.1, 134.5, 130.4, 129.1, 128.3, 84.0, 83.5, 80.4, 79.5, 76.3, 76.2, 74.5, 73.7, 65.4, 56.6, 46.1, 43.0, 33.5, 32.9, 27.9, 21.0, 18.7, 14.4, 11.1. Anal. Calcd $C_{36}H_{42}N_2O_{13}$: C, 60.84; H, 5.96; N, 3.94. Found: C, 60.70; H, 5.85; N, 4.03.

4.1.7. 7-TES-13-oxo-14β-azido-baccatin III (4). A solution of 1.40 g (2.0 mmol) of **1** in 7.5 mL of THF and 3.7 mL of DMPU, was added to a solution of ^{t}BuOK (5.2 mL, 5.2 mmol, 1.0 M in THF) at −72 °C under stirring. Tosyl azide (0.70 g, 3.6 mmol), dissolved in 5.8 mL of THF, was added after 10 min. The temperature was raised to −50 °C and the reaction was quenched after 2 h by addition of 10.0 mL of saturated aqueous NH_4Cl. The reaction mixture was left at 25 °C for 12 h, diluted with 50.0 mL of Et_2O and extracted. The organic phase was washed with water, dried, filtered and concentrated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/EtOAc/Et_2O, 1.8:0.7:0.4) gave 1.34 g (1.8 mmol, 92%) of **4** as a white solid. IR (KBr, cm^{-1}): 3497, 2956, 2878, 2117, 1730, 1689, 1370, 1238, 1094; $[\alpha]_D^{20}$ +79.4 (*c* 0.9, CH_2Cl_2); MS (*m/z*) ESI: 741 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02–8.04 (m, 2H, arom) 7.60–7.65 (m 1H, arom), 7.47–7.53 (m, 2H, arom), 6.53 (s, 1H, H-10), 5.82 (d, 1H, H-2, $J=6.7$ Hz), 4.92 (dd, 1H, H-5, $J=2.0$, 9.5 Hz), 4.46 (dd, 1H, H-7, $J=6.7$, 10.7 Hz), 4.33 (d, 1H, H-20, $J=8.6$ Hz), 4.25 (s, 1H, H-14), 4.24 (d, 1H, H-20, $J=8.6$ Hz), 3.86 (d, 1H, H-3, $J=6.7$ Hz), 3.09 (s, 1H, OH), 2.54 (ddd, 1H, Hα-6, $J=6.7$, 10.7, 14.2 Hz), 2.25 (s, 3H, Me), 2.22 (s, 3H, Me), 2.19 (s, 3H, Me), 1.91 (ddd, 1H, Hβ-6, $J=2.0$, 9.5, 14.2 Hz), 1.72 (s, 3H, Me), 1.27 (s, 3H, Me), 1.00 (s, 3H, Me), 0.90–0.96 (m, 9H, 3 Me), 0.55–0.64 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 199.5, 196.5, 169.9, 169.0, 165.3, 155.4, 138.2, 134.0, 129.9, 129.2, 129.0, 84.0, 81.3, 76.3, 75.6, 75.5, 72.8, 72.5, 65.5, 59.6, 45.7, 43.4, 37.4, 34.0, 22.1, 21.2, 19.4, 14.4, 10.1, 7.2, 5.6. Anal. Calcd $C_{37}H_{49}N_3O_{11}Si$: C, 60.06; H, 6.68; N, 5.68. Found: C, 59.87; H, 6.79; N, 5.80.

4.1.8. 7-BOC-13-oxo-14β-azido-baccatin III (5). A solution of **2** (0.15 g, 0.22 mmol) in THF (1.8 mL) and DMPU (0.8 mL) was added to a suspension of ^{t}BuOK (0.06 g, 0.57 mmol) in anhydrous THF (1.5 mL) at −72 °C, under nitrogen and stirring. After 15 min, 0.08 g (0.40 mmol) of tosyl azide, dissolved in 0.7 mL of THF, were added in 2 min at −75 °C. After 30 min, the temperature was raised to −50 °C and the reaction was quenched after 2 h by addition of 5.0 mL of saturated NH_4Cl. The reaction mixture was extracted with Et_2O and the organic phase was dried, filtered and evaporated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/EtOAc, 1.7:1.0) gave 0.14 g (0.19 mmol, 85%) of **5** as a white solid. IR (KBr, cm^{-1}): 2976, 2935, 2122, 1731, 1272, 1094; $[\alpha]_D^{20}$ +69.4 (*c* 0.9, CH_2Cl_2); MS (*m/z*) ESI: 727 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02–8.05 (m, 2H, arom), 7.60–7.66 (m, 1H, arom), 7.48–7.52 (m, 2H, arom), 6.56 (s, 1H, H-10), 5.81 (d, 1H, H-2, $J=6.8$ Hz), 5.37 (dd, 1H, H-7, $J=7.2$, 10.8 Hz), 4.93 (dd, 1H, H-5, $J=2.0$, 9.6 Hz), 4.33 (d, 1H, H-20, $J=8.4$ Hz), 4.26 (s, 1H, H-14), 4.24 (d, 1H, H-20, $J=8.4$ Hz), 3.98 (d, 1H, H-3, $J=6.8$ Hz), 3.11 (s, 1H, OH), 2.62 (ddd, 1H, Hα-6, $J=7.2$, 9.6, 14.0 Hz), 2.24 (s, 3H, Me), 2.20 (s, 3H, Me), 2.19 (s, 3H, Me), 1.96 (ddd, 1H, Hβ-6, $J=2.0$, 10.8, 14.0 Hz), 1.81 (s, 3H, Me), 1.47 (s, 9H,

3 Me), 1.22 (s, 3H, Me), 1.01 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.8, 196.6, 170.0, 168.2, 165.4, 153.8, 152.5, 138.8, 134.1, 130.0, 129.2, 129.1, 83.7, 83.5, 81.0, 76.1, 75.8, 75.5, 74.4, 72.5, 65.4, 57.2, 45.8, 43.3, 33.7, 33.5, 27.9, 21.9, 20.9, 19.2, 14.4, 10.8. Anal. Calcd $C_{36}H_{43}N_3O_{13}$: C, 59.58; H, 5.97; N, 5.79. Found: C, 59.71; H, 5.90; N, 5.83.

4.1.9. Synthesis of 7-TES-13-oxo-1,2-[α-(β-*O*-TMS)-benzylideneacetal)]-baccatin III (21); 7-TES-13-oxo-1,2-[α-(β-*O*-TMS)-benzylideneacetal)]-baccatin III (22); 7-TES-13-TMS-13,14-dehydro-1, 2-[α-(β-*O*-TMS)-benzylideneacetal)]-baccatin III (23); 7-TES-13-TMS-13,14-dehydro-1,2-[α-(β-*O*-TMS)-benzylideneacetal)]-baccatin III (24). A. *DBU induced silylation of* **1** *with Me_3SiCl.* (i) A solution of 0.30 g (0.42 mmol) of **1**, 0.13 g (0.84 mmol) of DBU, 0.11 g (1.05 mmol) of Me_3SiCl, in 8.0 mL of CH_2Cl_2 was refluxed under nitrogen for 2 h. The reaction solution was treated with saturated aqueous solution of NH_4Cl. The organic layer was separated and extracted with water, dried, filtered, and evaporated under reduced pressure. The ^{1}H NMR spectrum of the crude mixture (CD_3COCD_3) showed a product distribution of **21/22/23/24**=41:36:11:7 and minor amounts of unreacted **1** and of the silyl enol ether **3**. Chromatography (SiO_2, *n*-hexane/CH_2Cl_2/EtOAc, 14:6:3) gave 0.24 g (0.30 mmol, 71%) of a mixture of compounds **21** and **22** (**21/22**=0.94), 0.06 g (0.07 mmol, 16%) of a mixture of compounds **23** and **24** (**23/24**=1.1). All compounds are solid. (ii) A solution of 0.30 g (0.42 mmol) of **1**, 0.39 g (2.52 mmol) of DBU, 0.38 g (2.94 mmol) of Me_3SiCl, in 8.0 mL of CH_2Cl_2 was refluxed under nitrogen for 2 h. The crude reaction mixture, obtained after the above described work up, was chromatographed on Al_2O_3, (*n*-hexane/EtOAc, 10:1) to give a mixture of **23** and **24** (0.33 g, 0.38 mmol, 92%, **23/24**=1.4). B. *Silylation of* **1** *with BSA*. (i) 0.25 g (0.35 mmol) of 7-TES-13-oxo-baccatin III **1** and BSA (0.18 g, 0.88 mmol) were reacted in 5.0 mL of CD_3CN at 25 °C for 24 h at 20 °C. The crude reaction mixture, obtained after the above described work up, was chromatographed on Al_2O_3, (*n*-hexane/EtOAc, 10:1) to give compounds **3** (0.09 g, 0.11 mmol, 33%), **21** (0.03 g, 0.04 mmol, 12%), **22** (0.02 g, 0.03 mmol, 8%) and unreacted **1** (0.12 g, 0,17 mmol, 47%). (ii) 0.25 g (0.35 mmol) of **1** and BSA (0.18 g, 0.88 mmol) were reacted in 5.0 mL of CD_3CN and in the presence of 0.01 g (0.07 mmol) of DMAP for 8 h. The reaction solution was treated with saturated aqueous solution of NH_4Cl. The organic layer was separated and extracted with water, dried, filtered, and evaporated under reduced pressure. Chromatography (Al_2O_3, *n*-hexane/EtOAc, 10:1) gave 0.18 g (0.23 mmol, 65%) of a mixture of compounds **21** and **22** (**21/22**=1.5) and 0.10 g (0.12 mmol, 35%) of a mixture of compounds **23** and **24** (**23/24**=4.0). All compounds are solid. Compounds **21** and **22**. Anal. Calcd for $C_{40}H_{58}O_{11}Si_2$: C, 62.31; H, 7.58. Found: C, 62.44; H, 7.62; IR (nujol, cm^{-1}): 3474, 1724, 1369, 1254; MS (*m*/*z*) ESI: 772 $(M+H)^+$. (**21**); ^{1}H NMR (CD_3COCD_3, 400 MHz) δ 7.60–7.64 (m, 2H, arom), 7.48–7.52 (m, 1H, arom), 7.37–7.46 (m, 2H, arom), 6.57 (s, 1H, H-10), 5.02 (dd, 1H, H-5, J=0.5, 9.0 Hz), 4.68 (s, 2H, H-20), 4.55 (dd, 1H, H-7, J=7.6, 9.6 Hz), 4.39 (d, 1H, H-2, J=5.2 Hz), 3.50 (d, 1H, H-3, J=5.2 Hz), 2.59–2.69 (m, 1H, H-6), 2.53 (d, 1H, H-14, J=20.0 Hz), 2.29 (d, 1H, H-14, J=20.0 Hz), 2.20 (s, 3H, Me), 2.11 (s, 3H, Me), 1.97 (s, 3H, Me), 1.76–1.88 (m, 1H, H-6), 1.78 (s, 3H, Me), 1.33 (s, 3H, Me), 1.20 (s, 3H, Me), 0.90–0.98 (m, 9H, 3 Me), 0.60–0.68 (m, 6H, 3 CH_2), −0.03 (s, 9H, 3 Me); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ: 204.4, 201.4, 173.5, 172.2, 155.1, 145.1, 144.0, 132.2, 131.6, 128.9, 120.8, 87.1, 87.0, 83.1, 80.4, 80.3, 79.4, 75.5, 64.3, 46.6, 45.7, 45.0, 41.3, 34.8, 24.3, 23.3, 21.3, 17.0, 13.1, 9.7, 8.4, 3.7. (**22**); ^{1}H NMR (CD_3COCD_3, 100 MHz) δ 7.60–7.64 (m, 2H, arom), 7.48–7.52 (m, 1H, arom), 7.37–7.46 (m, 2H, arom), 6.54 (s, 1H, H-10), 5.02 (dd, 1H, H-5, J=0.5, 9.0 Hz), 4.70 (s, 2H, H-20), 4.55 (dd, 1H, H-7, J=7.6, 9.6 Hz), 3.90 (d, 1H, H-2, J=5.2 Hz), 3.57 (d, 1H, H-3, J=5.2 Hz), 3.07 (d, 1H, H-14, J=20.4 Hz), 2.91 (d, 1H, H-14, J=20.4 Hz), 2.59–2.69 (m, 1H, Hα-6), 2.15 (s, 3H, Me), 2.14 (s, 3H, Me), 2.08 (s, 3H, Me), 1.76–1.88 (m, 1H, Hβ-6), 1.65 (s, 3H, Me), 1.25 (s, 3H, Me), 0.98 (s, 3H, Me), 0.90–0.98 (m, 9H, 3 Me), 0.60–0.68 (m, 6H, 3 CH_2), 0.00 (s, 9H, 3 Me); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ 204.1, 201.7, 173.7, 172.2, 154.9, 144.8, 144.0, 132.2, 131.8, 128.3, 120.8, 89.1, 87.2, 82.9, 82.7, 80.1, 79.4, 75.4, 64.0, 46.9, 46.1, 45.1, 41.3, 34.9, 24.4, 23.3, 21.1, 12.8, 9.7, 8.3, 3.8. Compounds **23** and **24**. Anal. Calcd for $C_{43}H_{66}O_{11}Si_3$: C, 61.25; H, 7.89. Found: C, 61.03; H, 7.75; IR (nujol, cm^{-1}): 1718, 1368, 1254, 1060, 842; MS (*m*/*z*) ESI: 844 $(M+H)^+$. (**23**); ^{1}H NMR (CD_3COCD_3, 400 MHz) δ 7.64–7.68 (m, 2H, arom), 7.46–7.50 (m, 1H, arom), 7.34–7.44 (m, 2H, arom), 6.43 (s, 1H, H-10), 5.02 (dd, 1H, H-5, J=0.5, 9.2 Hz), 4.64 (s, 2H, H-20), 4.52 (dd, 1H, H-7, J=8.0, 9.6 Hz), 4.48 (d, 1H, H-2, J=5.6 Hz), 4.46 (s, 1H, H-14), 3.35 (d, 1H, H-3, J=5.6 Hz), 2.56–2.66 (m, 1H, Hα-6), 2.14 (s, 3H, Me), 2.02 (s, 3H, Me), 2.00 (s, 3H, Me), 1.78–1.88 (m, 1H, Hβ-6), 1.78 (s, 3H, Me), 1.37 (s, 3H, Me), 1.15 (s, 3H, Me), 0.90–0.98 (m, 9H, 3 Me), 0.58–0.66 (m, 6H, 3 CH_2), 0.09 (s, 9H, 3 Me), −0.01 (s, 9H, 3 Me); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ 206.2, 173.1, 172.3, 156.3, 154.4, 142.3, 137.4, 131.9, 131.4, 128.9, 122.0, 114.2, 91.2, 87.2, 82.8, 82.7, 80.1, 79.8, 75.5, 62.3, 45.8, 41.7, 41.4, 31.8, 24.4, 23.5, 21.6, 17.4, 13.5, 9.8, 8.5, 3.7, 3.1. (**24**); ^{1}H NMR (CD_3COCD_3, 400 MHz) δ 7.64–7.68 (m, 2H, arom), 7.46–7.50 (m, 1H, arom), 7.34–7.44 (m, 2H, arom), 6.41 (s, 1H, H-10), 5.42 (s, 1H, H-14), 5.00 (dd, 1H, J=0.5, 8.4 Hz), 4.67 (d, 1H, H-20, J=8.4 Hz), 4.64 (d, 1H, H-20, J=8.4 Hz), 4.52 (dd, 1H, H-7, J=8.0, 9.6 Hz), 4.02 (d, 1H, H-2, J=6.0 Hz), 3.40 (d, 1H, H-3, J=6.0 Hz), 2.56–2.66 (m, 1H, Hα-6), 2.12 (s, 3H, Me), 2.09 (s, 3H, Me), 2.06 (s, 3H, Me), 1.78–1.88 (m, 1H, Hβ-6), 1.63 (s, 3H, Me), 1.42 (s, 3H, Me), 0.90–0.98 (m, 9H, 3 Me), 0.80 (s, 3H, Me), 0.58–0.66 (m, 6H, 3 CH_2), 0.34 (s, 9H, 3 Me), 0.03 (s, 9H, 3 Me); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ 205.9, 173.4, 172.2, 155.9, 146.1, 142.4, 137.1, 132.0, 131.7, 128.3, 121.7, 115.4, 93.1, 87.3, 82.7, 80.7, 80.0, 79.6, 75.4, 62.5, 45.5, 41.8, 41.3, 31.9, 24.6, 23.4, 21.5, 17.5, 13.2, 9.7, 8.5, 3.8, 2.8.

4.1.10. Synthesis of 7,13-bis-TES-13,14-dehydro-1,2-[α-(β-*O*-TES)-benzylidene-acetal)]-baccatin III (25); 7,13-bis-TES-13,14-dehydro-1,2-[α-(β-*O*-TES)-benzylidene-acetal)]-baccatin III (26), 7- TES-13-oxo-1,2-[α-(β-*O*-TES)-benzylideneacetal)]-baccatin III (27). *Procedure A*. A solution of 0.35 g (0.49 mmol) of 7-TES-13-oxo-baccatin III **1**, 0.53 g (3.43 mmol) of DBU, 0.44 g (2.94 mmol) of TESCl, in 8.0 mL of CH_3CN was left at 20 °C for 5 h. After, the solution was treated with saturated solution of NH_4Cl. The organic layer was separated, the aqueous phase was

extracted with CH_2Cl_2. The organic phases were combined, dried, filtered, and evaporated under reduced pressure. The ^1H NMR spectrum of the crude mixture (CD_3COCD_3) showed a product distribution of **25/26**=1.2. Chromatography (Al_2O_3, cyclohexane/EtOAc, 97:3 to 95:5) gave 0.43 g (0.46 mmol, 93%) of the mixture of **25** and **26**. *Procedure B*: (i) Compound **1** (0.14 g, 0.2 mmol) was dissolved in THF (5.0 mL) and the solution was cooled to −70 °C. ^{t}BuOK (1.0 M in THF, 0.5 mmol) was added and the reaction mixture stirred for 15 min at −70 °C, then TESCl (0.07 mL, 0.40 mmol) was added. After 45 min the reaction was quenched with saturated aqueous solution of NH_4Cl (8.0 mL) and extracted with EtOAc, dried, and the solvent was evaporated. The crude mixture was purified by chromatography (Al_2O_3, *n*-hexane/EtOAc, 10:1) to afford compounds **27** (0.13 g, 0.16 mmol, 80%) and **25** (0.04 g, 0.04 mmol, 20%). Attempted purification of 0.20 g of the 80:20 mixture of **25/27** (cyclohexane/EtOAc, 9:1) caused a partial solvolysis of **25** and **27** affording the silyl enol ether **28** and the reagent **1**. Final product distribution was **1/27/28**=31:49:20. (ii): Compound **1** (0.14 g, 0.2 mmol) was dissolved in THF (4.0 mL) and the solution was cooled to −60 °C. ^{t}BuOK (1.0 M in THF, 1.0 mL, 1.0 mmol) was added and the reaction mixture stirred for 15 min at −60 °C, then TESCl (0.21 mL, 1.2 mmol) was added. After 1 h the reaction was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc, dried, and the solvent was evaporated. The crude was purified by chromatography (Al_2O_3, *n*-hexane/EtOAc, 10:1) to obtain compound **25** (0.17 g, 0.19 mmol, 94%). Compounds **25** and **26**. Anal. Calcd for $C_{49}H_{78}O_{11}Si_3$: C, 63.46; H, 8.48. Found: C, 63.67; H, 8.55; IR (nujol, cm^{-1}): 1735, 1719, 1376, 1232. (**25**): $[\alpha]_D^{20}$ +8.7 (*c* 0.40, CH_3COCH_3); MS (*m/z*) ESI: 928 $(M+H)^+$; ^1H NMR (CD_3COCD_3, 400 MHz) δ: 7.68–7.73 (m, 2H), 7.40–7.44 (m, 3H, arom), 6.45 (s, 1H, H-10), 5.05 (dd, 1H, H-5 *J*=0.9, 7.7 Hz), 4.64–4.68 (m, 2H), 4.52 (dd, 1H, *J*=7.0, 10.2 Hz), 4.50 (1H, H-2, *J*=5.9 Hz), 4.46 (s, 1H), 3.37 (d, 1H, H-3, *J*=5.9 Hz), 2.57–2.68 (m, 1H, Hα-6), 2.13 (s, 3H, Me), 2.07 (s, 3H, Me), 2.03 (s, 3H, Me), 1.80–1.90 (m, 1H, Hβ-6), 1.79 (s, 3H, Me), 1.37 (s, 3H, Me), 1.17 (s, 3H, Me), 0.85–1.00 (m, 18H, 9 CH_2), 0.50–0.70 (m, 27H, 9 Me); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ: 202.9, 169.8, 168.9, 153.0, 143.1, 138.9, 134.0, 128.6, 128.0, 125.7, 118.6, 110.9, 89.7, 83.9, 79.6, 77.7, 76.8, 76.6, 72.2, 59.3, 42.3, 38.6, 38.1, 28.3, 21.2, 20.3, 18.5, 14.0, 10.1, 6.5, 6.3, 6.2, 5.3, 5.2, 4.8. (**26**); ^1H NMR (CD_3COCD_3, 400 MHz) δ: 7.48–7.53 (m, 2H, arom), 7.40–7.44 (m, 3H, arom), 6.40 (s, 1H, H-10), 5.36 (s, 1H, H-14), 4.98 (dd, 1H, H-5, *J*=0.9, 7.7 Hz), 4.64–4.68 (m, 2H, H-20), 4.52 (dd, 1H, H-7, *J*=9.2, 6.8 Hz), 3.97 (d, 1H, H-2, *J*=6.0 Hz), 3.40 (d, 1H, H-3, *J*=6.0 Hz), 2.57–2.68 (m, 1H, Hα-6), 2.14 (s, 3H, Me), 2.07 (s, 3H, Me), 2.02 (s, 3H, Me), 1.76–1.86 (m, 1H, Hβ-6), 1.62 (s, 3H, Me), 1.42 (s, 3H, Me), 0.85–1.00 (m, 27H, 9 Me), 0.80 (s, 3H, Me), 0.50–0.70 (m, 18H, 9 CH_2); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ: 202.5, 170.1, 168.9, 152.6, 142.3, 139.0, 133.9, 128.7, 128.4, 125.1, 118.5, 112.9, 87.1, 84.0, 79.4, 79.0, 76.7, 76.4, 72.1, 59.2, 42.4, 38.6, 38.1, 28.4, 21.3, 20.2, 18.4, 14.2, 9.9, 6.5, 5.3. (**27**): $[\alpha]_D^{20}$ +8.8 (*c* 0.40, CH_3COCH_3); IR (nujol, cm^{-1}): 3470, 1727, 1371, 1250; MS (*m/z*) ESI: 814 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.54–7.58 (m, 2H, arom), 7.32–7.35 (m, 3H, arom), 6.55 (s, 1H, H-10), 4.99 (dd, 1H, *J*=8.8, 0.9 Hz), 4.75 (s, 2H, H-20), 4.49 (dd, 1H, H-7, *J*=7.0, 9.6 Hz), 4.35 (d, 1H, H-2, *J*=6.9 Hz), 3.45 (d, 1H, H-3, *J*=6.9 Hz), 2.56–2.64 (m, 1H, Hα-6), 2.26–2.32 (m, 2H, H-14), 2.23 (s, 3H, Me), 2.14 (s, 3H, Me), 2.01 (s, 3H, Me), 1.87–1.95 (m, 1H, Hβ-6), 1.79 (s, 3H, Me), 1.34 (s, 3H, Me), 1.22 (s, 3H, Me), 0.90–1.03 (m, 18H, 6 Me), 0.40–0.85 (m, 12H, 6 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 201.1, 198.0, 170.2, 168.9, 151.7, 142.1, 140.7, 128.6, 128.1, 125.6, 117.5, 85.7, 83.9, 79.8, 77.4, 77.0, 76.2, 72.2, 61.0, 43.4, 42.4, 41.8, 38.1, 31.5, 21.0, 20.0, 18.0, 13.7, 9.7, 6.5, 6.3, 5.9, 5.3. Anal. Calcd for $C_{43}H_{64}O_{11}Si_2$: C, 63.51; H, 7.93. Found: C, 63.74; H, 8.04.

4.1.11. Desilylation of compounds 23 and 24 into 7-TES-13-TMS-13,14-dehydro-baccatin III (3). A mixture of **23/24**=0.89 (0.20 g, 0.24 mmol) was dissolved in 4.0 mL of CH_2Cl_2 at 20 °C, then 0.03 g (0.02 mmol) of PTSA was added. After 20 min the reaction solution was treated with saturated aqueous solution of NH_4Cl. The organic layer was separated and extracted with water, dried, filtered, and evaporated under reduced pressure. Chromatography (SiO_2, *n*-hexane/CH_2Cl_2/EtOAc, 14:6:3) gave compound **3** as a white solid (0.18 g, 0.23 mmol, 95%). IR (nujol, cm^{-1}): 1721, 1255, 1238, 1107, 1068; $[\alpha]_D^{20}$ −44.0 (*c* 1.14, $CHCl_3$); MS (*m/z*) ESI: 772 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08 (m, 2H, arom), 7.56–7.62 (m, 1H, arom), 7.44–7.50 (m, 2H, arom), 6.41 (s, 1H, H-10), 5.76 (d, 1H, H-2, *J*=7.2 Hz), 4.97 (dd, 1H, H-5, *J*=9.6, 0.5 Hz), 4.73 (s, 1H, H-14), 4.44 (dd, 1H, H-7, *J*=6.9, 10.5 Hz), 4.29 (d, 1H, H-20, *J*=8.4 Hz), 4.14 (d, 1H, H-20, *J*=8.4 Hz), 3.71 (d, 1H, H-3, *J*=7.2 Hz), 2.46–2.56 (m, 1H, Hα-6), 2.19 (s, 3H, Me), 2.18 (s, 3H, Me), 2.05 (s, 3H, Me), 1.82–1.90 (m, 1H, Hβ-6), 1.69 (s, 3H, Me), 1.26 (s, 3H, Me), 1.12 (s, 3H, Me), 0.88–0.95 (m, 9H, 3 Me), 0.52–0.60 (m, 6H, 6 CH_2), 0.25 (s, 9H, 3 Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.2, 170.2, 169.6, 166.9, 153.5, 138.0, 135.2, 133.8, 130.3, 129.7, 128.8, 110.6, 84.2, 81.4, 80.7, 76.5, 76.2, 73.6, 72.4, 58.3, 45.1, 41.0, 37.4, 29.0, 21.9, 21.3, 19.1, 14.2, 10.3, 7.0, 5.5, 0.6. Anal. Calcd for $C_{40}H_{58}O_{11}Si_2$: C, 62.31; H, 7.58. Found: C, 62.50; H, 7.68.

4.1.12. Desilylation of compounds 25 and 26 into 7, 13-bis-TES-13,14-dehydro-baccatin III (28). A mixture of **25/26**=1.25 (0.25 g, 0.27 mmol) was dissolved in 4.0 mL of CH_2Cl_2 at 20 °C then 0.03 g (0.02 mmol) of PTSA was added. After 12 h the reaction was treated with saturated aqueous solution of NH_4Cl. The organic layer was separated and extracted with water, dried, filtered, and evaporated under reduced pressure. Chromatography (SiO_2, *n*-hexane/CH_2Cl_2/EtOAc, 14:6:3) gave compound **28** (0.20 g, 0.25 mmol, 93%) as a white solid. (**28**): IR (nujol, cm^{-1}): 3483, 1739, 1722, 1704, 1376, 1242; $[\alpha]_D^{20}$ −6.0 (*c* 1.0, $CHCl_3$); MS (*m/z*) ESI: 814 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.06–8.10 (m, 2H, arom), 7.54–7.60 (m, 1H, arom), 7.40–7.46 (m, 2H, arom), 6.42 (s, 1H, H-10), 5.75 (d, 1H, H-2, *J*=7.3 Hz), 4.95 (dd, 1H, H-5, *J*=0.9, 9.7 Hz), 4.73 (s, 1H, H-14), 4.43 (dd, 1H, H-7, *J*=6.9, 10.0 Hz), 4.27 (d, 1H, H-20, *J*=8.0 Hz), 4.13 (d, 1H, H-20, *J*=8.0 Hz), 3.71 (d, 1H, H-3, *J*=7.3 Hz), 2.44–2.53 (m, 1H, Hα-6, *J*=7.3, 9.7, 14.5 Hz), 2.19 (s, 3H, Me), 2.17 (s, 3H, Me), 2.05 (s, 3H, Me), 1.80–1.88 (m, 1H, Hβ-6), 1.67 (s, 3H, Me), 1.24 (s, 3H, Me), 1.10 (s, 3H, Me), 0.88–0.96 (m, 18H, 3 Me), 0.54–0.78 (m, 12H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 202.1, 170.1, 169.6, 166.9, 153.5, 137.9, 135.1, 133.7,

130.2, 129.7, 128.8, 110.6, 84.4, 81.4, 80.7, 76.5, 76.2, 73.8, 72.3, 58.3, 45.2, 40.9, 37.4, 28.7, 21.9, 21.2, 19.2, 14.0, 10.3, 7.0, 6.9, 5.5, 5.2. Anal. Calcd for $C_{43}H_{64}O_{11}Si_2$: C, 63.51; H, 7.93. Found: C, 63.29; H, 7.84.

4.1.13. 7-TES-13-TIPS-13,14-dehydro-baccatin III (29). Compound **1** (0.57 g, 0.81 mmol) was dissolved in 4:1 THF/DMPU mixture (21.0 mL) and the solution was cooled to −78 °C. ^{t}BuOK (1.0 M in THF, 0.5 mmol) was added and the reaction mixture stirred for 15 min at −70 °C, then TIPSCl (0.06 mL, 0.34 mmol) was added. After 3.0 h the reaction was quenched with saturated NH_4Cl (8.0 mL) and extracted with EtOAc, dried, and the solvent was evaporated. The crude mixture was purified by chromatography (SiO_2, *n*-hexane/EtOAc/Et_2O, 18:6:4) gave the reagent **1** (0.17 g, 0.31 mmol, 31%) and compound **29** (0.38 g, 0.45 mmol, 55%) as a white solid. (**29**): IR (nujol, cm^{-1}): 3483, 1725, 1376, 1239; $[\alpha]_D^{20}$ −21.0 (*c* 0.9, $CHCl_3$); MS (*m*/*z*) ESI: 856 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 8.05–8.10 (m, 2H, arom), 7.57–7.61 (m, 1H, arom), 7.44–7.49 (m, 2H, arom), 6.40 (s, 1H, H-10), 5.77 (d, 1H, H-2, *J*=7.6 Hz), 4.95 (dd, 1H, H-5, *J*=1.2, 9.5 Hz), 4.82 (s, 1H, H-14), 4.47 (dd, 1H, H-7, *J*=6.4, 10.0 Hz), 4.28 (d, 1H, H-20, *J*=8.4 Hz), 4.17 (d, 1H, *J*=8.4 Hz), 3.74 (d, 1H, H-3, *J*=7.6 Hz), 2.45–2.54 (ddd, 1H, Hα-6, *J*=7.6, 9.5, 14.5 Hz), 2.22 (s, 3H, Me), 2.19 (s, 3H, Me), 2.10 (s, 3H, Me), 1.84–1.92 (m, 1H, Hβ-6), 1.70 (s, 3H, Me), 1.25 (s, 3H, Me), 1.15 (s, 3H, Me), 1.05–1.15 (m, 21H), 0.90–0.94 (t, 9H, 2 Me), 0.54–0.72 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 201.7, 170.0, 169.3, 166.7, 153.5, 137.8, 134.8, 133.6, 130.2, 129.7, 128.7, 110.6, 84.4, 81.9, 80.8, 76.5, 76.2, 74.2, 72.4, 58.4, 45.6, 41.0, 37.5, 28.5, 22.3, 21.4, 19.8, 18.5, 18.4, 14.2, 13.0, 10.7, 7.2, 5.7. Anal. Calcd for $C_{46}H_{70}O_{11}Si_2$: C, 64.60; H, 8.25 Found: C, 64.45; H, 8.17.

4.1.14. 7-TES-13-oxo-14 β-azido-baccatin III (4). A solution of 0.21 g (0.27 mmol) of **3** in 5.0 mL of CH_3CN were added 0.08 g of NaN_3 (1.2 mmol) and 0.45 g (0.81 mmol) of CAN under nitrogen stream at 0 °C. The mixture was stirred for 1.0 h, diluted with 7.0 mL of H_2O and extracted with 5.0 mL of Et_2O. The organic phase was dried, the solvent evaporated and the residue was chromatographed (SiO_2, cyclohexane/EtOAc/Et_2O, 8:1:1) giving 0.19 g of compound **4** (0.26 mmol, 95%) as a white solid. In a similar experiment compound **29** (0.07 g, 0.08 mmol) was reacted with 0.06 g of NaN_3 (0.57 mmol) and 0.49 g of CAN (0.9 mmol) to afford compound **4** (0.03 g, 0.04 mmol, 55%).

4.1.15. 7-TES-13-oxo-14β-amino-baccatin III (30). PPh_3 (0.11 g, 0.43 mmol) was added to a solution of 0.29 g (0.39 mmol) of **4** in 11.7 mL of a CH_3CN/H_2O=9:1 mixed solvent. The reaction was cooled at 5 °C, and after 18 h was evaporated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/EtOAc/Et_2O, 1.8:0.7:0.3) afforded 0.24 g (0.34 mmol, 88%) of **30** as a white solid. IR (KBr, cm^{-1}): 3396, 3204, 2956, 2878, 2255, 1728, 1452, 1370, 1105; $[\alpha]_D^{20}$ +18.1 (*c* 0.5, CH_2Cl_2); MS (*m*/*z*) ESI: 715 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.99–8.01 (m, 2H, arom), 7.61–7.66 (m, 1H, arom), 7.43–7.45 (m, 2H, arom), 6.50 (s, 1H, H-10), 5.86 (d, 1H, H-2, *J*=6.8 Hz), 4.89 (dd, 1H, H-5, *J*=2.0, 9.6 Hz), 4.47 (dd, 1H, H-7, *J*=6.4, 10.4 Hz), 4.30 (d, 1H, H-20, *J*=8.8 Hz), 4.24 (d, 1H, H-20, *J*=8.8 Hz), 3.84 (d, 1H, H-3, *J*=6.8 Hz), 3.57 (s, 1H, H-14), 2.52 (ddd, 1H, Hα-6, *J*=6.4, 9.2, 14.0 Hz), 2.21 (s, 3H, Me), 2.19 (s, 3H, Me), 2.12 (s, 3H, Me), 1.90 (ddd, 1H, Hβ-6, *J*=2.0, 11.2, 14.0 Hz), 1.73 (s, 3H, Me), 1.27 (s, 3H, Me), 0.93 (m, 9H, 3 Me), 0.84 (s, 3H, Me), 0.55–0.62 (m, 6H, 3 CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 201.5, 200.2, 169.9, 169.2, 165.4, 151.7, 138.1, 133.7, 129.9, 129.8, 128.9, 84.1, 81.4, 76.4, 75.5, 73.4, 72.9, 72.4, 59.1, 57.9, 45.4, 43.1, 37.3, 33.1, 21.8, 21.0, 19.9, 14.1, 10.1, 6.9, 5.5. Anal. Calcd $C_{37}H_{51}NO_{11}Si$: C, 62.25; H, 7.20; N, 1.96. Found: C, 62.33; H, 7.29; N. 1.90.

4.1.16. 7-BOC-13-oxo-14β-amino-baccatin III (31). PPh_3 (0.09 g, 0.34 mmol) was added to a solution of 0.20 g (0.27 mmol) of **5** in 7.5 mL of a mixture of acetonitrile/water =7:1. After 2 h the reaction mixture was concentrated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/EtOAc, 1.4:1.0) yielded 0.14 g (0.21 mmol, 77%) of **31** as a white solid. IR (KBr, cm^{-1}): 3053, 2960, 1726, 1478, 1434, 1090; $[\alpha]_D^{20}$ +31.7 (*c* 0.4, CH_2Cl_2); MS (*m*/*z*) ESI: 701 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.8–8.15 (m, 2H, arom), 7.58–7.63 (m, 1H, arom), 7.44- 7.50 (m, 2H, arom), 6.55 (s, 1H, H-10), 5.86 (d, 1H, H-2, *J*=6.8 Hz), 5.40 (dd, 1H, H-7, *J*=10.8, 7.0 Hz), 4.94 (dd, 1H, H-5, *J*=2.1, 9.6 Hz), 4.33 (d, 1H, H-20, *J*=8.4 Hz), 4.26 (d, 1H, H-20, *J*=8.4 Hz), 4.01 (d, 1H, H-3, *J*=6.4 Hz), 3.58 (s, 1H, H-14), 2.61 (ddd, 1H, Hα-6, *J*=7.0, 9.6, 14.4 Hz), 2.22 (s, 3H, Me), 2.19 (s, 3H, Me), 2.14 (s, 3H, Me), 1.98 (ddd, 1H, Hβ-6, *J*=2.1, 10.8, 14.4 Hz), 1.84 (s, 3H, Me), 1.48 (s, 9H, 3 Me), 1.25 (s, 3H, Me), 0.89 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 201.2, 200.1, 170.0, 168.0, 165.3, 151.8, 150.5, 138.2, 133.9, 130.0, 129.2, 129.1, 83.6, 82.4, 80.7, 76.9, 75.6, 75.4, 74.6, 72.4, 65.0, 56.2, 45.1, 42.9, 33.7, 33.7, 26.7, 21.9, 20.5, 19.1, 14.4, 10.7. Anal. Calcd $C_{36}H_{45}NO_{13}$: C, 61.79; H, 6.48; N, 2.00. Found: C, 61.86; H, 6.42; N. 2.12.

4.1.17. 7-TES-13-oxo-14β-amino-baccatin III 14,1-carbamate (32). A 1.93 M solution of phosgene in toluene (0.32 mL, 0.62 mmol) and 0.1 mL (1.20 mmol) of pyridine were added under stirring to a solution of 0.44 g (0.62 mmol) of **30** in 6.0 mL of CH_2Cl_2 at −78 °C. After 1 h the reaction mixture was quenched by addition of 10.0 mL of water and extracted with 10.0 mL of CH_2Cl_2; the organic phase was washed with brine, dried, filtered, and evaporated under reduced pressure. Chromatography (SiO_2, *n*-hexane/EtOAc/Et_2O, 1.8:0.7:0.3) gave 0.39 g (0.53 mmol, 86%) of **32** as a white solid. IR (KBr, cm^{-1}): 3342, 2956, 1732, 1452, 1238, 1090; $[\alpha]_D^{20}$ +28.5 (*c* 1.0, CH_2Cl_2); MS (*m*/*z*) ESI: 741 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.96–7.98 (m, 2H, arom), 7.58–7.61 (m, 1H, arom), 7.42–7.45 (m, 2H, arom), 6.48 (s, 1H, H-10), 6.06 (d, 1H, H-2, *J*=6.9 Hz), 6.02 (s, 1H, N-H), 4.90 (dd, 1H, H-5, *J*=1.9, 9.5 Hz), 4.46 (dd, 1H, H-7, *J*=10.7, 6.5 Hz), 4.32 (d, 1H, H-20, *J*=8.8 Hz), 4.23 (d, 1H, H-20, *J*=8.8 Hz), 4.17 (s, 1H, H-14), 3.83 (d, 1H, H-3, *J*=6.9 Hz), 2.52 (ddd, 1H, Hα-6, *J*=6.5, 9.7, 14.0 Hz), 2.22 (s, 3H, Me), 2.20 (s, 3H, Me), 2.15 (s, 3H, Me), 1.92 (ddd, 1H, Hβ-6, *J*=1.9, 10.8, 14.0 Hz), 1.73 (s, 3H, Me), 1.34 (s, 3H, Me), 1.14 (s, 3H, Me), 0.91–0.95 (m, 9H, 3 Me), 0.58–0.62 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 199.3, 195.6, 170.1, 168.9, 164.6, 155.7, 151.1, 138.9, 134.2, 129.9, 129.0,

128.4, 86.2, 84.2, 80.9, 76.3, 74.9, 72.3, 69.7, 59.3, 59.2, 45.4, 42.6, 37.3, 32.9, 22.1, 21.1, 19.8, 14.2, 10.4, 7.2, 5.7. Anal. Calcd $C_{38}H_{49}NO_{12}Si$: C, 61.69; H, 6.68; N, 1.89. Found: C, 61.76; H, 6.75; N, 1.81.

4.1.18. 13α-OH and 13β-OH epimers of 7-TES-14β-amino-baccatin III 14,1-carbamate (13α-33 and 13β-34). Sodium borohydride (0.18 g, 4.5 mmol) was added, under stirring, to a solution of 0.22 g (0.30 mmol) of **32** in 8.0 mL of ethanol at −40 °C. The temperature was raised to −18 °C, then an additional amount of sodium borohydride (0.12 g, 3.0 mmol) was added. After 18 h, the reaction mixture was quenched by addition of 2.0 mL of acetic acid and extracted with 10.0 mL of EtOAc. The organic phase was dried, filtered, and evaporated under reduced pressure. The ^{1}H NMR spectrum of the residue showed the presence of 7-TES-14β-amino-baccatin III 14,1-carbamate as a mixture of epimers 13α-**33** and 13β-**34** in an α/β ratio of 1.6:1. Chromatography (SiO_2, CH_2Cl_2/EtOAc, 1.0:0.9) yielded 0.12 g of 13α-**33** (0.17 mmol, 56%) and 0.08 g of 13β-**34** (0.11 mmol, 35%) as solids. (13α-**33**): IR (KBr, cm^{-1}): 3364, 2955, 1731, 1452, 1372, 1089; $[\alpha]_D^{20}$ +16.2 (*c* 0.7, CH_2Cl_2); MS (*m/z*) ESI: 742 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98–8.01 (m, 2H, arom), 7.58–7.61 (m 1H, arom), 7.41–7.45 (m, 2H, arom), 6.73 (s, 1H, N-H), 6.42 (s, 1H, H-10), 5.98 (d, 1H, H-2, *J*=7.2 Hz), 4.93 (dd, 1H, H-5, *J*=2.0, 9.5 Hz), 4.66 (m, 1H, H-13), 4.44 (dd, 1H, H-7, *J*=7.2, 10.0 Hz), 4.23 (d, 1H, H-20, *J*=8.4 Hz), 4.15 (d, 1H, H-20, *J*=8.4 Hz), 3.98 (d, 1H, H-14, *J*=6.0 Hz), 3.75 (d, 1H, H-3, *J*=7.2 Hz), 3.66 (b, 1H, OH), 2.52 (ddd, 1H, Hα-6, *J*=7.2, 9.5 Hz, 13.5 Hz), 2.19 (s, 3H, Me), 2.17 (s, 3H, Me), 2.15 (s, 3H, Me), 1.88 (ddd, 1H, Hβ-6, *J*=2.0, 10.0, 13.5 Hz), 1.70 (s, 3H, Me), 1.26 (s, 3H, Me), 1.08 (s, 3H, Me), 0.90–0.96 (m, 9H, 3 Me), 0.55–0.59 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.3, 170.3, 169.2, 165.3, 158.2, 143.1, 134.0, 132.5, 129.9, 128.9, 128.8, 88.9, 84.3, 80.7, 75.4, 73.4, 72.3, 71.1, 61.1, 58.9, 46.5, 42.2, 37.4, 30.1, 26.2, 22.6, 22.1, 21.3, 15.1, 10.6, 7.2, 5.7. Anal. Calcd $C_{38}H_{51}NO_{12}Si$: C, 61.52; H, 6.93; N, 1.89. Found: C, 61.38; H, 6.84; N, 1.85. (13β-**34**): IR (KBr, cm^{-1}): 3360, 1734; MS (*m/z*) ESI: 743 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97–8.01 (m, 2H, arom), 7.60–7.64 (m, 1H, arom), 7.44–7.48 (m, 2H, arom), 7.00 (s, 1H, N-H), 6.38 (s, 1H, H-10), 5.98 (d, 1H, H-2, *J*=6.8 Hz), 4.82 (dd, 1H, H-5, *J*=2.4, 8.0 Hz), 4.38 (dd, 1H, H-7, *J*=6.8, 10.4 Hz), 4.25 (m, 1H, H-13), 4.23 (d, 1H, H-20, *J*=8.4 Hz), 4.12 (d, 1H, H-20, *J*=8.4 Hz), 3.98 (d, 1H, H-14, *J*=5.9 Hz), 3.62 (d, 1H, H-3, *J*=6.8 Hz), 2.50 (ddd, 1H, Hα-6, *J*=8.0, 6.8, 13.6 Hz), 2.19 (s, 3H, Me), 2.17 (s, 3H, Me), 1.98 (s, 3H, Me), 1.87 (ddd, 1H, Hβ-6, *J*=2.4, 10.4, 13.6 Hz), 1.68 (s, 3H, Me), 1.30 (s, 3H, Me), 1.28 (s, 3H, Me), 0.89–0.93 (m, 9H, 3 Me), 0.55–0.68 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.7, 169.9, 169.1, 165.1, 158.9, 141.0, 138.1, 134.0, 129.9, 129.0, 128.9, 93.4, 84.3, 81.1, 76.3, 75.5, 72.1, 70.0, 68.2, 59.2, 54.0, 46.1, 41.4, 30.8, 30.1, 22.0, 21.4, 21.2, 20.2, 10.4, 7.2, 5.7. Anal. Calcd $C_{38}H_{51}NO_{12}Si$: C, 61.52; H, 6.93; N, 1.89. Found: C, 61.70; H, 7.01; N, 1.88.

4.1.19. 13α-OH and 13β-OH epimers of 7-TES-14β-azido-baccatin III (13α-37 and 13β-38). Sodium borohydride (0.47 g, 12.5 mmol) was added at −40 °C to a solution of 0.46 g (0.62 mmol) of **4** in 0.7 mL of THF and 12.0 mL of EtOH under stirring. The temperature was raised to −30 °C. After 4 days, at −30 °C, the reaction was quenched by addition of 2.0 mL of acetic acid and extracted three times with 15.0 mL of EtOAc. The organic phase was dried, filtered and evaporated under reduced pressure. ^{1}H NMR spectrum of the residue showed the presence of 7-TES-14β-azido-baccatin III (13α-**37**) and its 13β epimer (13β-**38**) in an α/β =91:9 ratio. Chromatography (SiO_2, *n*-hexane/EtOAc, 2.1:1.0) afforded 0.35 g of 13α-**37** (0.47 mmol, 76%) and 0.04 g of 13β-**38** (0.06 mmol, 9%) as white solids. (13α-**37**): IR (KBr, cm^{-1}): 3493, 2956, 2881, 2112, 1728, 1371, 1233; $[\alpha]_D^{20}$ +20.0 (*c* 0.8, CH_2Cl_2); MS (*m/z*) ESI: 743 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07–8.1 (m, 2H, arom), 7.58–7.62 (m, 1H, arom), 7.44–7.50 (m, 2H, arom), 6.41 (s, 1H, H-10), 5.82 (d, 1H, H-2, *J*=7.1 Hz), 4.97 (dd, 1H, H-5, *J*=1.9, 9.5 Hz), 4.80 (m, 1H, H-13), 4.46 (dd, 1H, H-7, *J*=6.5, 10.4 Hz), 4.33 (d, 1H, H-20, *J*=8.4 Hz), 4.23 (d, 1H, H-20, *J*=8.4 Hz), 3.98 (d, 1H, H-14, *J*=7.3 Hz), 3.82 (d, 1H, H-3, *J*=7.1 Hz), 3.00 (s, 1H, OH), 2.82 (b, 1H, OH), 2.53 (ddd, 1H, Hα-6, *J*=6.5, 9.5, 14.2 Hz), 2.34 (s, 3H, Me), 2.20 (s, 3H, Me), 2.18 (s, 3H, Me), 1.90 (ddd, 1H, Hβ-6, *J*=1.9 Hz, 10.7, 14.2 Hz), 1.71 (s, 3H, Me), 1.24 (s, 3H, Me), 0.98 (s, 3H, Me), 0.90–0.96 (m, 9H, 3 Me), 0.55–0.60 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.4, 170.4, 169.4, 165.8, 140.9, 134.3, 133.8, 130.1, 129.4, 128.8, 84.3, 81.3, 76.9, 76.6, 75.7, 75.4, 74.6, 72.5, 68.8, 59.0, 46.8, 43.3, 37.5, 30.1, 26.6, 22.8, 22.1, 21.3, 15.2, 10.4, 7.2, 5.7. Anal. Calcd $C_{37}H_{51}N_3O_{11}Si$: C, 59.90; H, 6.93; N, 5.66. Found: C, 60.11; H, 6.89; N, 5.70. Compound 13β-**38**: MS (*m/z*) ESI: 743 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01–8.17 (m, 2H, arom), 7.52–7.58 (m 1H, arom), 7.42–7.48 (m, 2H, arom), 6.51 (s, 1H, H-10), 5.88 (d, 1H, H-2, *J*=6.8 Hz), 4.95 (dd, 1H, H-5, *J*=2.2, 9.6 Hz), 4.70 (m, 1H, H-13), 4.48 (dd, 1H, H-7, *J*=7.1, 9.9 Hz), 4.33 (d, 1H, H-20, *J*=8.4 Hz), 4.25 (d, 1H, H-20, *J*=8.4 Hz), 3.90 (d, 1H, H-14, *J*=7.4 Hz), 3.78 (d, 1H, H-3, *J*=6.8 Hz), 2.52 (ddd, 1H, Hα-6, *J*=9.6, 7.1, 14.1 Hz), 2.30 (s, 3H, Me), 2.22 (s, 3H, Me), 2.12 (s, 3H, Me), 1.92 (ddd, 1H, Hβ-6, *J*=2.2, 9.9, 14.1 Hz), 1.72 (s, 3H, Me), 1.30 (s, 3H, Me), 1.26 (s, 3H, Me), 0.88–0.92 (m, 9H, 3 Me), 0.55–0.60 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.8, 170.0, 169.3, 165.6, 138.9, 138.3, 135.8, 131.5, 129.4, 128.8, 84.3, 81.0, 76.9, 76.6, 76.3, 75.1, 74.3, 71.2, 69.4, 59.4, 54.5, 47.2, 40.5, 30.5, 30.0, 22.2, 21.6, 21.2, 20.2, 10.2, 7.2, 5.7. Anal. Calcd $C_{37}H_{51}N_3O_{11}Si$: C, 59.90; H, 6.93; N, 5.66. Found: C, 60.21; H, 6.99; N, 5.60.

4.1.20. 7-TES-13-[*N*-BOC-*N*,*O*-(2,4-dimethoxybenzyl-idene)-β-isobutylisoserinoyl]-14β-azido-baccatin III (39). A solution of 0.45 g (1.12 mmol) of **35** in 5.0 mL of toluene, cooled to 0 °C, was added under nitrogen stream and stirring, with 0.50 g (0.67 mmol) of α-**37**, 0.23 g (1.12 mmol) of DCC, 0.90 g (0.08 mmol) of DMAP, and 0.02 g (0.12 mmol) of *p*-toluenesulfonic acid (PTSA). After 1 h at 70 °C the reaction mixture was cooled and filtered. The solid was extracted with CH_2Cl_2, and the organic phase was evaporated under reduced pressure. Chromatography of the crude mixture (SiO_2, *n*-hexane/EtOAc, 2.2:1.0) afforded 0.63 g (0.54 mmol, 80%) of **39** as a white solid. IR (KBr, cm^{-1}): 3491, 2957, 2111, 1731, 1614, 1508, 1368; $[\alpha]_D^{20}$ +1.8 (*c* 0.7, CH_2Cl_2); MS (*m/z*) ESI: 1134 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07–8.1 (m, 2H, arom), 7.58–7.62 (m, 1H, arom), 7.42–7.50 (m, 1H, arom), 7.22–7.28 (m,

1H, arom), 6.40–6.52 (m, 4H, 2H arom, H-10, N–C*H*–O), 6.25 (d, 1H, H-13, $J=8.8$ Hz), 5.88 (d, 1H, H-2, $J=7.6$ Hz), 4.94 (dd, 1H, H-5, $J=1.5$, 9.7 Hz), 4.45–4.62 (m, 3H, H-7, H′-3, H′-2), 4.32 (d, 1H, H-20, $J=8.0$ Hz), 4.24 (d, 1H, H-20, $J=8.0$ Hz), 4.04 (d, 1H, H-14, $J=8.8$ Hz), 3.87 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.83 (d, 1H, H-3, $J=7.6$ Hz), 2.52 (ddd, 1H, Hα-6, $J=6.8$, 9.6, 14.0 Hz), 2.33 (s, 3H, Me), 2.19 (s, 3H, Me), 2.11 (s, 3H, Me), 1.91 (ddd, 1H, Hβ-6, $J=1.5$, 11.2, 14.0 Hz), 1.72–1.82 (m, 2H, H′-4, H′-5), 1.71 (s, 3H, Me), 1.54–1.64 (m, 1H, H′-4), 1.27 (s, 3H, Me), 1.22–1.40 (s, 9H, 3 Me), 1.16 (s, 3H, Me), 1.06 (d, 6H, 2 Me, $J=6.0$ Hz), 0.90–0.98 (m, 9H, 3 Me), 0.58–0.4 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.2, 170.7, 170.1, 169.4, 165.9, 161.8, 159.3, 153.5, 137.1, 135.8, 134.0, 130.2, 130.1, 129.4, 128.9, 104.4, 101.5, 91.8, 86.5, 84.3, 81.2, 80.5, 76.6, 76.4, 74.8, 74.7, 72.3, 65.5, 58.7, 58.1, 55.6, 55.5, 46.4, 43.8, 43.5, 37.3, 28.4, 28.3, 26.6, 25.8, 23.2, 22.9, 22.6, 22.2, 21.0, 14.4, 10.3, 6.9, 5.5. Anal. Calcd $C_{58}H_{80}N_4O_{17}Si$: C, 61.47; H, 7.11; N, 4.94. Found: C, 61.60; H, 7.17; N, 5.05.

4.1.21. 7-TES-13-[*N*-BOC-*N*,*O*-(2,4-dimethoxy-benzylidene)-β-isobutylisoserinoyl]-14β-amino-baccatin III (40). A solution of 0.25 g (0.23 mmol) of **39** in 9.0 mL of MeOH was reduced under balloon pressure of H_2 in the presence of 10% Pd/C (0.05 g). After 18 h at room temperature, the reaction mixture was filtered through celite bed, and the solid was washed with 25.0 mL of EtOAc. The organic phase was heated to 45 °C for 20 min and subsequently evaporated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/EtOAc/CH_2Cl_2, 0.7:0.3:1.0) yielded 0.22 g (0.20 mmol, 90%) of **40** as a white solid. IR (KBr, cm^{-1}): 3449, 2957, 1726, 1617, 1368, 1237, 1105; $[\alpha]_D^{20}$ −39.6 (*c* 0.5, CH_2Cl_2); MS (*m*/*z*) ESI: 1108 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00–8.02 (m, 2H, arom), 7.54–7.60 (m, 1H, arom), 7.42–7.45 (m, 2H, arom), 7.22–7.28 (m, 1H, arom), 6.45–6.59 (m, 4H, 2H arom, H-10, N–C*H*–O), 6.06 (m, 1H, H-13), 5.85 (d, 1H, H-2, $J=7.2$ Hz), 4.93 (d, 1H, H-5, $J=2.0$, 10.5 Hz), 4.46–4.60 (m, 3H, H-7, H′-3, H′-2), 4.20–4.28 (m, 2H, H-20), 3.88 (s, 3H, OMe), 3.80–3.84 (m, 4H, OMe, H-3), 3.35 (d, 1H, H-14, $J=8.8$ Hz), 2.51 (ddd, 1H, Hα-6, $J=6.4$, 10.4, 14.4 Hz), 2.30 (s, 3H, Me), 2.18 (s, 3H, Me), 2.12 (s, 3H, Me), 1.91 (ddd, 1H, Hβ-6, $J=2.0$, 10.5, 13.5 Hz), 1.74–1.84 (m, 1H, H′-5), 1.72 (s, 3H, Me), 1.54–1.64 (m, 2H, H′-4), 1.20–1.40 (s, 9H, 3 Me), 1.11 (s, 3H, Me), 1.09 (d, 3H, Me, $J=6.0$ Hz), 1.06 (d, 3H, Me, $J=6.0$ Hz), 0.90–0.97 (m, 9H, 3 Me), 0.54–0.62 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.4, 172.4, 169.9, 169.5, 165.6, 161.8, 159.3, 153.5, 136.9, 136.0, 133.5, 130.1, 129.9, 128.9, 128.8, 128.5, 104.4, 98.6, 84.2, 81.3, 81.1, 80.1, 78.8, 76.4, 75.2, 75.1, 75.0, 72.3, 58.8, 58.5, 55.6, 54.1, 46.1, 43.8, 43.4, 37.4, 28.3, 28.1, 26.5, 25.7, 23.4, 23.1, 22.6, 22.3, 21.0, 14.7, 10.4, 7.0, 5.5. Anal. Calcd $C_{58}H_{82}N_2O_{17}Si$: C, 62.91; H, 7.46; N, 2.53. Found: C, 63.03; H, 7.35; N, 2.62.

4.1.22. 7-TES-13-[*N*-BOC-*N*,*O*-(2,4-dimethoxybenzylidene)-β-isobutylisoserinoyl]-14β-amino-baccatin III 14,1-thiocarbamate (41). A solution of 0.17 g (0.15 mmol) of **40** in 7.0 mL of CH_3CN was added, at 20 °C, with 0.14 g (0.61 mmol) of di-2-pyridyl-thionocarbonate. After 2 h, the reaction mixture was quenched by addition of 4.0 mL of water and extracted with CH_2Cl_2. The organic phase was dried, filtered, and evaporated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/EtOAc/CH_2Cl_2, 1.4:1.0:2.0) afforded 0.13 g (0.11 mmol, 73%) of **41** as a white solid. IR (KBr, cm^{-1}): 3446, 2958, 1732, 1694, 1595, 1278, 1167; $[\alpha]_D^{20}$ −21.3 (*c* 0.9, CH_2Cl_2); MS (*m*/*z*) ESI: 1150 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C) δ 8.54–8.68 (b, 1H, *H*NCS), 7.96–7.98 (m, 2H, arom), 7.54–7.57 (m, 1H, arom), 7.37–7.41 (m, 2H, arom), 7.19 (m, 1H, arom), 6.42–6.54 (m, 4H, 2H arom, H-10, N–C*H*–O), 6.03–6.13 (m, 2H, H-13, H-2), 4.90 (dd, 1H, H-5, $J=1.5$, 9.7 Hz), 4.53–4.62 (m, 2H, H′-2, H′-3), 4.49 (dd, 1H, H-7, $J=6.6$, 10.5 Hz), 4.23–4.29 (m, 3H, H-14, H-20, H-20), 3.87 (s, 3H, Me), 3.82 (s, 3H, Me), 3.76 (d, 1H, H-3, $J=7.4$ Hz), 2.51 (ddd, 1H, Hα-6, $J=6.6$, 9.7, 14.3 Hz), 2.23 (s, 3H, Me), 2.19 (s, 3H, Me), 2.13 (s, 3H, Me), 1.86–1.94 (ddd, 1H, Hβ-6, $J=1.5$, 10.5, 14.3 Hz), 1.75–1.88 (m, 2H, H′-4, H′-5), 1.73 (s, 3H, Me), 1.50–1.60 (m, 1H, H′-4), 1.36 (s, 3H, Me), 1.20–1.40 (s, 9H, 3 Me), 1.27 (s, 3H, Me), 1.09 (d, 3H, Me, $J=6.0$ Hz), 1.05 (d, 3H, Me, $J=6.0$ Hz), 0.88–0.98 (m, 9H, 3 Me), 0.55–0.60 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.4, 187.5, 171.5, 169.9, 169.2, 164.8, 161.6, 159.0, 137.9, 134.7, 133.8, 129.9, 129.1, 128.8, 127.9, 118.9, 104.3, 98.6, 95.8, 87.0, 84.2, 81.6, 80.7, 80.3, 76.3, 76.0, 74.6, 72.1, 70.6, 62.8, 58.8, 55.7, 55.6, 46.4, 43.8, 42.7, 37.5, 30.8, 28.5, 26.3, 25.8, 23.3, 22.8, 22.6, 22.3, 21.2, 15.0, 10.7, 7.2, 5.7. Anal. Calcd $C_{59}H_{80}N_2O_{17}SSi$: C, 61.65; H, 7.02; N, 2.44. Found: C, 61.52; H, 7.10; N, 2.53.

4.1.23. 7-TES-13-[N-BOC-N,O-(2,4-dimethoxybenzylidene)-β-isobutylisoserinoyl]-14β-amino-baccatin III 14,1-carbamate (36). *Procedure A*. A solution of 0.12 g (0.30 mmol) of the acid **35** in 6.0 mL of toluene, cooled at 0 °C, was added with 0.10 g (0.14 mmol) of 13α-**33**, 0.06 g (0.30 mmol) of DCC, 0.02 g (0.15 mmol) of DMAP, and 0.005 g (0.03 mmol) of PTSA, under stirring and nitrogen stream. After 2 h at 70 °C, an additional amount of 0.04 g (0.11 mmol) of **36** and 0.02 g (0.11 mmol) of DCC were added. After 3 h, the reaction was cooled and filtered. The solid was washed with CH_2Cl_2, and the organic phase was concentrated under reduced pressure. Chromatography of the reaction mixture (SiO_2, *n*-hexane/EtOAc/CH_2Cl_2, 1.0:0.6:0.6) yielded 0.13 g (0.11 mmol, 80%) of **36** as a white solid. *Procedure B*. A 1.93 M solution of phosgene in toluene (0.50 mL, 0.81 mmol) and 0.1 mL (1.29 mmol) of pyridine were added to a solution of 0.36 g (0.32 mmol) of **40** in 9.0 mL of CH_2Cl_2 at 0 °C under stirring. After 12 h at room temperature the reaction mixture was quenched by addition of 10.0 mL of water and extracted with 10.0 mL of CH_2Cl_2. The organic phase was washed with brine, dried, filtered, and evaporated under reduced pressure. Chromatography (SiO_2, n-hexane/EtOAc/CH_2Cl_2, 0.7:0.3:1.0) gave 0.27 g (0.24 mmol, 74%) of **36** as a white solid. IR (KBr, cm^{-1}): 3435, 2956, 1735, 1454, 1369, 1235; $[\alpha]_D^{20}$ −38.7 (*c* 0.7, CH_2Cl_2); MS (*m*/*z*) ESI: 1134 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98–7.99 (m, 2H, arom), 7.56–7.60 (m, 1H, arom), 7.40–7.44 (m, 2H, arom), 7.18–7.22 (m, 1H, arom), 6.40–6.50 (m, 5H, 2H arom, H-10, N–C*H*–O, *H*NC═O), 6.00–6.08 (m, 2H, H-2, H-13), 4.90 (dd, 1H, H-5, $J=2.0$, 10.4 Hz), 4.53–4.62 (m, 2H, H′-2, H′-3), 4.49 (dd, 1H, H-7, $J=6.6$, 10.5 Hz), 4.26 (d, 1H, H-20, $J=7.6$ Hz), 4.22 (d, 1H, H-20, $J=7.6$ Hz), 4.08–4.14 (m, 1H, H-14), 3.88 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.76 (d, 1H,

H-3, J=7.2 Hz), 2.52 (ddd, 1H, Hα-6, J=6.6, 10.4, 14.4 Hz), 2.26 (s, 3H, Me), 2.19 (s, 3H, Me), 2.10–2.18 (s, 3H, Me), 1.91 (ddd, 1H, Hβ-6, J=2.0, 10.5, 14.4 Hz), 1.78–1.83 (m, 2H, H′-4, H′-5), 1.75 (s, 3H, Me), 1.60–1.64 (m, 1H, H′-4), 1.34 (s, 3H, Me), 1.22–1.38 (m, 9H, 3 Me), 1.26 (s, 3H, Me), 1.09 (d, 3H, Me, J=6.0 Hz), 1.06 (d, 3H, Me, J=6.0 Hz), 0.90–0.96 (m, 9H, 3 Me), 0.55–0.62 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.5, 173.5, 171.2, 169.6, 164.9, 156.4, 140.1, 134.1, 134.0, 130.0, 128.9, 128.7, 87.5, 84.4, 81.7, 81.2, 78.1, 76.4, 75.3, 73.0, 72.1, 71.2, 58.8, 57.8, 51.8, 44.9, 42.5, 41.8, 35.8, 30.1, 28.7, 26.3, 25.0, 23.8, 23.4, 21.8, 21.2, 15.4, 10.2. Anal. Calcd $C_{59}H_{80}N_2O_{18}Si$: C, 62.53; H, 7.11; N, 2.47. Found: C, 62.70; H, 7.15; N, 2.38.

4.1.24. 7-TES-13-[*N*-BOC-*N*,*O*-(2,4-dimethoxybenzylidene)-β-isobutylisoserinoyl]-14β-*t*-butoxy-carbamoylbaccatin III 14,1-carbamate (42). A solution of 0.11 g (0.10 mmol) of **40** in 3.0 mL of CH_2Cl_2 was added with 0.04 g (0.20 mmol) of BOC_2O, 0.03 mL (0.21 mmol) of Et_3N and 0.01 g (0.05 mmol) of DMAP, at 20 °C. After 3 h the reaction was quenched by addition of 4.0 mL of a NH_4Cl aqueous saturated solution and extracted with 6.0 mL of CH_2Cl_2. The organic phase was dried, filtered, and evaporated under reduced pressure. Chromatography (SiO_2, *n*-hexane/EtOAc/CH_2Cl_2, 8.0:3.0:5.0) gave 0.09 g (0.06 mmol, 69%) of **42** as a white solid. IR (KBr, cm^{-1}): 3450, 2961, 1803, 1733, 1370, 1239, 1089; MS (*m*/*z*) ESI: 1234 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92–7.98 (m, 2H, arom), 7.51–7.58 (m, 1H, arom), 7.32–7.42 (m, 2H, arom), 6.47–6.51 (m, 3H, 2H arom, N–C*H*–O), 6.40–6.44 (m, 1H, H-13), 6.36 (s, 1H, H-10), 6.01 (d, 1H, H-2, J=7.2 Hz), 4.93 (dd, 1H, H-5 J=2.2, 10.0 Hz), 4.76 (d, 1H, J=7.2 Hz, *H*NBOC), 4.56 (dd, 1H, H-7, J=6.4, 10.2 Hz), 4.48–4.60 (m, 2H, H′-2, H′-3), 4.24 (d, 1H, H-20), 4.18 (d, 1H, H-20, J=8.0 Hz), 3.88 (s, 3H, OMe), 3.85 (d, 1H, H-3, J=7.2 Hz), 3.82 (s, 3H, OMe), 2.52 (ddd, 1H, Hα-6, J=6.4, 10.0, 14.8 Hz), 2.46 (s, 3H, Me), 2.23 (s, 3H, Me), 2.19 (s, 3H, Me), 1.90 (ddd, 1H, Hβ-6, J=2.2, 10.2, 14.5 Hz), 1.72 (s, 3H, Me), 1.64–1.70 (m, 1H, H′-5), 1.38–1.50 (m, 2H, H′-4), 1.37 (s, 9H), 1.35 (s, 3H, Me) 1.28 (s, 3H, Me), 1.12–1.16 (m, 6H, 2 Me), 0.92–0.96 (m, 9H, 3 Me), 0.56–0.63 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) relevant resonances at δ 200.7, 171.0, 170.5 (b), 169.2 (b), 164.6, 161.6, 159.2, 151.2, 150.4, 148.0 (b), 139.5, 134.2, 133.9, 129.9, 129.0, 128.5, 127.4 (b), 117.8 (b), 104.5, 86.5, 85.5 (b), 84.8, (b), 84.4, 80.7 (b), 80.2, 76.2, 74.7, 74.1, 72.1, 71.3, 59.8, 58.7, 57.8 (b), 55.7, 55.5, 46.3, 43.7, 42.1, 37.4, 30.1 (b), 28.6 (b), 28.1, 26.7, 26.1 (CH), 23.7, 23.0, 22.4, 22.2, 21.2, 15.5, 10.7, 7.2, 5.7. Anal. Calcd $C_{64}H_{88}N_2O_{20}Si$: C, 62.32; H, 7.19; N, 2.27. Found: C, 62.41; H, 7.16; N, 2.34.

4.1.25. 13-(N-BOC-β-isobutylisoserinoyl)-14β-azidobaccatin III (44). Hydrofluoric acid-pyridine (1.6 mL, 0.1 mL/10 mg of substrate) was added, at 0 °C, to a solution of 0.16 g (0.14 mmol) of **39** in 4.0 mL of acetonitrile and 4 mL of pyridine. After half an hour, the temperature was raised to 25 °C. After 3 h the reaction was quenched by addition of 8.0 mL of a NH_4Cl saturated solution and extracted with EtOAc. The organic phase was washed with an aqueous saturated solution of $CuSO_4$, dried, filtered, and evaporated under reduced pressure. The residue was dissolved in 3.0 mL of CH_2Cl_2 and added at 0 °C to 1.4 mL of a 0.1 M solution of acetyl chloride in MeOH. After 3 h the reaction was quenched by addition of 6.0 mL of a NH_4Cl aqueous saturated solution. The organic phase was dried, filtered, and evaporated under reduced pressure. Chromatography (SiO_2, *n*-hexane/EtOAc, 1.0:1.2) yielded 0.08 g (0.10 mmol, 70%) of **44** as a white solid. IR (KBr, cm^{-1}): 3492, 2960, 2111, 1730, 1614, 1369, 1237, 1070; $[\alpha]_D^{20}$ −27.7 (*c* 0.5, CH_2Cl_2); MS (*m*/*z*) ESI: 872 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07–8.1 (m, 2H, arom), 7.58–7.62 (m, 1H, arom), 7.44–7.50 (m, 2H, arom), 6.28 (s, 1H, H-10), 6.07 (d, 1H, H-13, J=8.8 Hz), 5.88 (d, 1H, H-2, J=7.1 Hz), 4.98 (m, 1H, H-5, J=2.3, 9.6 Hz), 4.72 (d, 1H, *H*NBOC, J=9.6 Hz), 4.39 (dd, 1H, H-7, J=6.6, 10.7 Hz), 4.35 (d, 1H, H-20, J=8.8 Hz), 4.26 (m, 2H, H-20, H′-2), 4.08–4.12 (m, 1H, H′-3), 4.04 (d, 1H, H-14, J=8.8 Hz), 3.76 (d, 1H, H-3, J=7.1 Hz), 2.57 (ddd, 1H, Hα-6, J=6.6, 9.6, 14.9 Hz), 2.43 (s, 3H, Me), 2.24 (s, 3H, Me), 1.91 (ddd, 1H, Hβ-6, J=2.3, 10.7, 14.8 Hz), 1.88 (s, 3H, Me), 1.71 (s, 3H, Me), 1.62–1.76 (m, 3H, H-5′, 2H-4′), 1.41 (s, 9H, 3 Me), 1.21 (s, 3H, Me), 1.20 (s, 3H, Me), 0.99 (d, 3H, Me, J=6.0 Hz), 0.97 (d, 3H, Me, J=6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.9, 173.4, 171.1, 170.0, 165.7, 156.2, 139.1, 134.9, 133.9, 130.1, 129.1, 128.9, 84.5, 81.6, 80.5, 77.6, 77.2, 76.5, 75.5, 74.8, 74.1, 72.3, 65.5, 59.0, 52.0, 45.3, 43.5, 40.8, 35.9, 28.6, 27.1, 25.1, 23.6, 22.7, 22.3, 21.3, 15.3, 10.0. Anal. Calcd $C_{43}H_{58}N_4O_{15}$: C, 59.30; H, 6.71; N, 6.43. Found: C, 59.36; H, 6.62, N, 6.34.

4.1.26. 13-(*N*-BOC-β-isobutylisoserinoyl)-14β-aminobaccatin III (45). Hydrofluoric acid-pyridine (2.2 mL, 0.1 mL/10 mg of substrate) was added, at 0 °C, to a solution of 0.22 g (0.18 mmol) of **40** in 5.4 mL of acetonitrile and 5.4 mL of pyridine. After 30 min the temperature was raised to 25 °C. After 3 h, the reaction was quenched by addition of 12.0 mL of a NH_4Cl aqueous saturated solution and extracted with 16.0 mL of EtOAc. The organic phase was washed three times with a $CuSO_4$ aqueous saturated solution, dried, filtered, and evaporated under reduced pressure. The residue was dissolved in 7.0 mL of CH_2Cl_2, and added, at 0 °C, to 2.3 mL of a 0.1 M acetyl chloride solution in MeOH. After 3 h, the reaction was quenched by addition of 10.0 mL of a NH_4Cl aqueous saturated solution and extracted with 16.0 mL of EtOAc. The organic phases was dried, filtered, and evaporated under reduced pressure. Chromatography (SiO_2, *n*-hexane/EtOAc, 1.0:1.2) yielded 0.10 g (0.12 mmol, 70%) of **45** as a white solid. IR (KBr, cm^{-1}): 3428, 2957, 1729, 1615, 1360, 1237; $[\alpha]_D^{20}$ −39.4 (*c* 0.8, CH_2Cl_2); MS (*m*/*z*) ESI: 846 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.0–8.06 (d, 2H, arom); 7.52–7.61 (m, 1H, arom), 7.42–7.46 (m, 2H, arom), 6.27 (s, 1H, H-10), 5.90 (dd, 1H, H-13, J=1.2, 9.2 Hz), 5.81 (d, 1H, H-2, J=7.6 Hz), 4.92–4.96 (dd, 1H, H-5, J=2.5, 9.6 Hz), 4.70 (d, 1H, *H*NBOC, J=9.6 Hz), 4.39–4.43 (m, 1H, H-7), 4.18–4.33 (m, 4H, H-2′, H-3′, H-20, H-20), 3.74 (d, 1H, H-3, J=7.2 Hz), 3.35 (d, 1H, H-14, J=9.2 Hz), 2.55 (m, 1H, Hα-6, J=6.4, 9.6, 14.8 Hz), 2.39 (s, 3H, Me), 2.24 (s, 3H, Me), 1.84–1.94 (m, 1H, Hβ-6, J=2.5, 11.2, 14.8 Hz), 1.88 (m, 3H, Me), 1.62–1.80 (m, 3H, 2H′-4, H-5′), 1.71 (s, 3H, Me), 1.32 (s, 9H, 3 Me), 1.19 (s, 3H, Me), 1.14 (s, 3H, Me), 1.01 (d, 3H, Me, J=6.0 Hz), 0.98 (d, 3H, Me, J=6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.3, 174.4, 171.4, 169.8, 165.6, 156.1, 138.8, 135.0, 133.4, 130.0, 129.8, 128.8, 84.5,

81.5, 80.6, 76.6, 75.7, 75.3, 75.1, 72.9, 72.3, 58.7, 53.5, 51.4, 45.0, 43.3, 42.2, 35.8, 28.6, 26.9, 25.1, 24.4, 23.7, 23.0, 22.3, 21.3, 15.3, 10.1. Anal. Calcd $C_{43}H_{60}N_2O_{15}$: C, 61.12; H, 7.16; N, 3.32. Found: C, 61.33; H, 7.09; N, 3.24.

4.1.27. 13-(*N*-BOC-β-isobutylisoserinoyl)-14β-amino-baccatin III 14,1-thiocarbamate (46). Hydrofluoric acid-pyridine (1.7 mL, 0.1 mL/10 mg of substrate) was added, at 0 °C, to a solution of 0.17 g (0.15 mmol) of **41** in 4.0 mL of acetonitrile and 4.0 mL of pyridine. After 30 min the temperature was raised to 25 °C. After 3 h, the reaction was quenched by addition of 12.0 mL of a NH_4Cl aqueous saturated solution and extracted with 16.0 mL of EtOAc. The organic phase was washed with aqueous saturated $CuSO_4$, dried, filtered, and evaporated under reduced pressure. The residue was dissolved in 6.0 mL of CH_2Cl_2 and chilled at 0 °C. A 0.1 M solution of acetyl chloride in MeOH (1.2 mL) was added. The reaction was quenched after 3 h by addition of 12.0 mL of saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was dried, filtered, and evaporated under reduced pressure. Chromatography of the residue (SiO_2, EtOAc/*n*-hexane, 1.4:1) gave 0.09 g (0.01 mmol, 67%) of **46** as a white solid. IR (KBr, cm^{-1}): 3343, 2960, 1733, 1686, 1595, 1239, 1088, 733; $[\alpha]_D^{20}$ −4.7 (*c* 0.4, CH_2Cl_2); MS (*m*/*z*) ESI: 888 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.34 (s, 1H, *H*NCS), 7.99–8.01 (m, 2H, arom), 7.49–7.52 (m, 1H, arom), 7.40–7.45 (m, 2H, arom), 6.26 (s, 1H, H-10), 6.09–6.14 (m, 2H, H-2, H-13), 4.94 (dd, 1H, H-5, *J*=2.5, 9.7 Hz), 4.78 (d, 1H, *H*NBOC, *J*=9.2 Hz), 4.34–4.40 (m, 2H, H-7, H-14), 4.28–4.32 (m, 2H, H-20, H′-20), 4.10–4.18 (m, 2H, H-3′, H-2′), 3.72 (d, 1H, H-3, *J*=7.5 Hz), 2.48 (m, 1H, Hα-6, *J*=6.6, 9.7, 14.5 Hz), 2.31 (s, 3H, Me), 2.24 (s, 3H, Me), 1.90 (m, 3H, Hβ-6, *J*=2.5, 10.8, 14.5 Hz), 1.86 (s, 3H, Me), 1.70–1.85 (m, 3H, 2H′-4, H′-5), 1.73 (s, 3H, Me), 1.41 (s, 9H, 3 Me), 1.29 (s, 6H, 2 Me), 1.02 (d, 3H, Me, *J*=6.0 Hz), 0.98 (d, 3H, Me, *J*=6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.3, 173.5, 171.0, 169.5, 164.8, 156.2, 139.9, 134.1, 133.9, 130.0, 129.8, 128.8, 94.8, 84.4, 82.1, 81.6, 81.2, 76.7, 76.4, 75.3, 72.8, 72.0, 70.7, 62.0, 58.9, 52.0, 45.3, 42.7, 41.6, 35.9, 28.7, 26.2, 25.0, 23.7, 23.1, 21.9, 21.2, 15.3, 10.2. Anal. Calcd $C_{44}H_{58}N_2O_{15}S$: C, 59.58; H, 6.59; N, 3.16. Found: C, 59.40; H, 6.64; N, 3.22.

4.1.28. 13-*N*-BOC-β-isobutylisoserinoyl-14β-amino-baccatin III 14,1-carbamate (43). Hydrofluoric acid-pyridine (1.1 mL, 0.1 mL/10 mg of substrate) was added, at 0 °C, to a solution of 0.11 g (0.10 mmol) of **36** in 2.7 mL of acetonitrile and 2.7 mL of pyridine. After 30 min the temperature was raised to 25 °C. After 3 h, the reaction was quenched by addition of 6.0 mL of a NH_4Cl aqueous saturated solution and extracted with 16.0 mL of EtOAc. The organic phase was washed three times with a $CuSO_4$ aqueous saturated solution, dried, filtered, and evaporated under reduced pressure. The residue was dissolved in 3.5 mL of CH_2Cl_2, and then, at 0 °C, added with 1.15 mL of a 0.1 M acetyl chloride solution in MeOH. After 3 h, the reaction was quenched by addition of 5.0 mL of a NH_4Cl aqueous saturated solution and extracted with 8.0 mL of EtOAc. The organic phase was dried, filtered, and evaporated under reduced pressure. Chromatography (SiO_2, *n*-hexane/EtOAc/Et_2O 1:0.7:0.3) afforded 0.06 g (0.06 mmol, 66%) of **43** as a white solid. IR (KBr, cm^{-1}): 3420, 2089, 1742, 1636, 1370, 1093; $[\alpha]_D^{20}$ −53.4 (*c* 0.7, CH_2Cl_2); MS (*m*/*z*) ESI: 872 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02–8.1 (m, 2H, arom), 7.54–7.58 (m, 1H, arom), 7.54 (d, 1H, *H*NCO, *J*=8.6 Hz), 7.42–7.45 (m, 2H, arom), 6.26 (s, 1H, H-10), 6.11 (dd, 1H, H-13, *J*=1.5, 6.8 Hz), 6.02 (d, 1H, H-2, *J*=7.2 Hz), 4.94 (dd, 1H, H-5, *J*=2.6, 9.8 Hz), 4.73 (d, 1H, *H*NBOC, *J*=9.6 Hz), 4.36–4.39 (m, 1H, H-7), 4.24–4.32 (m, 2H, H-20, H′-20), 4.15–4.22 (m, 3H, H-14, H-2′, H-3′), 3.76 (d, 1H, H-3, *J*=7.2 Hz), 2.55 (ddd, 1H, Hα-6, *J*=6.5, 9.8, 14.5 Hz), 2.33 (s, 3H, Me), 2.25 (s, 3H, Me), 1.86–1.96 (ddd, 1H, Hβ-6, *J*=2.5, 11.0, 14.5 Hz), 1.86 (s, 3H, Me), 1.78–1.84 (m, 1H, H′-5), 1.73 (s, 3H, Me), 1.66–1.76 (m, 1H, H′-4), 1.37 (s, 9H, 3 Me), 1.31 (s, 3H, Me), 1.20–1.40 (m, 9H, 3 Me), 1.25 (s, 3H, Me), 1.25–1.30 (m, 1H, H′-4), 1.01 (d, 3H, 1 Me, *J*=6.5 Hz), 0.98 (d, 3H, 1 Me, *J*=6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.5, 173.5, 171.2, 169.6, 164.9, 156.4, 140.1, 134.1, 134.0, 130.0, 128.9, 128.7, 87.5, 84.4, 81.7, 81.2, 78.1, 76.4, 75.3, 73. 0, 72.1, 71.2, 58.8, 57.8, 51.8, 44.9, 42.5, 41.8, 35.8, 30.1, 28.7, 26.3, 25.0, 23.8, 23.4, 21.8, 21.2, 15.4, 10.2. Anal. Calcd $C_{44}H_{58}N_2O_{16}$: C, 60.68; H, 6.71; N, 3.22. Found: C, 60.52; H, 6.79; N, 3.16.

4.1.29. 13-(*N*-BOC-β-isobutylisoserinoyl)-14β-*t*-butoxy-carbamoyl-baccatin III 14,1-carbamate (47). Hydrofluoric acid–pyridine (1.6 mL, 0.1 mL/10 mg of substrate) was added, at 0 °C, to a solution of 0.16 g (0.14 mmol) of **42** in 4.0 mL of acetonitrile and 4.0 mL of pyridine. After 30 min the temperature was raised to 25 °C. After 3 h, the reaction was quenched by addition of 12.0 mL of a NH_4Cl aqueous saturated solution and extracted with 12.0 mL of EtOAc. The organic phase was washed with a saturated aqueous solution of $CuSO_4$, dried, filtered, and evaporated under reduced pressure. The residue ws dissolved in 6.0 mL of CH_2Cl_2, then added with 1.6 mL of a 0.1 M solution of acetyl chloride in MeOH, at 0 °C. After 3 h the reaction was quenched by addition of 15.0 mL of saturated aqueous NH_4Cl and extracted with 15.0 mL of EtOAc. The organic phase is dried, filtered, and evaporated under reduced pressure. Chromatography of the residue (SiO_2, *n*-hexane/EtOAc, 1.0:1.2) yield 0.08 g (0.08 mmol, 57%) of **47** as a white solid. IR (KBr, cm^{-1}): 3450, 2961, 1803, 1733, 1506, 1370, 1239, 1089, 732; $[\alpha]_D^{20}$ −37.2 (*c* 0.8, CH_2Cl_2); MS (*m*/*z*) ESI: 972 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95–7.97 (m, 2H, arom), 7.54–7.58 (m, 1H, arom), 7.38–7.42 (m, 2H, arom), 6.26 (m, 2H, H-10, H-13), 6.01 (d, 1H, H-2, *J*=7.2 Hz), 4.96 (dd, 1H, H-5, *J*=2.4, 9.2 Hz), 4.89 (d, 1H, *H*NBOC, *J*=8.8 Hz), 4.74 (d, 1H, H-14, *J*=7.6 Hz), 4.42 (dd, 1H, H-7, *J*=6.4, 10.8 Hz), 4.22–4.28 (m, 3H, 2H-20, H-2′), 4.20–4.12 (m, 1H, H-3′), 3.82 (d, 1H, H-3, *J*=7.2 Hz), 2.57 (ddd, 1H, Hα-6, *J*=6.4, 9.2, 14.5 Hz), 2.53 (s, 3H, Me), 2.25 (s, 3H, Me), 1.91 (s, 3H, Me), 1.86–1.94 (ddd, 1H, Hβ-6, *J*=2.4, 10.8, 14.5 Hz), 1.72 (s, 3H, Me), 1.62–1.72 (m, 2H, H′-4, H′-5), 1.48–1.58 (m, 1H, H′-4), 1.43 (s, 9H, 3 Me), 1.38 (s, 9H, 3 Me), 1.31 (s, 3H, Me), 1.28 (s, 3H, Me), 0.97 (d, 3H, 1 Me, *J*=6.5 Hz), 0.98 (d, 3H, 1 Me, *J*=6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.5, 171.2, 171.0, 169.5, 164.4, 155.9, 150.2, 141.4, 134.0, 133.3, 129.9, 129.0, 128.4, 85.4, 84.6, 80.7, 80.1, 76.3, 75.3, 74.2, 72.1, 71.2, 59.5, 58.9, 51.6, 45.2, 42.0, 40.6, 35.9, 33.4, 32.0, 30.0, 28.7, 28.1, 27.0, 25.3, 23.5, 23.3, 22.6, 21.2, 16.0, 10.2. Anal. Calcd $C_{49}H_{66}N_2O_{18}$: C, 60.61; H, 6.85; N, 2.88. Found: C, 60.44; H, 6.74; N, 2.93.

Table 2. Relevant ^{1}H NMR resonances of 13-oxo *ortho* esters (**21**, **22**, and **27**), 13-silyl enol ethers (**3**, **28**, and **29**), and 13, 21-bis-silyl-enol *ortho* esters (**23**–**26**)

Resonances	29	28	3	27	26	25	24	23	22	21
H-2	5.77	5.75	5.76	4.35	3.97	4.50	4.02	4.48	3.90	4.39
H-14	4.82	4.73	4.73	2.37	5.36	4.46	5.42	4.46	3.07	2.53
H-14′	—	—	—	2.37	—	—	—	—	2.91	2.29
H-3	3.74	3.71	3.71	3.45	3.40	3.37	3.40	3.35	3.57	3.50
Me-19	1.70	1.67	1.69	1.79	1.62	1.79	1.63	1.78	1.65	1.78
Me-16	1.15	1.10	1.12	1.22	0.80	1.17	0.80	1.15	0.98	1.20

Appendix A. Stereochemical assessments of *ortho* esters 21, 22, and 27, of 13-enol derivatives 3, 28, and 29 and 13-enol *ortho* esters 23–26 based on ^{1}H and ^{13}C NMR spectroscopic evidences

(a): ^{1}*H NMR evidences*. The structures of 13-oxo-*ortho* esters **21**, **22**, and **27** were supported by the presence of two relevant resonances for the hydrogen atoms at C-14 (H-14 and H′-14), and one resonance for the silyl subsituent at C-21. The 13-silyl enol ethers **3**, **28**, and **29** showed one resonance for the H-14 hydrogen atom, and one for the silyl substituent at C-13. The 13, 21-bis-silyl *ortho* esters **23**–**26** showed one resonance for the H-14 hydrogen atom, and two resonances for the silyl substituents at the C-13 and C-21 oxygen atoms, respectively, (Table 2).

(b): ^{13}*C NMR evidences*. The structures of the 13-oxo-*ortho* esters **21**, **22**, and **27** were supported by the relevant ^{13}C NMR resonances (Table 3) of the keto group at C-13, in the range of 198.0–201.7 ppm, the *ortho* ester group at C-21 (117.5–120.8 ppm), and the CH_2 at C-14 (41.3–42.4 ppm). The structures of the 13-enol derivatives **3**, **28**, and **29** were supported by the resonances of the O–*C*=CH carbon atom at C-13 (153.5 ppm), the O–C=*C*H enolic carbon atom at C-14 (110.6 ppm), and the C_6H_5C=O at C-2 (166.7–166.9 ppm). The structures of the 13-enol *ortho* esters **24**–**26** were supported by the resonances of the O–*C*=CH enolic carbon atom at C-13 (152.6–155.9 ppm), the O–C=*C*H enolic carbon atom at C-14 (110.9–115.4 ppm), and the *ortho* ester group at C-21 (118.5–121.7 ppm).

(c) *ASIS effect*. The ASIS effect of the C-21 phenyl substituent on the absorptions of H-2, H-14, H-14′, H-3, Me-19, and Me-16 protons (Table 2) was a proper tool for the stereochemical assessment at C-21 of *ortho* esters **21**–**26**. In fact, the relative positions of these resonances of the 21-α/β epimers are explained by the shielding effect of the phenyl substituent, which is located in the α-face of the C-21 carbon atom of the 21β-OTMS epimers **21**, **23**, and **25**, and in the β-face of the 21α-OTMS epimers **22**, **24** and **26**. In particular, the following trends were observed: (*i*) *ASIS effect on the H-14 protons*. These protons are located on the α-face, being *syn* to the phenyl group of the 21β-OTMS epimers. Hence, the two H-14 protons of the β-epimer **21** absorbed at higher field (2.53 and 2.29 ppm) with respect to those of its α-epimer **22** (3.07 and 2.91 ppm). Similarly, the H-14 protons of the β-epimers **23** and **25** absorbed at higher field (4.46 ppm) with respect to those of the α-epimers **24** and **26** (5.42 and 5.36 ppm, respectively). (*ii*) *ASIS effect on the H-3 protons*. The H-3 protons of the 21β-OTMS epimers **21**, **23**, and **25** absorbed at higher field with respect to those of the α-epimers **22**, **24**, and **29**. since this proton and the phenyl substituent are both located in the α-face. (*iii*) *ASIS effect on the H-2 protons*. The trends on the H-2 protons, are opposite to those of H-14 and H-3 because this proton is located in the opposite β-face. (*iv*) *ASIS effect on the Me-19 and Me-16*. The Me-16 and Me-19 substituents are located on the α-face and for this reason behave similarly to the H-2 protons. In particular, the Me-16 protons of the β-epimers **21**, **23**, and **25** absorbed at lower field (1.20, 1.15, and 1.17 ppm, respectively) with respect to those of the α-epimers **22**, **24**, and **26** (0.98, 0.80 and 0.80 ppm). Similarly, the Me-19 protons of the β-epimers **21**, **23**, and **25** absorbed at lower field (1.78, 1.78 and 1.79 ppm, respectively) with respect to those of the α-epimers **22**, **24**, and **26** (1.65, 1.63 and 1.79 ppm). The β-stereochemistry of compound **27** was assigned on the basis that the H-2, H-14, H-14′, H-3, Me-19, and Me-16 proton resonances were fully consistent with those of the β-epimeric 13-oxo *ortho* ester **21** instead of the α-epimer **22**. In particular, the Me-16 and Me-19 resonances of **27** were typical of all β-epimers.

(d) *Qualitative homonuclear NOE difference spectra studies*. NOE difference spectra studies allowed the stereochemical assessment at the C-21 stereogenic center of the *ortho* esters **21**–**24**. The irradiation of the 21β-OTMS substituents of **21** and **23** (−0.03 and −0.01 ppm, respectively) caused a consistent enhancement (7–9%) of their corresponding H-2 protons, this suggesting that the TMSO group are located on the β-face. No enhancement of the H-2 protons was observed upon irradiation of the TMSO groups of **22** and **24**.

Table 3. Relevant ^{13}C NMR resonances (C-13, C-14, C-21, O–C=O at C2) of 13-oxo *ortho* esters (**21**, **22**, and **27**), 13-silyl enol ethers (**3**, **28**, and **29**) and 13, 21-bis-enol *ortho* esters (**23**–**26**)

Resonances	29	28	3	27	26	25	24	23	22	21
C-13	153.5	153.5	153.5	198.0	152.6	153.0	155.9	156.3	201.7	201.4
C-14	110.6	110.6	110.6	42.4	112.9	110.9	115.4	114.2	41.3	41.3
C-21	—	—	—	117.5	118.5	118.6	121.7	—	120.8	120.8
O–C=O at C_2	166.7	166.9	166.9	—	—	—	—	—		—

References and notes

1. Abbreviations and Acronyms: 10-Deacetylbaccatin (10-DAB), trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), *tert*-butoxycarbonyl (BOC), 1,8-Diazabicyclo[5.4.0] undec-7-ene (DBU), potassium hexamethyldisilazide (KHMDS), *m*-chloroperbenzoic acid (MCPBA), *N*,*O*-bis(trimethylsilyl) acetamide (BSA), di-*tert*-butyl dicarbonate (BOC_2O), *N*-methylimidazole (MEIM), 4-dimethylaminopyridine (DMAP), acetic anhydride (Ac_2O), 2,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidone (DMPU), *m*-chloroperbenzoic acid (mCPBA), *p*-toluenesulphonic acid (PTSA).
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