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ORIGINAL PAPER

Synthesis and antitumor activity of 1-deoxybaccatin III analogs from 1-deoxybaccatin VI

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Abstract Several new 1-deoxybaccatin III analogs were conveniently synthesized from 1-deoxybaccatin VI with the aim of having modified ester groups at C-2 and C-4. The antitumor activity of these compounds was evaluated. The preliminary SAR analysis showed that the electronic properties of the terminal group in the substituent on C4, C9, and C10 constituted important factors to the cytotoxic activities against A 549 and MCF-7 cell lines. The present studies provide a new synthetic basis for development of new 1-deoxypaclitaxel analogs.

Keywords 1-Deoxybaccatin III · 1-Deoxybaccatin VI · Analogs · Bioactivity

Introduction

The extensive utilization of paclitaxel (Taxol®, **1**) as an anticancer agent has stimulated interest in taxoids to find alternative sources of paclitaxel or related compounds with improved activities [1, 2]. Structure-activity relationship (SAR) studies have revealed that the 1-hydroxyl group is not necessary for the activity of paclitaxel [3]. Deoxygenation of the 1-hydroxyl group of paclitaxel or baccatin III (**2a**) had been reported to be a difficult procedure [4–6]. Thus, development of a procedure for synthesis of 1-deoxypaclitaxel analogs will be very significant. Its structural congruence with taxinine and sinenxan stimulated several groups to investigate possible approaches to 1-deoxy analogs, starting from taxinine or sinenxan [7, 8]. However, these approaches required constructing an oxetane moiety, leading to long synthetic sequences and considerably low overall yields. On the other hand, 1-deoxybaccatin VI (**3**), which possesses the typical 6/8/6/4 taxoid ring and lacks 1-hydroxyl group, is readily available from *Taxus chinensis, Rehd. Var. mairei* in good yield [9, 10]. Therefore, 1-deoxybaccatin VI (**3**) represents a more efficient starting material than taxinine or sinenxan for the preparation of selected 1-deoxyanalogs with potentially greater therapeutic benefits.

As a result of extensive SAR study at the diterpenoid core, the northern part of the taxane skeleton, including the C7, C9, and C10 positions, can survive structural modifications without great loss of activity as the taxane skeleton retains its rigid conformation [11]. This leads to the conclusion that this part of the molecule is not directly involved in the interaction with tubulin. However, other studies have shown that the hydrophobic character of C7 and C10 substituents can modulate the interaction of these drugs with microtubules [12], and changes in this region of taxanes may affect the specific binding of paclitaxel to P-glycoprotein. Anticancer taxoids with high potency against drug-resistant cancer cells have been prepared based on these observations. Cabazitaxel, which was approved by the US Food and Drug Administration (FDA) in 2010 [13], is a semisynthetic taxane that has different substituents at C7 and C10 compared with docetaxel and paclitaxel. It has been confirmed that cabazitaxel has poor binding ability with P-gp and shows activity in both docetaxel-sensitive and docetaxel-resistant cancers. And the functionalities on the bottom part of the molecule (including C2, C4, oxetane ring, and C13) are involved in the intimate interaction with the receptor. Several interesting approaches to C2, C4 modifications have been disclosed [14, 15].

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Paclitaxel is a complex molecule and is expensive to produce from natural sources. It would be highly desirable if future generations of this class of drugs were structurally much simpler than paclitaxel, while retaining the full activity of the parent compound. It has been reported that 2-(*m*-azidobenzoyl)baccatin III (**2b**) has taxol-like activity [16]. Its exact role, however, remains a matter of debate. These results suggest that further exploration of the effect of different acyl groups at the C2 and C4 positions could be fruitful for the discovery of further candidates for drug development. In addition, some taxoids without C13 side chain, which showed MDR (multidrug resistance)-reversal activities, have also been reported [17]. For the above reasons, the development of a procedure using 1-deoxybaccatin VI as a starting material for the preparation of new bioactive taxoids would be significant. In continuation of our drug discovery program for anticancer agents [18, 19], we report here the preparation of a small library of 1-deoxybaccatin III analogs with the general structures of **4** and **5** from 1-deoxybaccatin VI and the evaluation of their antitumor activities (Fig. 1).

Results and Discussion

As reported, taxol analogs with *meta*-substituted benzoyl groups at C2 such as *m*-azidobenzoyl and *m*-methoxybenzoyl derivatives can be more active than taxol. Initially, we synthesized and investigated a series of C2-ester derivatives with *meta*-substituted benzoyl groups **4a**–**4c**, **5a**, **5b**. As depicted in Scheme 1, 4,7,9,10,13-penta(deacetyl)-1-deoxybaccatin VI (**6**) was prepared by hydrazinolysis using the procedure previously developed in our laboratory [20]. Treatment of **6** with 2,2-dimethoxypropane (DMP) in the presence of montmorillonite K10 resulted in the formation of 9,10-acetonide **7** in 95 % isolated yield. Subsequently, **7** was treated with triton B (trimethylbenzylammonium hydroxide) to give the C2 deacylated baccatin **8** in 87 % yield. Selective C13 acetylation of **8** by means of 4-dimethylaminopyridine (DMAP) and acetic anhydride in tetrahydrofuran afforded the desired 13-acetyl derivative **9** in 84 % yield, which reacted with the corresponding *m*-substituted benzoic acid in the presence of dicyclohexylcarbodiimide (DCC) and DMAP at 50 °C to furnish compounds **10a**–**10c**. None of the C4-acylated baccatin was obtained, probably because of the much hindered position of the C4 hydroxyl group. To install the acetyl group on the C4 position, selective acetylation of the C7 hydroxy group, followed by further reaction with lithium bis(trimethylsilyl)amide (LiHMDS), AcCl afforded 4-*O*-acetoacetates **4a**–**4c** in total 57–65 % yields by 5 steps. Deprotection of the acetonide of compounds **4a**, **4b** under acidic conditions afforded the 9, 10-diol derivatives **5a**, **5b** in moderate yield.

The C4 cyclopropyl ester was found to be more potent than paclitaxel in the bioassays [21]. This trend indicates that the four-carbon chain at C4 is probably the optimal

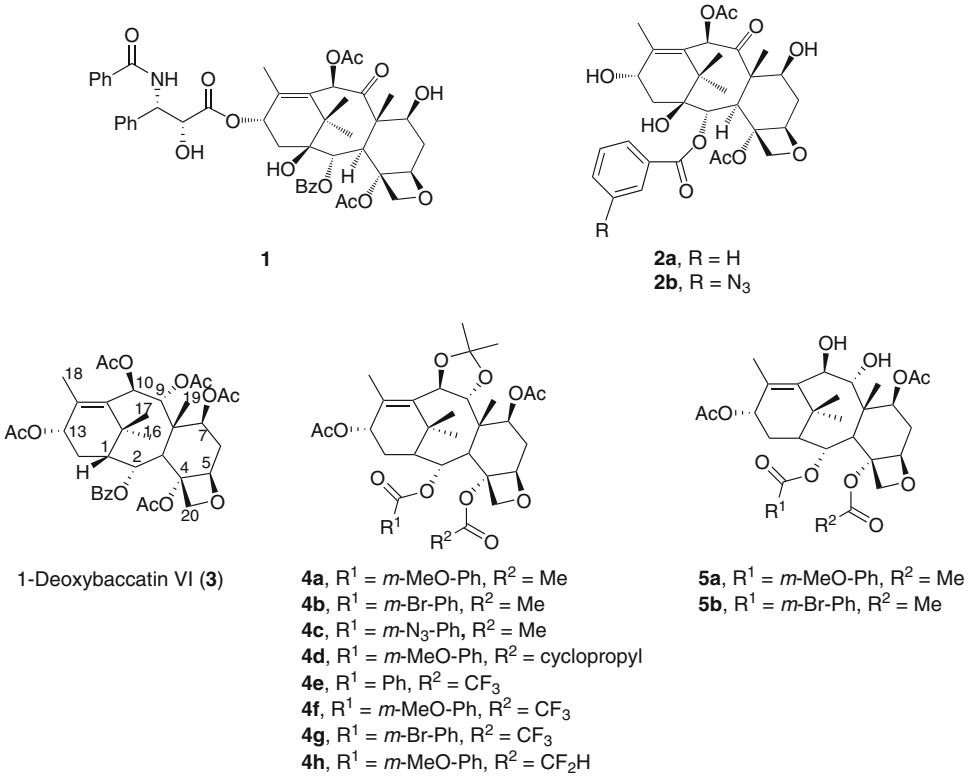
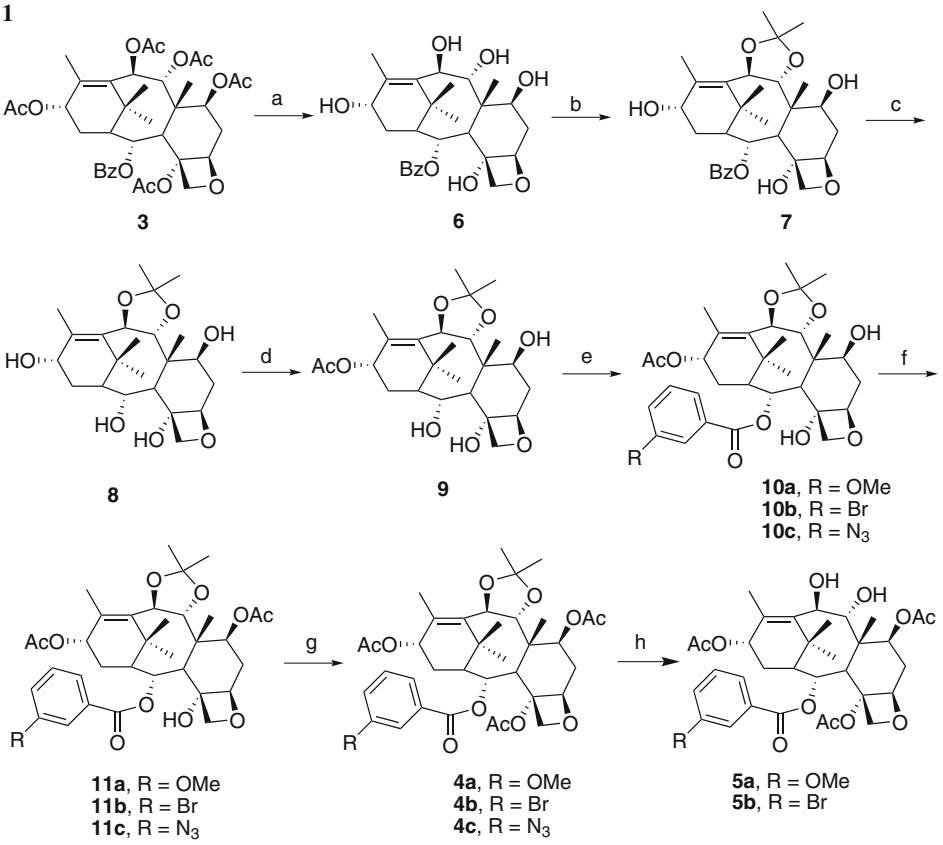


Fig. 1 Taxol and 1-deoxybaccatin VI analogs

Scheme 1

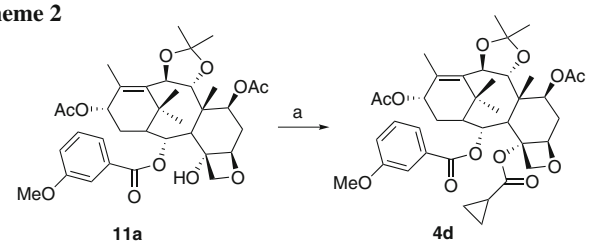


Reagents and conditions: (a) NH_2NH_2, r.t., 71%; (b) 2,2-DMP, Montmorillonite K10, r.t., 95 %; (c) Triton B, r.t., 87%; (d) Ac_2O, DMAP, THF, 0 °C., 84%; (e) appropriate *m*-substituted benzoic acids, DMAP, DCC/Toluene, 50 °C, 91% (**10a**), 88% (**10b**) and 74% (**10c**); (f) Ac_2O, DMAP, DCC, Toluene, 55 °C, 82% (**11a**), 80% (**11b**) and 82% (**11c**); (g) AcCl, LiHMDS, THF, 0 °C, 79% (**4a**), 78% (**4b**) and 70% (**4c**); (h) 0.1 N HCl, MeOH, r.t., 24 h, 63% (**5a**) and 74% (**5b**).

size for the effective receptor binding. In order to further optimize activity, the cyclopropylcarbonyl group was introduced to the C4 position by treating **11a** with LiHMDS, cyclopropylcarboxyl chloride in THF at 0 °C to give the desired compound **4d** (Scheme 2).

In the course of our SAR study of taxoids, we set out to incorporate fluorine into taxoids to study the effects of fluorine incorporation on the cytotoxicity of the resulting analogs. Novel taxoids bearing a 2,2,2-trifluoroacetyl group at the C4 position and modifications at the C2 position were synthesized. From compound **7**, the first acetylation of C7 and C13 hydroxyl groups, followed by treatment with trifluoroacetic anhydride in the presence of DMAP in toluene at 60 °C, afforded compound **4e**. Using similar methods, compounds **4f** and **4g** were obtained from **11a** and **11b** in 80 and 88 % yield, respectively. Compound **4h** was obtained from **11a** by treatment with 2,2-difluoroacetic anhydride, DMAP in toluene at r.t. for 12 h in 86 % yield (Scheme 3).

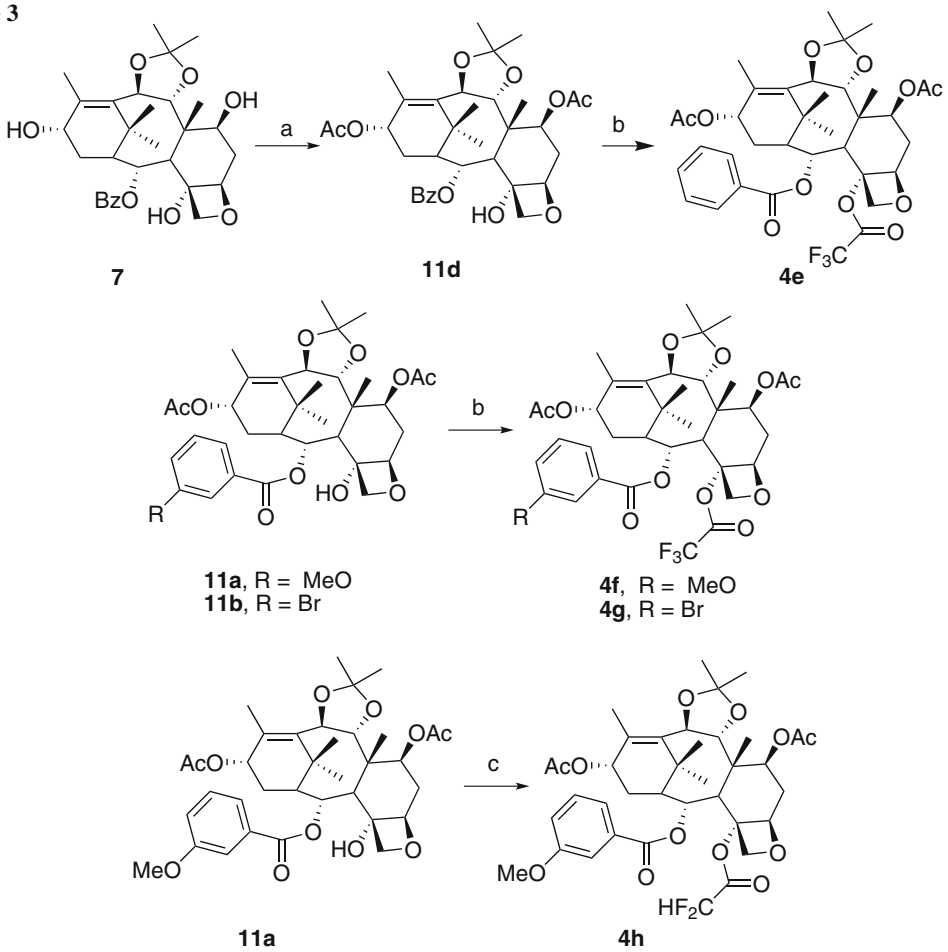
Scheme 2



Reagents and conditions: (a) LiHMDS, cyclopropylcarbonyl chloride, THF, 0 °C, 77%.

Biological activities of synthesized taxoids **4a**–**4h**, **5a**, **5b** were evaluated in cytotoxicity assays against two tumor cell lines including A 549 (human lung carcinoma) and MCF-7 (breast cancer) cell lines. We employed these acetonide compounds because the 9,10 positions were reported not to interact directly with tubulin [2] and the effectiveness of acetal groups in the 9,10-positions of the taxane skeleton [22]. Also, the 9,10-deprotected derivatives

Scheme 3



Reagents and conditions: (a) Ac_2O, DMAP, THF, r.t., 83%; (b) $(CF_3CO)_2O$, DMAP, toluene, r.t, 83% (**4e**), 88% (**4f**) and 80% (**4g**); (c) $(CHF_2CO)_2O$, DMAP, toluene, r.t., 12 h, 86% .

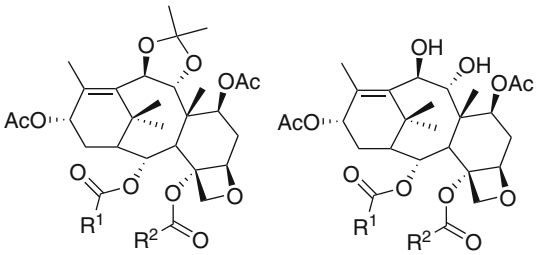
5a, **5b** were synthesized for comparison. The results are presented in Table 1. 1-Deoxybaccatin VI (**3**) showed no cytotoxic activities against A 549 and MCF-7 cell lines. For the acetonide derivatives, compounds with acetyl (**4a**–**4c**), 2,2,2-trifluoroacetyl (**4e**–**4g**) or 2,2-difluoroacetyl group (**4i**) at the C4 position showed no activity, regardless of the properties of C2 substituents. On the contrary, replacement of the 4-acetyl group with the cyclopropylcarbonyl group leads to analogs possessing enhanced cytotoxicity against the A 549 cell line (compound **4d** vs. **4a**). On the other hand, the 9,10-diol derivatives **5a**, **5b** exhibited improved activity against the A549 tumor cell line compared to the corresponding 9,10-acetonide compounds **4a**, **4b**. Obviously, electronic properties of the terminal group in the substituents on C4, C9, and C10 constitute important factors.

In conclusion, several new 1-deoxybaccatin III analogs were conveniently synthesized from readily available 1-deoxybaccatin VI, a major taxoid component in *Taxus chinensis, Rehd. Var. mairei*. These include 1-deoxybaccatin III analogs (taxoids) modified with 3-oxobutyryl, 2-methyl-3-oxopentoyl groups, or others instead of the acetyl group at the C4 position. 1-Deoxybaccatin VI (**3**) showed no cytotoxicity activities against A 549 and MCF-7 cell lines. The present SAR studies showed that the electronic properties of the terminal group in the substituent on C4, C9, and C10 constituted important factors in the cytotoxic activities against A 549 and MCF-7 cell lines. Since 1-deoxybaccatin III derivatives are very difficult to prepare through deoxygenation of baccatin III and paclitaxel, the synthetic methodology described here and better understanding of the chemical reactivity of taxoids would be useful for more efficient syntheses of selected 1-deoxypaclitaxel analogs with potentially greater therapeutic benefits.

Experimental

All reported yields are isolated yields after column chromatography or crystallization. Column chromatography

Table 1 Cytotoxicity of paclitaxel and analogs **4a**–**4h**, **5a**, **5b**



4 **5**

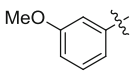
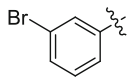
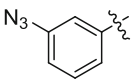
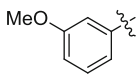
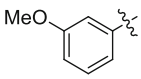
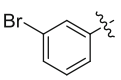
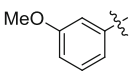
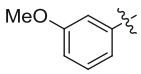
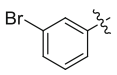
Compounds	R^1	R^2	Cytotoxic activity IC_{50}/μg cm^{-3}	
			A 549	MCF-7
Taxol	–	–	0.00244	0.421
3	–	–	>100	>100
4a		CH_3	>100	>100
4b		CH_3	>100	>100
4c		CH_3	>100	>100
4d			23.29	>100
4e		CF_3	>100	>100
4f		CF_3	>100	>100
4g		CF_3	>100	>100
4h		CF_2H	>100	>100
5a		CH_3	29.68	>100

Table 1 continued

Compounds	R^1	R^2	Cytotoxic activity IC_{50}/μg cm^{-3}	
			A 549	MCF-7
5b		CH_3	63.51	>100

was performed with silica-gel H (Qingdao Haiyang Chemical Plant, P.R. China). The NMR spectra were recorded with a Bruker Avance/AV 500. Chemical shifts are reported in parts per million (ppm), and coupling constants (*J*) are reported in hertz (Hz). Chemical shifts in $CDCl_3$ were reported on a scale relative to $CHCl_3$ (7.26 ppm) for ^1H NMR and to $CDCl_3$ (77.23 ppm) for ^{13}C NMR as internal references. Chemical shifts in ^{19}F NMR spectra were reported in ppm downfield from internal fluorotrichloromethane ($CFCl_3$). MSs were recorded on a Thermo Finnigan LCQ Advantage Mass spectrometer. All chemicals were dried or purified according to standard procedures prior to use.

4,7-Bis(deacetyl)-9,10-O-isopropylidene-2-(3-methoxybenzoyl)-1-deoxybaccatin VI (**10a**, $C_{33}H_{44}O_{10}$)

To a stirred solution of 165.2 mg 4,7-deacetyl-2-debenzoyl-9,10-*O*-isopropylidene-1-deoxybaccatin VI (**9**, 0.35 mmol) in 4 cm^3 toluene was added 161.1 mg *m*-methoxybenzoic acid (1.06 mmol), 130.2 mg DMAP (1.06 mmol), and 218.7 mg DCC (1.06 mmol). The reaction mixture was stirred at 50 °C for about 6 h. The solvent was evaporated, followed by adding 8 cm^3 EtOAc. Solids were removed by filtration, and the filtrate was concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using EtOAc and *n*-hexane (1/2 v/v) to afford **10a** (598 mg, 94 %) as white solid. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 8.0$ Hz, Bz-6′-H), 7.54–7.55 (m, Bz-2′-H), 7.35 (t, $J = 8.0$ Hz, Bz-5′-H), 7.09–7.11 (m, Bz-4′-H), 5.81 (dd, $J = 5.0$, 2.0 Hz, C2-H), 5.71 (dd, $J = 10.0$, 2.0 Hz, C13-H), 4.98 (s, 1H, C7-OH), 4.97 (d, $J = 9.5$ Hz, C10-H), 4.74 (dd, $J = 9.5$, 3.0 Hz, C7-H), 4.48 (d, $J = 9.5$ Hz, C9-H), 4.27 (d, $J = 8.0$ Hz, C20-H), 4.25 (d, $J = 8.0$ Hz, C20-H), 4.00 (dd, $J = 10.5$, 7.0 Hz, C5-H), 3.84 (s, 3H, Bz-3′-OMe-H), 2.65 (m, C6-H), 2.55 (s, 1H, C4-OH), 2.49 (m, C14-H), 2.26 (d, $J = 5.0$ Hz, C3-H), 2.18–2.22 (m, C1-H), 2.16 (s, 3H, C13-OAc-H), 1.92–1.98 (m, C6-H), 1.88 (s, 3H, C18-H), 1.85–1.86 (m, C14-H), 1.71 (s, 3H, C16-H), 1.57 (s, 3H, C17-H), 1.51 (s, 6H, 9,10-acetonide-H), 1.08 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.8$, 165.1, 159.6, 138.5, 136.2, 130.8, 129.6, 122.0, 119.6, 114.7, 107.7, 87.7, 83.4, 79.6, 75.0, 74.9, 72.1, 70.7, 69.7, 55.4, 46.8, 45.9, 41.9, 37.8, 36.6, 33.1, 27.5, 27.0, 26.8, 24.8, 21.2, 16.9, 12.5 ppm; MS (ESI): $m/z = 623.3$ $[M + Na]^+$.

4,7-Bis(deacetyl)-2-(3-bromobenzoyl)-9,10-O-isopropylidene-1-deoxybaccatin VI (**10b**, $C_{32}H_{41}BrO_9$)

10b was prepared from 4,7-deacetyl-2-debenzoyl-9,10-*O*-isopropylidene-1-deoxybaccatin VI (**9**) and *m*-bromobenzoic acid by using the procedure described for preparation of **10a**; yield 88 %; white solid. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.17$ (t, $J = 1.5$ Hz, Bz-2′-H), 7.98 (dt, $J = 7.5$, 1.0 Hz, Bz-6′-H), 7.68 (dq, $J = 7.5$, 1.0 Hz, Bz-4′-H), 7.33 (t, $J = 7.5$ Hz, Bz-5′-H), 5.62–5.66 (m, C2, C13-H), 5.46 (t, $J = 8.5$ Hz, C7-H), 4.88 (d, $J = 9.5$ Hz, C10-H), 4.81 (dd, $J = 8.5$, 2.5 Hz, C5-H), 4.42 (q, $J = 2.5$ Hz, 2H, C20-H), 4.22 (d, $J = 9.5$ Hz, C9-H), 2.67–2.71 (m, C6-H), 2.64 (s, C4-OH), 2.46–2.53 (m, C14-H), 2.36 (d, $J = 5.0$ Hz, C3-H), 2.13 (s, 3H, C13-OAc-H), 2.09–2.11 (m, C1-H), 2.05 (s, 3H, C7-OAc-H), 1.98 (s, 3H, C18-H), 1.96–1.95 (m, C6-H), 1.77–1.79 (m, C14-H), 1.75 (s, 3H, C16-H), 1.66 (s, 3H, C17-H), 1.33 (s, 6H, 9,10-acetonide-H), 1.07 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.2$, 169.2, 164.8, 137.6, 136.5, 135.8, 132.9, 132.8, 129.9, 128.5, 122.3, 106.8, 86.3, 81.7, 79.9, 74.8, 74.4, 71.9, 71.4, 69.7, 47.1, 46.0, 42.4, 37.8, 34.4, 32.9, 27.9, 26.9, 25.2, 21.6, 21.2, 16.8, 14.0 ppm; MS (ESI): $m/z = 671.2$ $[M + Na]^+$.

2-(3-Azidobenzoyl)-4,7-bis(deacetyl)-9,10-O-isopropylidene-1-deoxybaccatin VI (**10c**, $C_{32}H_{41}N_3O_9$)

10c was prepared from 4,7-deacetyl-2-debenzoyl-9,10-*O*-isopropylidene-1-deoxybaccatin VI (**9**) and *m*-azidobenzoic acid by using the procedure described for preparation of **10a**; yield 74 %; white solid. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 8.0$ Hz, Bz-6′-H), 7.71 (t, $J = 2.0$ Hz, Bz-2′-H), 7.44 (t, $J = 8.0$ Hz, Bz-5′-H), 7.23 (ddd, $J = 8.0$, 2.0, 1.0 Hz, Bz-4′-H), 5.80 (dd, $J = 5.0$, 2.5 Hz, C2-H), 5.72 (dd, $J = 10.5$, 1.5 Hz, C13-H), 4.99 (s, 1H, C7-OH), 4.97 (d, $J = 9.5$ Hz, C10-H), 4.75 (dd, $J = 9.5$, 3.0 Hz, C7-H), 4.47 (d, $J = 9.5$ Hz, C9-H), 4.26 (d, $J = 8.0$ Hz, C20-H), 4.22 (d, $J = 8.0$ Hz, C20-H), 4.00 (dd, $J = 10.5$, 7.0 Hz, C5-H), 2.62–2.69 (m, C6-H),

2.46–2.53 (m, 2H, C14-H, C4-OH), 2.28 (d, $J = 5.0$ Hz, C3-H), 2.19–2.22 (m, C6-H), 2.17 (s, 3H, C13-OAc-H), 1.92–1.98 (m, C1-H), 1.88 (s, 3H, C7-OAc-H), 1.86 (dd, $J = 8.0$, 2.0 Hz, C14-H), 1.71 (s, 3H, C18-H), 1.67 (s, 3H, C16-H), 1.57 (s, 3H, C17-H), 1.52 (s, 6H, 9,10-acetonide-H), 1.09 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.9$, 164.4, 141.0, 138.5, 136.4, 131.5, 130.2, 126.1, 124.0, 122.0, 107.9, 88.0, 83.5, 79.6, 75.1, 75.0, 72.2, 71.1, 69.8, 46.9, 46.0, 42.0, 37.9, 36.6, 33.2, 27.6, 27.1, 27.0, 24.9, 21.3, 17.0, 12.6 ppm; MS (ESI): $m/z = 634.3$ $[M + Na]^+$.

4-Deacetyl-9,10-O-isopropylidene-2-(3-methoxybenzoyl)-1-deoxybaccatin VI (**11a**, $C_{35}H_{46}O_{11}$)

To a stirred solution of 168.0 mg **10a** (0.31 mmol) and 190.5 mg DMAP (1.55 mmol) in 3 cm^3 dry toluene was added 0.24 cm^3 acetic anhydride (2.48 mmol) in one portion, and the reaction mixture was stirred at 50 °C for 5 h. After cooling to room temperature, the mixture was diluted with 50 cm^3 EtOAc, washed with saturated aq. $NaHCO_3$ (20 cm^3 × 2) and brine (20 cm^3 × 2). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give the crude residue, which was purified by column chromatography on silica gel using EtOAc and hexanes to afford **11a** (161.2 mg, 82 %) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 8.0$ Hz, Bz-6′-H), 7.54–7.55 (m, Bz-2′-H), 7.36 (t, $J = 8.0$ Hz, Bz-5′-H), 7.10–7.13 (m, Bz-4′-H), 5.89 (dd, $J = 5.0$, 2.0 Hz, C2-H), 5.70 (d, $J = 9.0$ Hz, C10-H), 5.24 (t, $J = 8.5$ Hz, C13-H), 4.89 (d, $J = 9.0$ Hz, C9-H), 4.74 (dd, $J = 8.5$, 2.5 Hz, C7-H), 4.27–4.31 (m, 3H, C5, C20-H), 3.85 (s, 3H, Bz-3′-OMe-H), 2.65–2.70 (m, 1H, C6-H), 2.63 (s, 1H, C4-OH), 2.40 (d, $J = 5.0$ Hz, C3-H), 2.35 (m, C14-H), 2.18–2.22 (m, C1-H), 2.15 (s, 3H, C13-OAc-H), 2.05 (s, 3H, C7-OAc-H), 1.96–2.01 (m, C6-H), 1.94 (s, 3H, C18-H), 1.82–1.84 (m, C14-H), 1.72 (s, 3H, C16-H), 1.64 (s, 3H, C17-H), 1.46 (s, 3H, 9,10-acetonide-H), 1.36 (s, 3H, 9,10-acetonide-H), 1.07 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.6$, 169.8, 165.0, 159.6, 137.3, 136.8, 130.8, 129.6, 122.0, 119.7, 114.6, 106.6, 87.1, 81.8, 79.5, 74.8, 74.4, 70.7, 70.1, 69.7, 55.4, 47.0, 45.8, 42.2, 37.7, 34.4, 33.0, 27.6, 27.1, 26.9, 25.1, 21.7, 21.1, 16.7, 13.7 ppm; MS (ESI): $m/z = 665.3$ $[M + Na]^+$.

2-(3-Bromobenzoyl)-4-deacetyl-9,10-O-isopropylidene-1-deoxybaccatin VI (**11b**, $C_{34}H_{43}BrO_{10}$)

11b was prepared from **10b** by using the procedure described for preparation of **11a**; yield 80 %; white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.18$ (t, $J = 1.5$ Hz, Bz-2′-H), 7.98 (dt, $J = 9.0$, 1.5 Hz, Bz-6′-H), 7.66 (dq, $J = 9.0$, 1.5 Hz, Bz-4′-H), 7.31 (t, $J = 8.0$ Hz, Bz-5′-H), 5.95 (t, $J = 9.0$ Hz, C13-H), 5.67 (t, $J = 9.0$ Hz, C7-H), 5.58 (dd, $J = 5.0$, 2.0 Hz, C2-H), 4.95–4.99 (m, 2H, C10, C5-H), 4.53 (d, $J = 8.0$ Hz, C9-H), 4.27 (d, $J = 8.0$ Hz, C20-H), 4.24 (d, $J = 8.0$ Hz, C20-H), 2.76 (d, $J = 5.0$ Hz, C3-H), 2.59–2.66 (m, C6-H), 2.42–2.48 (m, C14-H), 2.18 (s, 3H, C13-OAc-H), 2.17 (s, 3H, C7-OAc-H), 2.05 (s, 3H, C18-H), 1.95–2.03 (m, C1-H), 1.95 (s, 3H, C16-H), 1.84 (s, 3H, C17-H), 1.71 (s, 3H, 9,10-acetonide-H), 1.49–1.54 (m, C6, C14-H), 1.31 (s, 3H, 9,10-acetonide-H), 1.18 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.7$, 169.7, 169.4, 164.5, 138.6, 135.6, 133.8, 133.1, 132.9, 129.8, 128.6, 122.3, 106.3, 84.2, 82.0, 80.6, 76.6, 74.4, 72.1, 71.1, 47.9, 42.4, 38.4, 34.8, 31.3, 26.9, 26.8, 26.6, 22.7, 21.6, 21.3, 15.1, 14.0 ppm; MS (ESI): $m/z = 713.2$ $[M + Na]^+$.

2-(3-Azidobenzoyl)-4-deacetyl-9,10-O-isopropylidene-1-deoxybaccatin VI (**11c**, $C_{34}H_{43}N_3O_{10}$)

11c was prepared from **10c** by using the procedure described for preparation of **11a**; yield 82 %; white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.79$ (d, $J = 8.0$ Hz, Bz-6′-H), 7.71 (t, $J = 2.0$ Hz, Bz-2′-H), 7.45 (t, $J = 8.0$ Hz, Bz-5′-H), 7.24 (ddd, $J = 8.0$, 2.0, 1.0 Hz, Bz-4′-H), 5.87 (dd, $J = 5.0$, 2.0 Hz, C2-H), 5.71 (dd, $J = 10.5$, 1.5 Hz, C13-H), 5.24 (d, $J = 9.5$ Hz, C10-H), 4.89 (d, $J = 9.5$ Hz, C9-H), 4.74 (dd, $J = 8.5$, 2.5 Hz, C7-H), 4.25–4.28 (m, 3H, C5, C20-H), 2.64–2.70 (m, C6-H), 2.42 (d, $J = 5.0$ Hz, C3-H), 2.32–2.38 (m, C14-H), 2.19–2.23 (m, C6-H), 2.16 (s, 3H, C13-OAc-H), 2.06 (s, 3H, C7-OAc-H), 1.96–2.02 (m, C1-H), 1.94 (s, 3H, C18-H), 1.82–1.84 (m, C14-H), 1.72 (s, 3H, C16-H), 1.64 (s, 3H, C17-H), 1.46 (s, 3H, 9,10-acetonide-H), 1.36 (s, 3H, 9,10-acetonide-H), 1.07 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.8$, 169.9, 164.5, 141.0, 137.5, 137.1, 131.5, 130.2, 126.1, 124.0, 122.4, 106.9, 87.5, 82.0, 79.5, 75.0, 74.6, 71.1, 70.3, 69.9, 47.2, 46.0, 42.4, 37.9, 34.6, 33.2, 27.8, 27.2, 27.1, 25.3, 21.9, 21.3, 16.9, 13.9 ppm; MS (ESI): $m/z = 776.3$ $[M + Na]^+$.

9,10-O-Isopropylidene-2-(3-methoxybenzoyl)-1-deoxybaccatin VI (**4a**, $C_{37}H_{48}O_{12}$)

To a stirred solution of 160.5 mg **11a** (0.25 mmol) in 4 cm^3 dry THF was added a solution of 0.5 cm^3 LiHMDS (0.5 mmol, 1 M in THF) dropwise. After the reaction mixture was stirred at 0 °C for 1 h, a diluted solution of 38 mm^3 acetyl chloride (0.55 mmol) in 3.8 cm^3 THF was added slowly. The mixture was stirred at 0 °C for another 5 h, quenched with 2 cm^3 saturated aq. NH_4Cl, diluted with 60 cm^3 EtOAc, and washed with water (20 cm^3 × 2). The organic layer was washed with brine (20 cm^3 × 2), dried over anhydrous Na_2SO_4, and concentrated to give the crude residue, which was purified by column chromatography on silica gel using EtOAc and *n*-hexane (2/7 v/v) to afford **4a** (135.1 mg, 79 %) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 8.0$ Hz, Bz-6′-H), 7.60–7.61 (m, Bz-2′-H), 7.38 (t, $J = 8.0$ Hz, Bz-5′-H),

7.12–7.14 (m, Bz-4′-H), 5.96 (t, $J = 9.0$ Hz, C13-H), 5.82 (dd, $J = 5.0$, 2.0 Hz, C2-H), 5.47 (t, $J = 8.5$ Hz, C7-H), 4.98 (d, $J = 9.5$ Hz, C10-H), 4.96 (d, $J = 9.5$ Hz, C9-H), 4.40 (d, $J = 8.0$ Hz, C20-H), 4.32 (d, $J = 10.0$ Hz, C5-H), 4.13 (d, $J = 8.0$ Hz, C20-H), 3.87 (s, 3H, Bz-3′-OMe-H), 2.81 (d, $J = 5.0$ Hz, C3-H), 2.44–2.55 (m, 2H, C6, C14-H), 2.25–2.19 (m, C1-H), 2.18 (s, 3H, C13-OAc-H), 2.05 (s, 3H, C7-OAc-H), 1.92 (s, 3H, C4-OAc-H), 1.86–1.89 (m, C6-H), 1.79 (s, 3H, C16-H), 1.75 (s, 3H, C17-H), 1.60–1.65 (m, C14-H), 1.45 (s, 3H, 9,10-acetonide-H), 1.37 (s, 3H, 9,10-acetonide-H), 1.19 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.6$, 169.0, 164.9, 159.6, 138.5, 136.6, 130.8, 129.6, 122.1, 119.8, 114.5, 106.2, 84.0, 82.1, 80.9, 76.5, 74.4, 71.5, 70.8, 69.4, 55.3, 48.1, 42.7, 42.4, 38.3, 34.8, 31.3, 27.1, 27.0, 26.9, 26.6, 22.6, 21.9, 21.2, 15.0, 13.8 ppm; MS (ESI): $m/z = 707.3$ $[M + Na]^+$.

2-(3-Bromobenzoyl)-9,10-O-isopropylidene-1-deoxybaccatin VI (**4b**, $C_{36}H_{45}BrO_{11}$)

4b was prepared from **11b** by using the procedure described for preparation of **4a**; yield 78 %; white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.23$–8.24 (m, Bz-2′-H), 7.79 (d, $J = 8.0$ Hz, Bz-6′-H), 7.73 (t, $J = 8.0$ Hz, Bz-4′-H), 7.36 (t, $J = 8.0$ Hz, Bz-5′-H), 5.96 (t, $J = 9.0$ Hz, C13-H), 5.79 (dd, $J = 5.5$, 2.0 Hz, C2-H), 5.46 (t, $J = 8.5$ Hz, C7-H), 4.96–4.98 (m, C9, C10-H), 4.34 (d, $J = 8.0$ Hz, C20-H), 4.30 (d, $J = 9.5$ Hz, C5-H), 4.11 (d, $J = 8.0$ Hz, C20-H), 2.82 (d, $J = 5.5$ Hz, C3-H), 2.45–2.56 (m, 2H, C6, C14-H), 2.28 (s, 3H, C13-OAc-H), 2.19 (s, 3H, C7-OAc-H), 2.05 (s, 3H, C4-OAc-H), 1.93 (s, 3H, C18-H), 1.91–1.92 (m, C1-H), 1.86–1.89 (m, C6-H), 1.78 (s, 3H, C16-H), 1.75 (s, 3H, C17-H), 1.58–1.63 (m, C14-H), 1.45 (s, 3H, 9,10-acetonide-H), 1.36 (s, 3H, 9,10-acetonide-H), 1.18 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.6$, 170.4, 168.9, 163.6, 138.5, 136.4, 133.6, 132.9, 131.5, 130.2, 128.3, 122.6, 106.2, 84.0, 82.0, 80.8, 76.3, 74.4, 71.9, 70.8, 69.2, 48.2, 42.7, 42.4, 38.2, 34.7, 31.3, 27.1, 27.0, 26.9, 26.6, 22.5, 21.9, 21.2, 15.1, 13.8 ppm; MS (ESI): $m/z = 755.2$ (95 %), 757.2 (100 %) $[M + Na]^+$.

2-(3-Azidobenzoyl)-9,10-O-isopropylidene-1-deoxybaccatin VI (**4c**, $C_{36}H_{45}N_3O_{11}$)

4c was prepared from **11c** by using the procedure described for preparation of **4a**; yield 70 %; white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J = 8.0$ Hz, Bz-6′-H), 7.75 (t, $J = 2.0$ Hz, Bz-2′-H), 7.47 (t, $J = 8.0$ Hz, Bz-5′-H), 7.24 (ddd, $J = 8.0$, 2.0, 1.0 Hz, Bz-4′-H), 5.97 (t, $J = 8.5$ Hz, C13-H), 5.83 (dd, $J = 5.0$, 2.5 Hz, C2-H), 5.48 (t, $J = 8.5$ Hz, C7-H), 4.98 (d, $J = 9.5$ Hz, C10-H), 4.96 (d, $J = 8.5$ Hz, C5-H), 4.37 (d, $J = 8.0$ Hz, C20-H), 4.32 (d, $J = 9.5$ Hz, C9-H), 4.12 (d, $J = 8.0$ Hz, C20-H), 2.82 (d, $J = 5.0$ Hz, C3-H), 2.51–2.55 (m, C6-H), 2.44–2.50 (m, C14-H), 2.26 (s, C4-OH), 2.19 (s, 3H, C13-OAc-H), 2.06 (s, 3H, C7-OAc-H), 1.93 (s, 3H, C4-OAc-H), 1.91–1.92 (m, C1-H), 1.86–1.89 (m, C6-H), 1.79 (s, 3H, C18-H), 1.59–1.64 (m, C14-H), 1.46 (s, 3H, 9,10-acetonide-H), 1.37 (s, 3H, 9,10-acetonide-H), 1.19 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.7$, 170.5, 169.1, 164.1, 140.8, 138.6, 133.6, 131.3, 130.1, 126.3, 124.2, 119.8, 106.3, 84.1, 82.1, 80.9, 76.4, 74.4, 72.0, 70.8, 69.3, 48.2, 42.7, 42.4, 38.3, 34.8, 31.3, 27.2, 27.1, 26.9, 26.6, 22.6, 21.9, 21.2, 15.1, 13.8 ppm; MS (ESI): $m/z = 718.2$ $[M + Na]^+$.

4-(Cyclopropanecarbonyl)-9,10-O-isopropylidene-2-(3-methoxybenzoyl)-1-deoxybaccatin VI (**4d**, $C_{39}H_{50}O_{12}$)

4d was prepared from **11a** and cyclopropanecarboxyl chloride by using the procedure described for preparation of **4a**; yield 77 %; white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 8.0$ Hz, Bz-6′-H), 7.57 (dd, $J = 2.5$, 1.0 Hz, Bz-2′-H), 7.37 (t, $J = 8.0$ Hz, Bz-5′-H), 7.13 (ddd, $J = 8.0$, 2.5, 1.0 Hz, Bz-4′-H), 5.74 (dd, $J = 10.5$, 1.5 Hz, C2-H), 5.26 (t, $J = 8.5$ Hz, C13-H), 4.90 (d, $J = 8.0$ Hz, C10-H), 4.75 (dd, $J = 8.5$, 3.0 Hz, C7-H), 4.32 (d, $J = 8.0$ Hz, C9-H), 4.27–4.29 (m, 2H, C20-H), 3.85 (s, 3H, Bz-3′-OMe-H), 2.61–2.68 (m, C6-H), 2.43 (d, $J = 5.0$ Hz, C3-H), 2.38 (s, 3H, C13-OAc-H), 2.22 (dd, $J = 16.0$, 3.5 Hz, cyclopropane-1′-H), 2.06 (s, 3H, C7-OAc-H), 1.97–2.02 (m, C14-H), 1.94 (s, 3H, C18-H), 1.83–1.86 (m, C1-H), 1.72 (s, 3H, C16-H), 1.64 (s, 3H, C17-H), 1.58–1.63 (m, C6-H), 1.46 (s, 3H, 9,10-acetonide-H), 1.36 (s, 3H, 9,10-acetonide-H), 1.08–1.13 (m, 2H, cyclopropane-H), 1.06 (s, 3H, C19-H), 0.94–0.98 (m, 2H, cyclopropane-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.9$, 170.8, 166.9, 165.2, 159.8, 137.9, 136.7, 131.0, 129.8, 122.1, 119.9, 114.7, 106.8, 87.3, 82.0, 79.7, 75.0, 74.6, 70.9, 70.3, 69.6, 55.6, 47.2, 45.9, 42.4, 37.9, 34.6, 33.1, 27.7, 27.2, 27.1, 25.3, 22.8, 21.9, 16.8, 14.0, 13.3, 9.1, 8.9 ppm; MS (ESI): $m/z = 733.3$ $[M + Na]^+$.

2-Benzoyl-9,10-O-isopropylidene-4-(trifluoroacetyl)-1-deoxybaccatin VI (**4e**, $C_{36}H_{43}F_3O_{11}$)

A solution of 64.2 mg **11a** (0.10 mmol), 122.0 mg DMAP (1.0 mmol), and 168.0 mg trifluoroacetic anhydride (0.80 mmol) in 8 cm^3 dry toluene was stirred at room temperature for 12 h. After being quenched with 2 cm^3 saturated aq. $NaHCO_3$, the mixture was diluted with 60 cm^3 EtOAc, washed with water (20 cm^3 × 2) and brine (20 cm^3 × 2). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give the crude residue, which was purified by column chromatography on silica gel using EtOAc and *n*-hexane (2/7 v/v) to afford **4e** (62.6 mg, 83 %) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.03$ (t, $J = 7.5$ Hz, 2H, Bz-2′,6′-H), 7.60 (t, $J = 7.5$ Hz, Bz-4′-H), 7.47 (t, $J = 7.5$ Hz, 2H, Bz-3′,5′-H), 5.94 (t, $J = 8.0$ Hz, C13-H), 5.86 (dd, $J = 5.0$, 2.0 Hz, C2-H),

5.45 (t, $J = 8.0$ Hz, C7-H), 4.97 (d, $J = 9.5$ Hz, C10-H), 4.92 (d, $J = 9.5$ Hz, C9-H), 4.42 (d, $J = 8.5$ Hz, C20-H), 4.34 (d, $J = 8.5$ Hz, C20-H), 4.21 (d, $J = 9.0$ Hz, C5-H), 2.83 (d, $J = 5.0$ Hz, C3-H), 2.48–2.59 (m, 2H, C6, C14-H), 2.12 (s, 3H, C13-OAc-H), 2.06 (s, 3H, C7-OAc-H), 1.98–1.97 (m, C1-H), 1.96–1.94 (m, C6-H), 1.91 (s, 3H, C18-H), 1.78 (s, 6H, C16, C17-H), 1.47–1.45 (m, C14-H), 1.46 (s, 3H, 9,10-acetonide-H), 1.37 (s, 3H, 9,10-acetonide-H), 1.18 (s, 3H, C19-H) ppm; ^{19}F NMR (470.5 MHz, $CDCl_3$): $\delta = -74.42$ ppm; MS (ESI): $m/z = 731.3$ $[M + Na]^+$.

9,10-O-Isopropylidene-2-(3-methoxybenzoyl)-4-(trifluoroacetyl)-1-deoxybaccatin VI (**4f**, $C_{37}H_{45}F_3O_{12}$)

4f was prepared from **11a** and trifluoroacetic anhydride by using the procedure described for preparation of **4e**; yield 88 %; white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.65$ (t, $J = 7.5$ Hz, Bz-6′-H), 7.53–7.54 (m, Bz-2′-H), 7.38 (t, $J = 8.0$ Hz, Bz-5′-H), 7.15 (dd, $J = 8.0$, 2.5 Hz, Bz-4′-H), 5.95 (t, $J = 8.5$ Hz, C13-H), 5.88 (d, $J = 4.0$ Hz, C2-H), 5.47 (t, $J = 9.0$ Hz, C7-H), 4.97 (d, $J = 9.0$ Hz, C5-H), 4.92 (d, $J = 8.5$ Hz, C10-H), 4.48 (d, $J = 8.5$ Hz, C9-H), 4.34 (d, $J = 9.0$ Hz, C20-H), 4.22 (d, $J = 9.0$ Hz, C20-H), 3.84 (s, 3H, Bz-3′-OMe-H), 2.84 (d, $J = 5.5$ Hz, C3-H), 2.54–2.59 (m, C6-H), 2.47–2.53 (m, C14-H), 2.14 (s, 3H, C13-OAc-H), 2.06 (s, 3H, C7-OAc-H), 1.96–1.98 (m, C1-H), 1.93–1.94 (m, C6-H), 1.91 (s, 3H, C18-H), 1.79 (s, 3H, C16-H), 1.78 (s, 3H, C17-H), 1.50 (dd, $J = 15.5$, 7.0 Hz, C14-H), 1.46 (s, 3H, 9,10-acetonide-H), 1.37 (s, 3H, 9,10-acetonide-H), 1.18 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.2$, 170.6, 165.0, 159.9, 155.4, 138.8, 133.9, 130.6, 129.9, 122.4, 120.9, 114.5, 113.7, 106.6, 85.6, 83.3, 81.9, 76.1, 74.5, 71.2, 70.3, 69.0, 55.4, 48.1, 43.0, 42.6, 38.4, 34.6, 31.3, 27.3, 27.2, 27.0, 26.7, 22.0, 20.8, 15.3, 14.0 ppm; ^{19}F NMR (470.5 MHz, $CDCl_3$): $\delta = -74.33$ ppm; MS (ESI): $m/z = 761.3$ $[M + Na]^+$.

2-(3-Bromobenzoyl)-9,10-O-isopropylidene-4-(trifluoroacetyl)-1-deoxybaccatin VI (**4g**, $C_{36}H_{42}BrF_3O_{11}$)

4g was prepared from **11b** and trifluoroacetic anhydride by using the procedure described for preparation of **4e**; yield 80 %; white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.18$ (s, 1H, Bz-2′-H), 7.96 (d, $J = 8.0$ Hz, Bz-6′-H), 7.74 (d, $J = 8.0$ Hz, Bz-4′-H), 7.36 (t, $J = 8.0$ Hz, Bz-5′-H), 5.94 (t, $J = 8.0$ Hz, C13-H), 5.84 (dd, $J = 5.5$, 2.0 Hz, C2-H), 5.46 (t, $J = 8.5$ Hz, C7-H), 4.97 (d, $J = 9.5$ Hz, C10-H), 4.93 (d, $J = 8.0$ Hz, C5-H), 4.42 (d, $J = 8.5$ Hz, C20-H), 4.32 (d, $J = 9.5$ Hz, C9-H), 4.19 (d, $J = 8.5$ Hz, C20-H), 2.83 (d, $J = 5.5$ Hz, C3-H), 2.54–2.59 (m, C6-H), 2.48–2.60 (m, C14-H), 2.13 (s, 3H, C13-OAc-H), 1.98–1.97 (m, C1-H), 1.95–1.94 (m, C6-H), 1.92 (s, 3H, C18-H), 1.78 (s, 6H, C16, C17-H), 1.53–1.46 (m, C14-H), 1.45 (s, 3H, 9,10-acetonide-H), 1.37 (s, 3H, 9,10-acetonide-H), 1.18 (s, 3H, C19-H) ppm; ^{19}F NMR (470.5 MHz, $CDCl_3$): $\delta = -74.26$ ppm; MS (ESI): $m/z = 809.2$ $[M + Na]^+$.

4-(Difluoroacetyl)-9,10-O-isopropylidene-2-(3-methoxybenzoyl)-1-deoxybaccatin VI (**4h**, $C_{37}H_{46}F_2O_{12}$)

4h was prepared from **11a** and difluoroacetic anhydride by using the procedure described for preparation of **4e**; yield 86 %; white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 8.0$ Hz, Bz-6′-H), 7.56 (dd, $J = 2.5$, 1.5 Hz, Bz-2′-H), 7.37 (t, $J = 8.0$ Hz, Bz-5′-H), 7.14 (ddd, $J = 8.0$, 2.5, 1.0 Hz, Bz-4′-H), 6.08 (t, $^2J_{H–C–F} = 53.5$ Hz, difluoroacetyl-H), 5.96 (t, $J = 9.0$ Hz, C13-H), 5.86 (dd, $J = 5.5$, 2.0 Hz, C2-H), 5.47 (t, $J = 8.5$ Hz, C7-H), 4.97 (d, $J = 9.5$ Hz, C10-H), 4.94 (d, $J = 8.5$ Hz, C5-H), 4.47 (d, $J = 8.5$ Hz, C20-H), 4.33 (d, $J = 9.5$ Hz, C9-H), 4.19 (d, $J = 8.5$ Hz, C20-H), 3.85 (s, 3H, Bz-3′-OMe-H), 2.82 (d, $J = 5.5$ Hz, C3-H), 2.52–2.84 (m, C6-H), 2.45–2.51 (m, C14-H), 2.14 (s, 3H, C13-OAc-H), 2.06 (s, 3H, C7-OAc-H), 1.93–1.95 (m, C1-H), 1.90 (s, 3H, C18-H), 1.78 (s, 3H, C16-H), 1.77 (s, 3H, C17-H), 1.53 (dd, $J = 15.5$, 7.0 Hz, C14-H), 1.45 (s, 3H, 9,10-acetonide-H), 1.36 (s, 3H, 9,10-acetonide-H), 1.17 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.8$, 170.6, 165.0, 160.6, 159.9, 138.6, 134.0, 130.7, 129.8, 122.4, 120.6, 113.9, 106.9, 104.9, 84.0, 83.5, 82.0, 76.1, 74.5, 71.3, 70.5, 69.3, 55.5, 48.0, 42.9, 42.6, 38.4, 34.7, 31.3, 27.3, 27.2, 27.0, 26.7, 22.0, 20.9, 15.2, 14.0 ppm; ^{19}F NMR (470.5 MHz, $CDCl_3$): $\delta = -126.50$ (dd, $J = 51.7$, 9.4 Hz, 2F) ppm; MS (ESI): $m/z = 743.3$ $[M + Na]^+$.

9,10-Bis(deacetyl)-2-(3-methoxybenzoyl)-1-deoxybaccatin VI (**5a**, $C_{34}H_{44}O_{12}$)

To a stirred solution of 11.6 mg **4a** (0.017 mmol) in 2 cm^3 methanol was added dil. HCl (0.1 N) to maintain pH 3–4. The reaction mixture was stirred at room temperature for 18–24 h and then quenched with 1 cm^3 saturated aq. $NaHCO_3$, diluted with 40 cm^3 EtOAc, and washed with water (10 $cm^3 \times 2$). The organic layer was washed with brine (10 $cm^3 \times 2$), dried over anhydrous Na_2SO_4, and concentrated to give a crude residue, which was purified by column chromatography on silica gel using EtOAc and *n*-hexane (1/2 v/v) to afford **5a** (8.1 mg, 74 %) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.65$ (m, Bz-6′-H), 7.61–7.60 (m, Bz-2′-H), 7.37 (t, $J = 8.0$ Hz, Bz-5′-H), 7.14–7.12 (m, Bz-4′-H), 6.16 (d, $J = 9.0$ Hz, C10-H), 5.93 (t, $J = 9.0$ Hz, C13-H), 5.72 (dd, $J = 5.5$, 2.0 Hz, C2-H), 5.00 (d, $J = 9.0$ Hz, C9-H), 4.45–4.46 (m, C7-H), 4.43–4.44 (m, C5-H), 4.40 (d, $J = 8.5$ Hz, C20-H), 4.16 (d, $J = 8.5$ Hz, C20-H), 3.86 (s, 3H, Bz-3′-OMe-H), 2.87 (d, $J = 5.5$ Hz, C3-H), 2.53–2.59 (m, C6-H), 2.38–2.47 (m, C14-H), 2.26 (s, 3H, C13-OAc-H), 2.18 (s, 3H, C7-OAc-H), 2.13 (s, 3H, C4-OAc-H), 1.96 (s, 1H, C16-H), 1.95 (s, 3H, C17-H),

1.91–1.93 (m, C6-H), 1.80 (s, 3H, C18-H), 1.63–1.67 (m, C14-H), 1.14 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.7$, 170.5, 169.3, 165.1, 159.8, 137.6, 134.6, 131.0, 129.7, 122.1, 120.0, 114.6, 84.1, 82.0, 74.2, 74.1, 71.8, 69.1, 55.5, 47.1, 45.0, 44.3, 38.2, 31.5, 29.8, 27.2, 26.7, 22.9, 21.5, 21.3, 14.9, 12.7 ppm; MS (ESI): $m/z = 667.3$ $[M + Na]^+$.

9,10-Bis(deacetyl)-2-(3-bromobenzoyl)-1-deoxybaccatin VI (**5b**, $C_{33}H_{41}BrO_{11}$)

5b was prepared from **4b** by using the procedure described for preparation of **5a**; yield 63 %; white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.24$ (d, $J = 2.0$ Hz, Bz-2′-H), 7.98–7.99 (m, Bz-6′-H), 7.72–7.74 (m, Bz-4′-H), 7.36 (t, $J = 8.0$ Hz, Bz-5′-H), 6.14 (d, $J = 9.0$ Hz, C10-H), 5.91–5.94 (m, C2-H), 5.68–5.69 (m, C13-H), 5.02 (d, $J = 9.0$ Hz, C9-H), 4.42–4.46 (m, 2H, C5, C7-H), 4.35 (d, $J = 8.0$ Hz, C20-H), 4.14 (d, $J = 8.0$ Hz, C20-H), 2.89 (d, $J = 6.0$ Hz, C3-H), 2.54–2.61 (m, C6-H), 2.40–2.47 (m, C14-H), 2.28 (s, 3H, C13-OAc-H), 2.19 (s, 3H, C7-OAc-H), 2.13 (s, 3H, C4-OAc-H), 1.96 (s, 3H, C18-H), 1.93–1.94 (m, C1-H), 1.86–1.89 (m, C6-H), 1.80 (s, 3H, C16-H), 1.73 (s, 3H, C17-H), 1.61–1.66 (m, C6-H), 1.15 (s, 3H, C19-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.7$, 170.4, 169.2, 163.7, 137.7, 136.6, 134.4, 133.1, 131.7, 130.4, 128.5, 122.8, 120.0, 84.0, 81.9, 77.3, 76.7, 74.2, 74.1, 72.2, 69.0, 47.2, 45.0, 44.3, 38.2, 38.1, 31.5, 27.2, 26.7, 22.8, 21.5, 21.3, 15.0, 12.7 ppm; MS (ESI): $m/z = 715.2$ (95 %), 717.2 (100 %) $[M + Na]^+$.

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