This article is dedicated to Professor Satoshi Ōmura in celebration of his 2015 Nobel Prize.

Note

Organocatalytic Site-Selective Acylation of 10-Deacetylbaccatin III

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Organocatalytic site-selective diversification of 10-deacetylbaccatin III, a key natural product for the semisynthesis of taxol, has been achieved. Various acyl groups were selectively introduced into the C(10)–OH of 10-deacetylbaccatin III. The C(10)–OH selective acylation was also applied to acylative site-selective dimerization of 10-deacetylbaccatin III to provide the structurally defined dimer.

Key words organocatalyst; site-selectivity; acylation; taxane; 10-deacetylbaccatin III; site-selective dimerization

Natural products have been utilized as the most productive candidates for controlling the cellular events and developing new therapeutic agents.¹⁾ Site-selective (de)functionalization of biologically active natural products was expected to be a useful protocol for further investigating the biological events and the medicinal application. Enzymatic site-selective acylation of complex natural products has been explored to provide derivatives with improved activity and pharmacokinetic properties.²⁾ For a beautiful example, enzymatic site-selective acylation of immunosuppressive rapamycin at the C(42)–OH enabled to convert to an antitumor drug, temsirolimus, in one-step.³⁾ Alternatively, site-selective modification of complex natural products by non-enzymatic protocol has also attracted increasing attention, because it enables to provide natural product derivatives with structural diversity and regiochemical profile different from those obtained by enzymatic protocol.⁴⁾ Site-selective acylation of natural products by non-enzymatic methods, however, often encounter difficulties in controlling the site-selectivity due to the structural complexity and the functional group diversity found in the natural substances. Under these backgrounds, we have developed a method for a non-enzymatic site-selective acylation of polyol compounds such as natural glycosides catalyzed by 4-dialkylaminopyridine-type nucleophilic organocatalyst **6** and the derivatives^{5–10)} (Fig. 1). For example, catalyst **6** could deliver an acyl group at the C(4''')–OH of lanatoside C (**5**) in 86% site-selectivity out of eight potentially reactive hydroxy groups. This site-selectivity seems independent from the intrinsic reactivity of **5** itself, because 4-dimethylaminopyridine (DMAP)-catalyzed acylation provided the corresponding 3'''-O-acylate in 97% site-selectivity.⁸⁾ Thus, introduction of the acyl group at the C(4''')–OH was performed by catalyst-controlled manner and that at C(3''')–OH was done by substrate-controlled manner. In the course of our continuous efforts for site-selective diversification of polyol natural products, we found that catalyst

6 promoted highly site-selective acylation of 10-deacetylbaccatin III (**1**) at the C(10)–OH, which is a natural terpenoid available in relatively abundant amount and used as a key intermediate for clinically widely used antitumor agents, taxol (**4**) and taxotere (**3**) (Fig. 1). The present site-selective acylation was applied to direct acylative dimerization of **1** to successfully provide structurally defined dimer of **1** connected by ester linkage at each of the C(10)–OH group.

Because of limited amount of taxol (**4**) available from natural resources, much efforts have been devoted to develop methods for efficient semisynthesis of **4** from the abundantly available taxane **1**.¹¹⁾ Reported semisynthesis commenced from the differentiation of the C(7)–OH and C(10)–OH with similar reactivity. The relative reactivity of the four hydroxy groups of **1** toward acetic anhydride in pyridine has been studied by Guéritte-Voegelein and co-workers, and suggested to be in the order of C(7)–OH > C(10)–OH > C(13)–OH > C(1)–OH.¹²⁾ Greene reported C(7)–OH-selective silylation by making use of the subtle difference in the reactivities of the hydroxy groups, which enabled a highly efficient semisynthesis of **4**.¹³⁾ Holton found that acylation took place at the C(10)–OH selectively using excess amount of acetic anhydride and Lewis acids (ZnCl₂, CeCl₃) in the absence of pyridine to achieve selective synthesis of baccatin III (**2**).^{14,15)} Under these backgrounds, we initiated our study to investigate site-selectivity in acylation of **1** with catalyst **6** and the related catalyst **7–10** (Table 1).

Results and Discussion

Site-selectivity in acylation of **1** was investigated with **6–10** and also DMAP for the control experiment (Table 1). Acylation catalyzed by DMAP with isobutyryl chloride at –20°C took place preferentially at C(10)–OH of **1** (entry 1). Use of isobutyric anhydride instead of isobutyryl chloride resulted in the higher yield and the similar site-selectivity (entry 2).¹⁶⁾

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Fig. 1. Structures of 10-Deacetylbaccatin III (**1**), Baccatin III (**2**), Taxotere (**3**), Taxol (**4**), and Lanatoside C (**5**)Catalyst **6** useful for site-selective acylation of **1** and **5**.Table 1. Site Selectivity Profile in Acylation of 10-Deacetylbaccatin III (**1**)

Entry	Acyl donor	Catalyst	Solvent	Temperature (°C)	Time (h)	Monoacylate (%)	Site-selectivity (1a : 1b :others)
1 ^{a)}	<i>i</i> -PrCOCl	DMAP	CHCl ₃ /THF (10/1)	-20	48	45	36:64:0
2	(<i>i</i> -PrCO) ₂ O	DMAP	CHCl ₃ /THF (10/1)	-20	48	95	38:62:0
3 ^{a)}	<i>i</i> -PrCOCl	6	CHCl ₃ /THF (10/1)	-20	72	29	38:62:0
4	(<i>i</i> -PrCO) ₂ O	6	CHCl ₃ /THF (10/1)	-20	33	87	7:93:0
5	(<i>i</i> -PrCO) ₂ O	7	CHCl ₃ /THF (10/1)	-20	192	35	11:89:0
6	(<i>i</i> -PrCO) ₂ O	8	CHCl ₃ /THF (10/1)	-20	240	52	38:62:0
7	(<i>i</i> -PrCO) ₂ O	9	CHCl ₃ /THF (10/1)	-20	192	56	9:91:0
8	(<i>i</i> -PrCO) ₂ O	10	CHCl ₃ /THF (10/1)	-20	432	39	38:62:0
9	(<i>i</i> -PrCO) ₂ O	6	CHCl ₃ /THF (10/1)	20	48	90	12:88:0
10	(<i>i</i> -PrCO) ₂ O	6	CHCl ₃ /THF (10/1)	0	48	89	9:91:0
11	(<i>i</i> -PrCO) ₂ O	6	CHCl ₃ /THF (10/1)	-40	48	89	5:95:0
12	(<i>i</i> -PrCO) ₂ O	6	THF	-20	48	78	10:90:0
13	(<i>i</i> -PrCO) ₂ O	6	DMF	-20	48	9	38:62:0

^{a)} *N,N*-Diisopropylethylamine (DIPEA) (1.5 eq.) was used instead of collidine.

Table 2. Site-Selective Acylation of **1** with Various Acid Anhydrides

Entry	R	Time (h)	Monoacylate (%)	Site selectivity (7- <i>O</i> :10- <i>O</i>)
1	Me	12	99	10:90
2	C ₁₁ H ₂₃	120	75	8:92
3 ^{a)}	Ph	168	84	5:95
4	(<i>E</i>)-Ph-CH=CH	72	93	3:97
5	2-Thiophenyl	120	75	3:97
6	3-Furyl	120	85	6:94
7 ^{b)}	CCl ₃	1	52	>99:<1

a) Bz₂O (5.0 eq) and collidine (7.5 eq) were used. *b)* (CCl₃CO)₂O (3.0 eq) and collidine (5.0 eq) were used.

Fig. 2. Direct Site-Selective Dimerization of 10-Deacetylbaccatin III (**1**) by Catalytic C(10)-OH Selective Acylation

In acylation of **1** with isobutyryl chloride, catalyst **6** showed selectivity profile quite similar to that with DMAP (entries 1, 3). On the other hand, acylation with isobutyric anhydride in the presence of catalyst **6** took place at C(10)-OH in high selectivity to provide 10-*O*-acylate **1b** in 81% yield (93% site-selectivity among the monoacylates obtained in a combined yield of 87%; entry 4). These results suggest that the carboxylate counter anion of the acylpyridinium intermediate generated from the anhydride and **6** may be critically involved in the molecular recognition process of the substrate **1** by catalyst **6**.¹⁷⁾ While 10-*O*-acylate **1b** was the major product throughout the acylation reactions promoted by catalysts **6**–**10**, the degree of the site-selectivity and the reaction rates were found to be dependent on both the functionalities and the stereochemistry of the side chains of catalysts **6**–**10** (entries 4–8). Considering that **6** is the best catalyst for the selective C(10)-OH acylation of **1**, temperature effects were investigated (entries 4, 9–11). At the lower reaction temperature, site-selectivity was slightly increased and the highest selectivity (95%) was observed at –40°C (entry 11). The reaction in polar solvents (tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF)) provided **1b**

with decreased site-selectivity for acylation of the C(10)-OH (entries 12, 13). In acylation with catalyst **6** in DMF, the site-selectivity was similar to that observed in acylation catalyzed by DMAP (entries 2 vs. 13). The reaction in DMF proceeded in a quite sluggish manner even in the presence of catalyst **6** (entries 4 vs. 13). All of these results suggest that H-bonding interaction between **1** and **6** may be responsible for the accelerative and site-selective acylation of the C(10)-OH.

Introduction of various acyl groups into C(10)-OH was performed under the optimum conditions shown in entry 4 in Table 1 (Table 2). Treatment of **1** with acetic anhydride in the presence of catalyst **6** selectively provided baccatin III (**2**) in 89% yield (entry 1). Thus, one-step conversion of **1** into **2** was achieved by organocatalytic site-selective acylation. Site-selective lipidation of **1** was also performed with lauric anhydride (entry 2). Aromatic acyl groups including heteroaromatic groups were also selectively introduced into C(10)-OH of **1** (entries 3–6). Contrary to these results, the complete reversal in the site-selectivity was observed in acylation with trichloroacetic anhydride, providing the 7-*O*-acylate exclusively in 52% yield (entry 7). There have been several reports that

trichloroacetylation of **1** took place at C(7)–OH.^{18,19} These results suggested that C(10)–O-acylation with acid anhydride except for trichloroacetic anhydride was performed in a catalyst-controlled manner by virtue of catalyst **6** and the C(7)–O-acylation with trichloroacetic anhydride was done in a substrate-controlled manner.

The observed high site-selectivity of acylation catalyzed by **6** prompted us to examine direct dimerization of **1** by site-selective diacylation (Fig. 2). Dimerization of bioactive compounds is potentially useful strategy toward the discovery of the agents with improved activity profiles including promising activity against the native-compound-resistant infections and cancers.^{20–25} It was expected that highly site-selective acylation promoted by catalyst **6** seemed suitable for acylative dimerization of **1** to provide structurally defined dimer of **1**. Treatment of **1** with mixed anhydride²⁶ **11** prepared from 0.5 eq of undecanedioic acid and pivaloyl chloride in the presence of **6** gave 10-deacetylbaaccatin III dimer **12** in 40% yield (Fig. 2). Thus, regioisomerically pure 10-deacetylbaaccatin III dimer was obtained in one-step from **1**. This protocol may be potentially applicable toward the discovery of new anticancer agents because previous structure–activity relationship studies of taxol (**4**) revealed that acyl group of C(10)–OH was not significantly involved in the main pharmacophore of **4**.^{11,27}

In summary, we have developed a method for organocatalytic site-selective acylation of 10-deacetylbaaccatin III (**1**). The C(10)–OH selective acylation was successfully applied for direct acylative dimerization of **1**, which is expected to become an convenient access to a new class of structurally defined and diverse taxol derivatives.

Experimental

General Remarks ¹H-NMR spectra were measured in CDCl₃ solution (tetramethylsilane (TMS): 0.00 ppm or CHCl₃: 7.26 ppm) using JEOL ECA-400 (400 MHz) spectrophotometer, unless otherwise stated. ¹³C-NMR spectra were measured in CDCl₃ solution and referenced to CDCl₃ (77.0 ppm) using JEOL ECA-400 (100 MHz) spectrophotometer, unless otherwise noted. IR spectra were recorded on JASCO FT/IR-4200 spectrometer. Mass spectra were obtained on JEOL JMS-700 mass spectrometer. Optical rotations were measured with JASCO P-2200. Purification of the reaction products was carried out by flash chromatography using Silica Gel (SiliaFlash® F60). Thin layer chromatography was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel 60F245), and compounds were visualized with UV light and *p*-anisaldehyde stain followed by heating. Preparative thin layer chromatography was performed on precoated plates (0.5 mm, silica gel Merck Kieselgel 60F245) and visualized with UV light. Preparative HPLC was performed with recycling HPLC system, which was equipped with COSMOSIL SSL-II column (20×250 mm) (flow: 4 mL/min, detection: 254 nm). Melting points were measured with Yanaco MICRO MELTING POINT APPARATUS. CHCl₃ was purchased from Kanto Kagaku and pre-treated with neutral alumina for more than 1 d.

General Procedure for Catalytic Site-Selective Acylation of **1 (Tables 1, 2)** **1** (1.0 eq), **6** (10 mol%) and 2,4,6-collidine (1.5 eq) were dissolved in CHCl₃ at 20°C. After the mixture was cooled to –20°C, an acid anhydride (1.1 eq) was added to the mixture. After stirred at the same temperature for the

period indicated in Tables 1 and 2, the reaction was quenched with MeOH. The mixture was diluted with AcOEt and washed with 1 M HCl, saturated aq. NaHCO₃, and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by preparative TLC (MeOH–CHCl₃=5:95) to give a mixture of 7-*O*- and 10-*O*-acylated products. The site-selectivity of the reaction was determined by ¹H-NMR integration. This mixture was further purified by preparative TLC (AcOEt–hexane=80:20) to give the 10-*O*-acylated product.

10-Isobutyryl 10-Deacetylbaaccatin III (**1b**)

Colorless oil. [α]_D²⁰ –89 (*c*=0.64, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ : 8.10 (dd, *J*=8.4, 0.8 Hz, 2H), 7.61 (t, *J*=7.2 Hz, 1H), 7.48 (t, *J*=7.6 Hz, 2H), 6.30 (s, 1H), 5.62 (d, *J*=6.8 Hz, 1H), 4.98 (dd, *J*=9.6, 2.4 Hz, 1H), 4.88 (t, *J*=7.6 Hz, 1H), 4.47 (dd, *J*=10.4, 6.8 Hz, 1H), 4.30 (d, *J*=8.4 Hz, 1H), 4.14 (d, *J*=8.4 Hz, 1H), 3.88 (d, *J*=7.2 Hz, 1H), 2.73 (heptet, *J*=6.8 Hz, 1H), 2.66–2.50 (m, 2H), 2.32–2.26 (m, 5H), 2.20 (brs, 1H), 2.04 (s, 3H), 1.91–1.80 (m, 1H), 1.66 (s, 3H), 1.32 (d, *J*=6.8 Hz, 3H), 1.24 (d, *J*=7.2 Hz, 3H), 1.10 (s, 6H). ¹³C-NMR (100 MHz, CDCl₃) δ : 204.2, 177.2, 170.6, 167.0, 146.2, 133.7, 131.9, 130.1, 129.2, 128.6, 84.4, 80.7, 79.1, 76.4, 75.8, 74.9, 72.3, 67.9, 58.6, 46.1, 42.6, 38.5, 35.5, 34.0, 26.9, 22.6, 20.9, 19.2, 18.6, 15.6, 9.4. IR (neat) 3485, 2976, 2941, 1715, 1452 cm^{–1}. MS (FAB) *m/z* (rel intensity) 615 (M+H⁺, 2), 252 (60), 73 (100). High resolution (HR)-MS (FAB) *m/z* Calcd for C₃₃H₄₃O₁₁ (M+H)⁺ 615.2805. Found 615.2800.

Baaccatin III (**2**)

Colorless amorphous. [α]_D²⁰ –77 (*c*=0.36, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ : 8.10 (dd, *J*=8.8, 1.6 Hz, 2H), 7.61 (t, *J*=7.6 Hz, 1H), 7.48 (t, *J*=7.6 Hz, 2H), 6.32 (s, 1H), 5.62 (d, *J*=7.6 Hz, 1H), 4.98 (dd, *J*=9.6, 2.0 Hz, 1H), 4.90 (t, *J*=7.4 Hz, 1H), 4.47 (dd, *J*=11.2, 6.8 Hz, 1H), 4.31 (d, *J*=8.0 Hz, 1H), 4.15 (d, *J*=8.0 Hz, 1H), 3.88 (d, *J*=6.8 Hz, 1H), 2.61–2.51 (m, 1H), 2.30–2.27 (m, 5H), 2.24 (s, 3H), 2.05 (s, 3H), 1.91–1.81 (m, 1H), 1.67 (s, 3H), 1.10 (s, 6H). ¹³C-NMR (100 MHz, CDCl₃) δ : 204.2, 171.4, 170.6, 167.0, 146.4, 133.7, 131.8, 130.1, 129.2, 128.6, 84.4, 80.7, 79.1, 76.4, 76.2, 74.8, 72.3, 67.9, 58.7, 46.1, 42.7, 38.5, 35.6, 26.9, 22.6, 20.9, 15.6, 9.4. IR (neat) 3515, 2943, 1716, 1241, 1071, 756 cm^{–1}. MS (FAB) *m/z* (rel intensity) 609 (M+Na⁺, 10), 587 (M+H⁺, 2), 154 (100). HR-MS (FAB) *m/z* Calcd for C₃₁H₃₈O₁₁Na (M+Na)⁺ 609.2312. Found 609.2315.

10-*O*-Lauryl-10-deacetylbaaccatin III

Colorless amorphous. [α]_D²⁰ –54 (*c*=0.75, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ : 8.10 (dd, *J*=7.2, 1.6 Hz, 2H), 7.61 (t, *J*=7.4 Hz, 1H), 7.48 (t, *J*=7.8 Hz, 2H), 6.31 (s, 1H), 5.62 (d, *J*=6.8 Hz, 1H), 4.98 (d, *J*=7.6 Hz, 1H), 4.89 (brt, 1H), 4.50–4.44 (m, 1H), 4.31 (d, *J*=8.4 Hz, 1H), 4.15 (d, *J*=8.4 Hz, 1H), 3.88 (d, *J*=6.8 Hz, 1H), 2.62–2.40 (m, 4H), 2.34–2.22 (m, 5H), 2.14 (brd, 1H), 2.04 (s, 3H), 1.91–1.81 (m, 1H), 1.71 (quint, *J*=7.0 Hz, 2H), 1.66 (s, 3H), 1.44–1.18 (br, 16H), 1.10 (s, 6H), 0.88 (t, *J*=7.0 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ : 204.2, 174.1, 170.6, 167.0, 146.2, 133.7, 131.9, 130.1, 129.3, 128.6, 84.5, 80.8, 79.1, 76.4, 75.9, 74.9, 72.3, 68.0, 58.7, 46.1, 42.7, 38.5, 35.5, 34.2, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 27.0, 24.8, 22.7, 22.6, 20.9, 15.6, 14.1, 9.4. IR (neat) 3505, 2925, 1715, 1240 cm^{–1}. MS (FAB) *m/z* (rel intensity) 749 (M+Na⁺, 60), 727 (M+H⁺, 3), 176 (100). HR-MS (FAB) *m/z* Calcd for C₄₁H₅₈O₁₁Na (M+Na)⁺ 749.3877. Found 749.3878.

10-*O*-Benzoyl-10-deacetylbaaccatin III

Colorless powder. mp 179–181°C. [α]_D²⁰ –63 (*c*=1.3, THF). ¹H-NMR (400 MHz, CDCl₃) δ : 8.13–8.07 (m, 4H), 7.62 (t,

$J=7.0$ Hz, 2H), 7.49 (t, $J=7.8$ Hz, 2H), 7.48 (t, $J=7.8$ Hz, 2H), 6.59 (s, 1H), 5.67 (d, $J=7.2$ Hz, 1H), 5.01 (d, $J=8.0$ Hz, 1H), 4.93 (t, $J=7.8$ Hz, 1H), 4.60–4.52 (m, 1H), 4.33 (d, $J=8.4$ Hz, 1H), 4.17 (d, $J=8.4$ Hz, 1H), 3.96 (d, $J=6.8$ Hz, 1H), 2.71–2.55 (m, 2H), 2.39–2.26 (m, 5H), 2.16 (brs, 1H), 2.11 (s, 3H), 1.95–1.84 (m, 1H), 1.693 (s, 3H), 1.690 (brs, 1H), 1.23 (s, 3H), 1.19 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 204.0, 170.7, 167.1, 166.4, 146.6, 133.7, 133.6, 131.8, 130.1, 130.0, 129.25, 129.17, 128.6, 128.5, 84.5, 80.8, 79.1, 76.6, 76.4, 74.9, 72.4, 68.0, 58.7, 46.2, 42.7, 38.5, 35.7, 27.2, 22.6, 21.2, 15.7, 9.4. IR (neat) 3483, 2942, 1717, 1451, 1270 cm^{-1} . MS (FAB) m/z (rel intensity) 671 ($\text{M}+\text{Na}^+$, 2), 154 (100). HR-MS (FAB) m/z Calcd for $\text{C}_{36}\text{H}_{40}\text{O}_{11}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 671.2468. Found 671.2462.

10-*O*-Cinnamoyl-10-deacetylbaaccatin III

Colorless microcrystal. mp 152–157°C. $[\alpha]_{\text{D}}^{20}$ –79 ($c=0.70$, CHCl_3). ^1H -NMR (400 MHz, CDCl_3) δ : 8.11 (dd, $J=7.2$, 1.2 Hz, 2H), 7.78 (d, $J=16.4$ Hz, 1H), 7.65–7.53 (m, 3H), 7.49 (t, $J=7.8$ Hz, 2H), 7.44–7.37 (m, 3H), 6.59 (d, $J=15.6$ Hz, 1H), 6.47 (s, 1H), 5.65 (d, $J=7.2$ Hz, 1H), 5.01 (d, $J=7.6$ Hz, 1H), 4.92 (brt, 1H), 4.56–4.50 (m, 1H), 4.32 (d, $J=8.4$ Hz, 1H), 4.17 (d, $J=8.0$ Hz, 1H), 3.92 (d, $J=7.2$ Hz, 1H), 2.73 (d, $J=4.0$ Hz, 1H), 2.65–2.53 (m, 1H), 2.34–2.25 (m, 5H), 2.18 (brd, 1H), 2.09 (s, 3H), 1.94–1.83 (m, 1H), 1.69 (s, 3H), 1.67 (s, 1H), 1.17 (s, 3H), 1.16 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 204.2, 170.7, 167.1, 166.9, 146.7, 146.6, 134.1, 133.7, 131.9, 130.7, 130.1, 129.3, 128.9, 128.6, 128.3, 116.9, 84.5, 80.8, 79.1, 76.4, 76.2, 74.9, 72.4, 68.0, 58.7, 46.1, 42.7, 38.5, 35.6, 27.1, 22.6, 21.1, 15.7, 9.4. IR (neat) 3523, 2942, 1715, 1633, 1452 cm^{-1} . MS (FAB) m/z (rel intensity) 697 ($\text{M}+\text{Na}^+$, 2), 676 ($\text{M}+\text{H}^+$, 1), 154 (100). HR-MS (FAB) m/z Calcd for $\text{C}_{38}\text{H}_{42}\text{O}_{11}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 697.2625. Found 697.2632.

10-*O*-2-Thiophenyl-10-deacetylbaaccatin III

Colorless powder. mp 175–179°C. $[\alpha]_{\text{D}}^{20}$ –60 ($c=0.55$, THF). ^1H -NMR (400 MHz, CDCl_3) δ : 8.11 (dd, $J=7.6$, 1.2 Hz, 2H), 7.89 (dd, $J=7.6$, 1.2 Hz, 1H), 7.65–7.57 (m, 2H), 7.49 (t, $J=7.8$ Hz, 2H), 7.15 (dd, $J=5.0$, 3.8 Hz, 1H), 6.53 (s, 1H), 5.66 (d, $J=6.8$ Hz, 1H), 5.00 (d, $J=8.0$ Hz, 1H), 4.92 (brt, 1H), 4.55–4.48 (m, 1H), 4.32 (d, $J=8.4$ Hz, 1H), 4.16 (d, $J=8.4$ Hz, 1H), 3.94 (d, $J=6.8$ Hz, 1H), 2.67–2.54 (m, 1H), 2.50 (d, $J=4.4$ Hz, 1H), 2.39–2.25 (m, 5H), 2.20–2.08 (m, 4H), 1.93–1.82 (m, 1H), 1.69 (s, 3H), 1.66 (s, 1H), 1.20 (s, 3H), 1.17 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 203.9, 170.7, 167.1, 161.9, 146.5, 134.5, 133.7, 133.4, 132.5, 131.6, 130.1, 129.2, 128.6, 128.0, 84.4, 80.8, 79.1, 76.5, 76.4, 74.8, 72.3, 68.0, 58.7, 46.2, 42.7, 38.5, 35.7, 27.0, 22.6, 21.0, 15.7, 9.4. IR (neat) 3477, 2937, 1715, 1259 cm^{-1} . MS (FAB) m/z (rel intensity) 677 ($\text{M}+\text{Na}^+$, 5), 154 (100). HR-MS (FAB) m/z Calcd for $\text{C}_{34}\text{H}_{38}\text{O}_{11}\text{SNa}$ ($\text{M}+\text{Na}$) $^+$ 677.2033. Found 677.2032.

10-*O*-3-Furyl-10-deacetylbaaccatin III

Colorless powder. mp 155–160°C. $[\alpha]_{\text{D}}^{20}$ –83 ($c=0.75$, THF). ^1H -NMR (400 MHz, CDCl_3) δ : 8.14–8.08 (m, 3H), 7.62 (t, $J=7.6$ Hz, 1H), 7.52–7.46 (m, 3H), 6.78 (d, $J=1.2$ Hz, 1H), 6.51 (s, 1H), 5.65 (d, $J=7.2$ Hz, 1H), 5.00 (d, $J=8.0$ Hz, 1H), 4.92 (brq, 1H), 4.57–4.47 (m, 1H), 4.32 (d, $J=8.4$ Hz, 1H), 4.16 (d, $J=8.4$ Hz, 1H), 3.93 (d, $J=6.8$ Hz, 1H), 2.65–2.52 (m, 2H), 2.36–2.26 (m, 5H), 2.11 (brs, 1H), 2.10 (s, 3H), 1.94–1.82 (m, 1H), 1.69 (s, 3H), 1.65 (s, 1H), 1.17 (s, 3H), 1.15 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 204.0, 170.7, 167.1, 162.8, 148.5, 146.5, 144.0, 133.7, 131.7, 130.1, 129.2, 128.6, 118.5, 109.9, 84.4, 80.8, 79.1, 76.4, 76.1, 74.8, 72.3, 68.0, 58.7, 46.2, 42.7, 38.5, 35.7, 27.1, 22.6, 21.1, 15.7, 9.4. IR (neat) 3505, 2943,

1714, 1272 cm^{-1} . MS (FAB) m/z (rel intensity) 661 ($\text{M}+\text{Na}^+$, 10), 639 ($\text{M}+\text{H}^+$, 1), 154 (100). HR-MS (FAB) m/z Calcd for $\text{C}_{34}\text{H}_{38}\text{O}_{12}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 661.2261. Found 661.2264.

7-*O*-Trichloroacetyl-10-deacetylbaaccatin III

Colorless needle. mp 218°C (dec.). $[\alpha]_{\text{D}}^{20}$ –27 ($c=0.50$, CHCl_3). ^1H -NMR (400 MHz, CDCl_3) δ : 8.10 (dd, $J=8.4$, 2.4 Hz, 2H), 7.62 (t, $J=7.2$ Hz, 1H), 7.49 (t, $J=7.6$ Hz, 2H), 5.65 (d, $J=6.8$ Hz, 1H), 5.56 (dd, $J=10.4$, 7.2 Hz, 1H), 5.32 (s, 1H), 4.99 (d, $J=8.4$ Hz, 1H), 4.88 (t, $J=7.6$ Hz, 1H), 4.35 (d, $J=8.8$ Hz, 1H), 4.19 (d, $J=8.0$ Hz, 1H), 4.10 (d, $J=6.8$ Hz, 1H), 3.99 (brs, 1H), 2.78–2.65 (m, 1H), 2.34–2.23 (m, 5H), 2.12 (s, 3H), 2.10–2.00 (m, 2H), 1.92 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 209.9, 170.9, 166.9, 161.0, 142.8, 134.3, 133.8, 130.1, 129.1, 128.7, 83.3, 80.1, 78.7, 77.9, 76.4, 74.9, 74.3, 67.8, 56.1, 46.7, 42.5, 38.5, 32.5, 26.6, 22.5, 19.4, 15.0, 10.8. IR (neat) 3466, 2949, 1767, 1715, 1452, 1244 cm^{-1} . MS (FAB) m/z (rel intensity) 689 ($\text{M}+\text{H}^+$, 2), 185 (60), 105 (100). HR-MS (FAB) m/z Calcd for $\text{C}_{31}\text{H}_{36}\text{O}_{11}\text{Cl}_3$ ($\text{M}+\text{H}$) $^+$ 689.1323. Found 689.1310.

10-Deacetylbaaccatin III Dimer 12

To a solution of pivaloyl chloride (28 μL , 230 μmol , 2.5 eq) was added undecanedioic acid (10 mg, 46 μmol , 0.5 eq) and DIPEA (47 μL , 347 μmol , 3.8 eq) in CH_2Cl_2 (1.0 mL) dropwise at room temperature, and the mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated *in vacuo* and diluted with CHCl_3 (1.0 mL). The resulting mixture was added to a precooled solution of **1** (50 mg, 92 μmol , 1.0 eq), **6** (7.6 mg, 9.2 μmol , 10 mol%) and collidine (37 μg , 280 μmol , 3.0 eq) in CHCl_3 (8.0 mL, total 9.0 mL) at –20°C (final concentration of **1**: 0.01 M). After stirred at –20°C for 30 h, the reaction mixture was quenched with methanol (5.0 mL) and stirred at room temperature for 1 h. The mixture was diluted with AcOEt and washed with 1 M HCl, saturated aq. NaHCO_3 , and brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by preparative TLC (AcOEt–hexane=80:20) to give a 10-deacetylbaaccatin III dimer **12** as colorless amorphous (23 mg, 40% yield as a single isomer). $[\alpha]_{\text{D}}^{20}$ –75 ($c=1.0$, THF). ^1H -NMR (400 MHz, CDCl_3) δ : 8.06 (dd, $J=8.4$, 1.2 Hz, 4H), 7.58 (t, $J=7.6$ Hz, 2H), 7.45 (t, $J=7.8$ Hz, 4H), 6.31 (s, 2H), 5.60 (d, $J=7.2$ Hz, 2H), 4.98 (d, $J=7.6$ Hz, 2H), 4.88 (t, $J=7.8$ Hz, 2H), 4.47 (dd, $J=10.4$, 6.8 Hz, 2H), 4.29 (d, $J=7.2$ Hz, 2H), 4.14 (d, $J=8.4$ Hz, 2H), 3.87 (d, $J=7.2$ Hz, 2H), 2.68 (brs, 2H), 2.59–2.41 (m, 6H), 2.32–2.26 (m, 10H), 2.04 (s, 6H), 1.90–1.76 (m, 4H), 1.71 (quint, $J=7.2$ Hz, 4H), 1.65 (s, 6H), 1.45–1.30 (m, 10H), 1.12 (s, 6H), 1.10 (s, 6H). ^{13}C -NMR (100 MHz, CDCl_3) δ : 204.2, 174.1, 170.6, 167.0, 146.5, 133.6, 131.8, 130.1, 129.3, 128.6, 84.4, 80.7, 79.0, 76.4, 76.0, 74.9, 72.3, 67.8, 58.6, 46.1, 42.6, 38.7, 35.5, 34.2, 29.0, 28.8, 27.0, 24.8, 22.6, 21.0, 15.6, 9.4. IR (neat) 3503, 2932, 1716, 1242, 1070 cm^{-1} . MS (FAB) m/z (rel intensity) 1292 ($\text{M}+\text{Na}^+$, 2), 154 (100). HR-MS (FAB) m/z Calcd for $\text{C}_{69}\text{H}_{88}\text{O}_{22}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 1291.5665. Found 1291.5660.

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Supplementary Materials The online version of this article contains supplementary materials.

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