JOC The Journal of Organic Chemistry

Article

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Regioselective Diversification of a Cardiac Glycoside, Lanatoside C, by Organocatalysis

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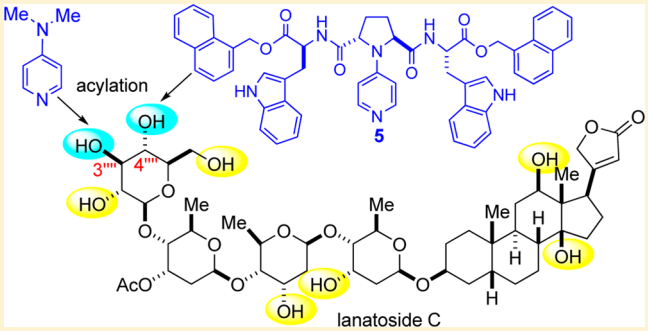
Supporting Information

ABSTRACT: Acylation of lanatoside C in the presence of organocatalyst **5** gave the C(4′′′′)-*O*-acylate in up to 90% regioselectivity (catalyst-controlled regioselectivity). Various functionalized acyl groups can be introduced at the C(4′′′′)-OH by a mixed anhydride method in the presence of **5** or the related organocatalyst. On the other hand, DMAP-catalyzed acylation of lanatoside C gave the C(3′′′′)-*O*-acylate in up to 97% regioselectivity (substrate-controlled regioselectivity). Thus, diverse regioselective introduction of acyl groups among eight free hydroxy groups of lanatoside C was achieved.

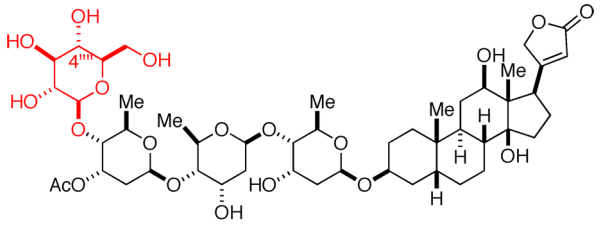


INTRODUCTION

Chemo- and regioselective manipulation of one of plural hydroxy groups of polyol natural products has been a fundamental challenge in organic synthesis because of the difficulties associated with the similar reactivities of the hydroxy groups. Enzymatic methods have been well developed for regioselective acylation of polyol natural products including carbohydrates.[1] On the other hand, nonenzymatic methods for regioselective acylation of polyol natural products have been limitedly developed. Miller and co-workers reported the pioneering examples of the regioselective acylation of erythromycin A and apoptolidin A with peptide-based organocatalysts.[2] We also reported regioselective acylation of a naturally occurring cardiac glycoside, digitoxin (**2**) (Scheme 1).[3,4] Because the hydroxy group at C(4‴) of **2** has high intrinsic reactivity, the 4‴-acetate was obtained as a sole monoacylate in 66% yield with concomitant formation of the 3‴-, 4‴-diacetate in 18% yield by treatment of **2** with acetic anhydride in the presence of 10 mol % of DMAP in $CHCl_3$ at 20 °C for 24 h. On the other hand, acetylation of **2** catalyzed by 10 mol % of **1** provided the 4′′′′-acetate a sole product in 98% yield without the concomitant formation of the diacylate.

We suppose that the observed perfect regioselectivity in the acylation promoted by **1** is the result from the combined effects of substrate-controlled regioselectivity due to the high intrinsic reactivity of the C(4‴)-OH and catalyst-controlled monoacylation. We have also developed an organocatalytic one-step procedure for the chemo- and regioselective acylation of a secondary hydroxy group of mono- and disaccharides.[5−7] Acylation of octyl β-D-glucopyranoside (**3**, R = C_8H_{17}) catalyzed by **1** took place exclusively at the intrinsically less reactive secondary hydroxy group at C(4) in the presence of an otherwise more reactive primary hydroxy group at C(6) and two other secondary hydroxy groups at C(2) and C(3) (Scheme 2).[8] This is in contrast to the typical examples of enzymatic acylation of natural and unnatural products with a terminal glucopyranoside, in which the C(6)-acylates are the major acylates.[1]

Here we report a regiochemical profile of acylaion of a more complex polyol natural product possessing eight free hydroxy groups, lanatoside C (**4**), a clinically used cardiac glycoside, which is composed of a tetrasaccharide containing a terminal glucopyranoside (shown in red) and an aglycon named digoxigenin. We had expected that acylation might take place selectively at C(4′′′′)-OH of the terminal glucopyranose moiety in the presence of **1** on the basis of our previous observation shown in Scheme 2 and found the regiochemical outcome as expected.

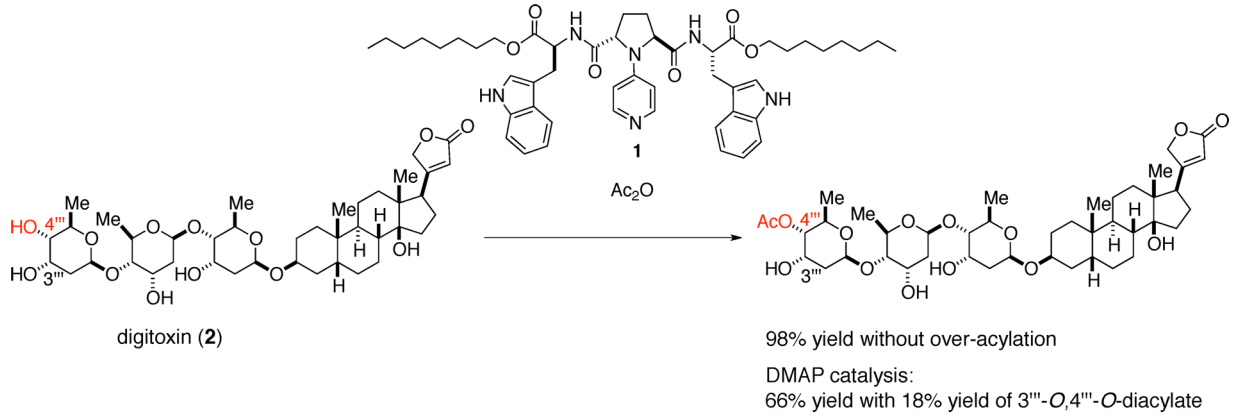


RESULTS AND DISCUSSION

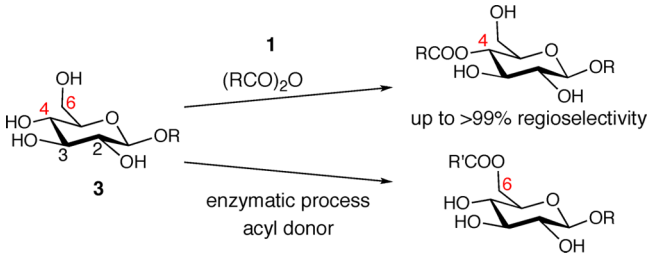
We have been interested in regioselective acylation of carbohydrates because it would provide opportunities to develop compounds with potent biological activity.[1c,9,10] We have developed the organocatalytic regioselective acylation of a secondary hydroxy group at C(4) of glucopyranosides.[5a,d,e]

Received: May 16, 2012
Published: August 7, 2012

Scheme 1. Combined Effects of Substrate-Controlled Regioselective Acylation and Catalyst-Controlled Monoacylation of Digitoxin (2)



Scheme 2. Organocatalytic Regioselective Acylation and Enzymatic Regioselective Acylation of Glucopyranoside Derivatives



Since regioselective acylation of glucopyranosides by catalyst **1** took place with high functional group tolerance,[5d] we had envisioned that this protocol would allow acyl groups to be selectively introduced at C(4′′′′)-OH of the terminal glucopyranoside moiety of **4**. The regiochemical profile of acylation of **4** with acid anhydrides was investigated in the presence of catalyst **1**, its diastereomeric catalysts **1a** and **1b**, its enantiomeric catalyst ***ent*-1**, its ester derivative **5**, and DMAP (Table 1). Acylation of **4** at 20 °C took place in a random manner by the treatment with isobutyric anhydride in the presence of 10 mol % of **1** in $CHCl_3$/THF (9:1) at 20 °C to give the C(6′′′′)-, C(4′′′′)-, C(3′′′′)-, and other isobutyrates in a ratio of 4:38:48:0 in a combined yield of 77% for monoacylation together with 9% of the diacylate (entry **2**). On the other hand, formation of the C(4′′′′)-isobutyrate was predominant (66% regioselectivity) in the reaction at −20 °C (entry 3). Acylation took place predominantly at C(4′′′′)-OH in 86% regioselectivity and 75% yield for monoacylation by treatment of **4** with isobutyric anhydride and 10 mol % of **1** in $CHCl_3$/THF (9:1) at −60 °C for 96 h (entry 4). Further improved regioselectivity was obtained in the acylation with catalyst **5**. The C(4′′′′)-isobutyrate was obtained in 90% regioselectivity and 87% yield for monoacylation by acylation of **4** with isobutyric anhydride in the presence of catalyst **5** (entry 8). Use of acetic anhydride instead of isobutyric anhydride gave diminished regioselectivity (76%) and yield (68%) for monoacylation (entry 9). While acylation of **4** with diastereomeric catalyst **1a** gave the C(4′′′′)-isobutyrate as the major monoacylate with diminished regioselectivity (73%), that with another diastereomeric catalyst, **1b**, gave the totally different regiochemical results (entries 5 and 6). The C(3′′′′)-isobutyrate was obtained as the major acylate in 80% regioselectivity and 65% yield for monoacylation by treatment of **4** with isobutyric anhydride in the presence of **1b**. The enantiomeric catalyst of **1**, ***ent*-1**, gave the similar results as those obtained by the reaction of **4** with catalyst **1b** (entries 6 and 7). By DMAP-catalyzed acylation of **4**, the C(3′′′′)-isobutyrate was obtained in an extremely high regioselectivity (entry 1). Treatment of **4** with isobutyric anhydride in the presence of 10 mol % of DMAP in $CHCl_3$/THF (9:1) at −60 °C for 96 h gave the C(3′′′′)-isobutyrate as the major acylate in 97% regioselectivity and 85% yield for monoacylation (entry 1). This result indicates that C(3′′′′)-OH has the highest intrinsic reactivity among eight hydroxy groups of **4** in a $CHCl_3$/THF (9:1) solution, i.e., *substrate-controlled regioselectivity*. On the other hand, regioselective acylation at C(4′′′′)-OH was attained by catalyst **1** and **5** in a $CHCl_3$/THF (9:1) solution by overcoming the extraordinary high intrinsic reactivity of C(3′′′′)-OH in the solution, i.e., *catalyst-controlled regioselectivity* (entries 1 vs 4 and 8). The C(3′′′′)-*O*-acylate was the major acylate in the acylation of **4** with catalysts **1b** and ***ent*-1**. These results suggest that **1**, **1a**, and **5** are *matched* catalysts for C(4′′′′)-*O*-acylation, while **1b** and ***ent*-1** are *mismatched* ones, which provides the regiochemical results mainly based on the substrate-controlled regioselectivity. Acylation of **4** in DMF gave the regiochemical results independent from the nature of catalysts. The C(6′′′′)-isobutyrate was obtained as the major acylate via acylation of the primary hydroxy group of **4** either by DMAP (70% regioselectivity) or catalyst **1** (76% regioselectivity) (entries 10 and 11), indicating that C(6′′′′)-OH has the highest intrinsic reactivity among eight hydroxy groups of **4** in DMF, and substrate-controlled regioselectivity was observed even in the acylation catalyzed by **1**. All of these results suggest that the hydrogen-bonding interaction between the catalyst and the substrate must be the key to the regioselective acylation promoted by the catalyst. The catalyst-controlled regioselectivity was attained in the reactions in a $CHCl_3$/THF (9:1) solution at low temperature, while it cannot to be attained in the reactions in DMF, because the hydrogen-bonding interaction is hampered by a strong hydrogen-bond acceptor, DMF.[11]

The solvent-dependency on the regiochemical profile observed in the acylation of **4** is quite comparable with our previous findings on that of glucopyranosides catalyzed by **1** (Scheme 2).[5a,c,d] The difference in the intrinsic reactivities of the hydroxy groups of **4** depending on the solvents is assumed to be ascribed to the difference in the conformation of **4** (see Figure 2).

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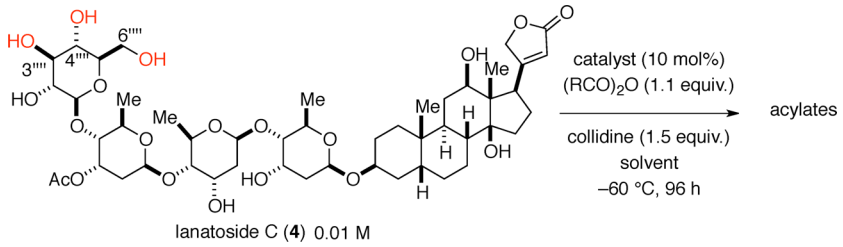
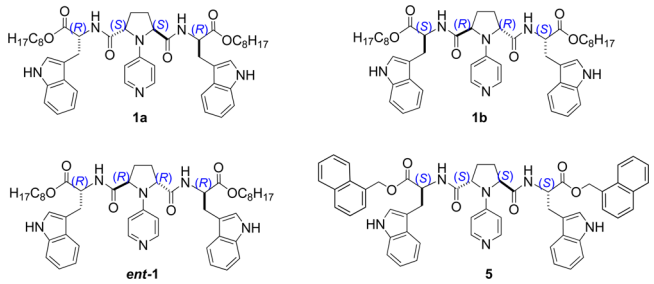
Table 1. Regiochemical Profile of Catalytic Acylation of Lanatoside C (4)



entry	catalyst	R	solvent	monoacylate[a] (%)	regioselectivity[b] 6′′′′-*O*:4′′′′-*O*:3′′′′-*O*:others	diacylate[c] (%)
1	DMAP	*i*-Pr	$CHCl_3$/THF = 9:1	85	0:3:97:0	trace
2[d]	**1**	*i*-Pr	$CHCl_3$/THF = 9:1	77	4:38:48:0	9
3[e]	**1**	*i*-Pr	$CHCl_3$/THF = 9:1	81	0:66:34:0	0
4	**1**	*i*-Pr	$CHCl_3$/THF = 9:1	75	0:86:14:0	0
5	**1a**	*i*-Pr	$CHCl_3$/THF = 9:1	77	0:73:27:0	0
6	**1b**	*i*-Pr	$CHCl_3$/THF = 9:1	65	7:13:80:0	6
7	***ent*-1**	*i*-Pr	$CHCl_3$/THF = 9:1	62	25:13:62:0	12
8	**5**	*i*-Pr	$CHCl_3$/THF = 9:1	87	0:90:10:0	0
9	**5**	Me	$CHCl_3$/THF = 9:1	68	0:76:24:0	19
10[f]	DMAP	*i*-Pr	DMF	51	70:13:13:0	24
11[f]	**1**	*i*-Pr	DMF	56	76:12:12:0	0

[a]Total yield of monoacylates. [b]Regioselectivity (%) among eight monacylates. [c]Total yield of diacylates. [d]Run at 20 °C for 48 h. [e]Run at −20 °C for 96 h. [f]The reaction was run at a substrate concentration of 0.05 M.



We then envisaged regioselective introduction of various functionalized acyl groups into C(4′′′′)-OH of **4**. Although functionalized acid anhydrides can be used for regioselective introduction of various functionalized acyl groups at C(4)-OH of glucopyranoside derivatives,[5d] use of a mixed anhydride method seems to be more beneficial from the viewpoints of operational and atom economy. In order to develop regioselective acylation of **4** employing a mixed anhydride method, we first examined conditions suitable for regioselective acylation of **3** (R = C_8H_{17}) with **6** as a functionalized acyl donor (Table 2). Since carboxylate ions have been not only proposed to be superior general bases for deprotonation of the reacting hydroxy group at the transition state of acylation[12] but also known to be the counteranions suitable for regioselective acylation of **3** (R = C_8H_{17}) catalyzed by **1**,[5a,b] various carboxylate donors were examined for the formation of the mixed anhydrides. A mixture of **6**, pivalic anhydride (1.1 equiv), and collidine (2.5 equiv) in $CHCl_3$ was stirred at room temperature for 1 h. This solution was added to a solution of **3** and 10 mol % of catalyst **1** in $CHCl_3$, and the resulting mixture was stirred at 20 °C for 72 h. The acyl group derived from **6** was introduced at C(4)-OH of **3** in 41% regioselectivity and 77% yield (entry 1). The corresponding reaction at −20 °C was very sluggish to give only trace amount of the acylates (entry 2). While a mixed anhydride method using benzoic anhydride gave the desired monoacylate in only 25% yield due to the formation of the corresponding benzoate in 39% yield, the desired 4-*O*-acylate **7** was obtained in 97% regioselectivity (entry 3). Use of 2-methyl-6-nitrobenzoic anhydride[13] was found to be ineffective for this purpose (entry 4). Use of pivaloyl chloride[14] in the presence of diisopropylethylamine (DIPEA) and **1** was found to be effective to give **7** in 82% yield and 98% regioselectivity (entry 5).

According to the mixed anyhydride method established in entry 5 of Table 2, several functionalized acyl groups were introduced regioselectively into lanatoside C (**4**) (Table 3). A mixture of **6**, pivaloyl chloride (1.1 equiv), and DIPEA (1.1 equiv) in $CHCl_3$ was stirred at room temperature for 1 h. This solution was added to a precooled solution of **4**, collidine (1.5 equiv), and 10 mol % of catalyst **1** in $CHCl_3$/THF (14:1) at −60 °C, and the resulting mixture was stirred for 168 h. The acyl group derived from **6** was introduced at C(4′′′′)-OH of **4** in 85% regioselectivity and 84% yield for monoacylation (entry 1). Regioselective lipidation of **4** was achieved with the mixed anhydrides derived from long chain fatty acids such as palmitic acid and eicosapentaenoic acid (EPA) in the presence of **1**, giving the C(4′′′′)-*O*-acylates in 82% and 82% regioselectivity, respectively (entries 2 and 3). Similarly, a levulinoyl group was introduced at C(4′′′′)-OH in 88% regioselectivity in the presence of catalyst **5** (entry 4).

We have proposed a model of the transition state assembly for regioselective acylation of octyl β-D-glucopyranoside catalyzed by **1**, in which two hydrogen bonds between the substrate and the catalyst are involved.[5a,c,d] The involvement of the hydrogen-bonding interaction in the regioselective acylation of **4** catalyzed by **1** was also suggested by the temperature and

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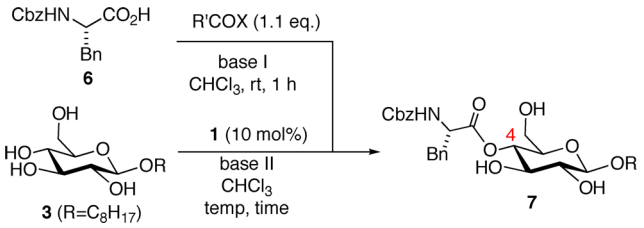
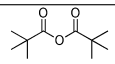
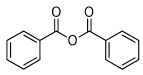
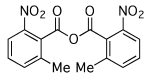
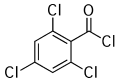
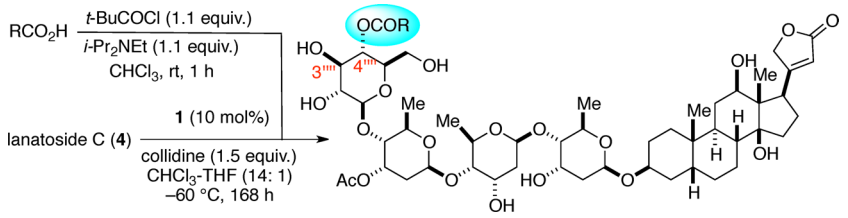
Table 2. Optimization of the Conditions for a Mixed Anhydride Method[a]

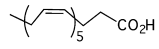
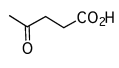


entry	R'COX	Base I (equiv.)	Base II (equiv.)	temp. (°C)	time (h)	monoacylate[b] (%)	regioselectivity[c] (%)
1		collidine (2.5)	–	20	72	77	41
2		collidine (2.5)	–	–20	120	trace	–
3		collidine (2.5)	–	–20	120	25[d]	97
4		collidine (2.5)	–	–20	168	trace	–
5		DIPEA (1.1)	collidine (1.5)	–20	24	82	98
6		DIPEA (1.1)	collidine (1.5)	–20	24	23	97

[a]The reactions were run at a substrate concentration of 0.1 M. [b]Total yield of monoacylates. [c]Regioselectivity (%) for the 4-*O*-monoacylate among four monoacylates. [d]Benzoylated product was obtained in 39% yield.

Table 3. Catalyst-Controlled Regioselective Introduction of Functionalized Acyl Groups into Lanatoside C (4) Using a Mixed Anhydride Method[a]



entry	RCO_2H	monoacylate[b] (%)	regioselectivity[c] 6''''-*O* : 4''''-*O* : 3''''-*O* : others	diacylate[d] (%)
1	**6**	84	0 : 85 : 15 : 0	0
2	$C_{15}H_{31}CO_2H$	86	0 : 82 : 18 : 0	0
3		86	0 : 82 : 18 : 0	0
4[e]		70	0 : 88 : 12 : 0	19

[a]The reactions were run at a substrate concentration of 0.01 M. [b]Total yield of monoacylates. [c]Regioselectivity (%) among eight monacylates. [d]Total yield of diacylates. [e]Catalyst **5** (10 mol %) was used.

solvent effects (Table 1, entries 2–4 and 11). Based on the previously proposed model for regioselective acylation of glucopyranosides by **1**, a hypothetical picture of the transition state assembly for regioselective acylation of **4** promoted by **1** is shown in Figure 1.[15,16] The catalyst–substrate interaction involving hydrogen bonds between C(6′′′′)-OH and C(3′′′′)-O and the catalyst may explain the observed catalyst-controlled C(4′′′′)-*O*-acylation.[17] However, it is hardly to believe that such particular hydrogen bonds are formed specifically among the numerous possible hydrogen bonds between the catalyst and the substrate. We assume that substrate **4** may undergo acylation at C(4′′′′)-OH when the particular catalyst–substrate interaction such as that shown in Figure 1 takes place, while the catalyst–substrate interaction could take place in various manners.

In order to gain insights into the intrinsic reactivity of **4** in $CHCl_3$/THF (9:1) different from that in DMF (Table 1, entries 1 vs 10), conformational analysis of **4** was performed by molecular modeling. As the model of the preferred conformation of **4** in $CHCl_3$/THF (9:1) and in DMF, the most stable structures of **4** were calculated with the GB/SA solvation model for chloroform and water, respectively, using MacroModel V 9.0 with MM3* force field (see Supporting Information) and are

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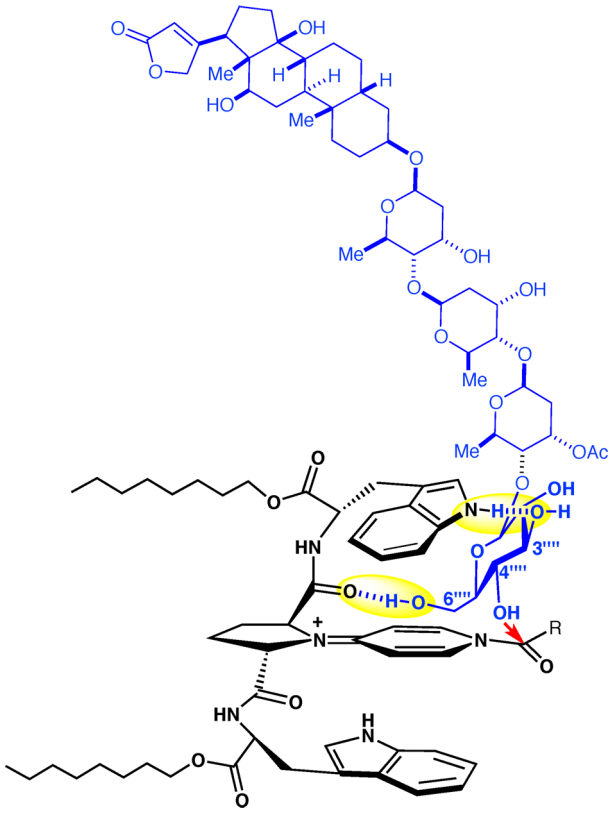

Figure 1. Hypothetical model of the transition state assembly for regioselective acylation of **4** catalyzed by **1**.

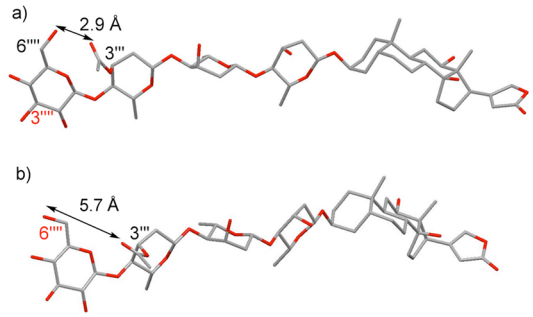

Figure 2. Calculated structure of lanatoside C (**4**) in (a) $CHCl_3$ and (b) H_2O. C(3′′′′)-OH and C(6′′′′)-OH are the most reactive hydroxy groups in (a) and (b), respectively.

shown in Figure 2a and b, respectively. The calculated distance between the oxygen of C(6′′′′)-OH and the carbonyl oxygen of C(3′′′)-OAc was 2.9 Å in $CHCl_3$ (Figure 2a), whereas that in water was 5.7 Å (Figure 2b). Since the primary hydroxy group at C(6′′′′) of **4** in a chloroform solution appears to be trapped by intramolecular hydrogen bond with the ester carbonyl of C(3′′′)-OAc, the C(3′′′′)-OH is expected to be most reactive. This is consistent with our previous observation of the extremely high reactivity of the C(3)-OH of octyl β-D-glucopyranoside when C(6)-OH is protected with Ac or TBDMS group.[18] On the other hand, the C(6′′′′)-OH of **4** seems to be most reactive in DMF, since it does not form a hydrogen bond with C(3′′′)-OAc[19] and hence behaves like a usual primary hydroxy group.

CONCLUSIONS

We have developed a method for organocatalytic regioselective acylation of lanatoside C (**4**) possessing eight free hydroxy groups. DMAP-catalyzed acylation of **4** proceeds in a substrate-controlled manner to give the C(3′′′′)-*O*- or C(6′′′′)-*O*-acylate as the major acylate in $CHCl_3$/THF (9:1) or DMF solution, respectively. On the other hand, acylation catalyzed by **1** and **5** in $CHCl_3$/THF (9:1) proceeds in a catalyst-controlled manner to give the C(4′′′′)-*O*-acylate predominantly. Several functionalized acyl groups were regioselectively introduced at C(4′′′′)-OH by acylation of **4** using a mixed anhydride method in the presence of **1** or **5**.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were obtained at 400 MHz with chemical shifts being given in ppm units. ^{13}C NMR spectra were obtained at 100 or 150 MHz, respectively, with chemical shifts being given in ppm units. IR spectra were recorded on a FT-IR spectrometer. Specific rotation was measured with an automatic digital polarimeter. A double-focusing magnetic sector mass spectrometer and an orbitrap spectrometer were used for both low- and high-resolution FAB MS and ESI MS. TLC analysis and preparative TLC were performed on commercial glass plates bearing a 0.25 or 0.5 mm layer of silica gel. Silica gel chromatography was performed with 150−325 mesh silica gel. Dry solvents (THF and dichloromethane <50 ppm water contents) obtained from commercial suppliers were used without further purification.

General Procedure for Catalytic Regioselective Acylation of 4 (Table 1). Lanatoside C (**4**) (10 mg, 10 μmol), catalyst (1.0 μmol), and 2,4,6-collidine (2.0 μL, 15 μmol) were dissolved in solvent as depicted in Table 1 at 20 °C. (*Caution*: Lanatoside C is a toxic cardiac glycoside. Avoid contact skin and eyes. Handling of lanatoside C must be carried out in a well-ventilated hood.) After the mixture was cooled to the temperature depicted in Table 1, an acid anhydride (11 μmol) was added to the mixture. The resulting mixture was stirred at the temperature for the period indicated in Table 1. The reaction was quenched with methanol and diluted with AcOEt. The organic layer was washed with aqueous 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography or preparative SiO_2 TLC to give the acylated products. The product ratio and the regiochemical outcome of the acylation were determined by the ^{1}H NMR integration and ^{1}H−^{1}H COSY of the acylates, respectively. The mixture of acylates was further purified by preparative HPLC to give the pure regioisomers for physical data.

Lanatoside C-4′′′′-Isobutyrate. According to the general procedure, lanatoside C was acylated with isobutyric anhydride in the presence of catalyst **1**. The crude residue was purified by SiO_2 column chromatography (MeOH/AcOEt = 0:100−5:95) to give a mixture of the monoacylates. The product ratio was determined by the ^{1}H NMR integration of the mixture and is shown in entry 4 of Table 1. The mixture of the acylates was further purified by preparative HPLC (column: COSMOSIL 5SL-II, solvent: MeOH/$CHCl_3$ = 10:90, flow rate: 2.0 mL/min) to give pure lanatoside C-4′′′′-isobutyrate. White amorphous powder. $[\alpha]^{20}_D$ = +19 (*c* 0.19, $CHCl_3$/MeOH = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.61−5.56 (m, 1H), 4.94−4.77 (m, 5H), 4.73 (t, *J* = 9.6 Hz, 1H), 4.39 (d, *J* = 7.8 Hz, 1H), 4.29−4.21 (m, 2H), 4.02 (br s, 1H), 3.99−3.89 (m, 1H), 3.88−3.72 (m, 2H), 3.68−3.57 (m, 3H), 3.53−3.44 (m, 2H), 3.44−3.28 (m, 4H), 3.27−3.18 (m, 2H), 3.06 (br s, 1H), 2.88 (br s, 1H), 2.61 (sept, *J* = 7.0 Hz, 1H), 2.20−1.10 (m, 44H), 2.14 (s, 3H), 0.93 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.4, 175.9, 174.5, 170.7, 116.3, 104.7, 99.4, 99.1, 95.8, 84.9, 82.4, 82.0, 79.7, 74.8, 74.3, 74.1, 73.8, 73.5, 72.6, 71.6, 70.6, 69.2, 68.1, 68.0, 66.8, 66.6, 61.5, 56.2, 45.7, 41.0, 38.9, 38.4, 36.8, 36.0, 35.2, 33.8, 32.9, 32.2, 30.7, 30.2, 30.1, 27.3, 26.9, 26.5, 24.2, 21.9, 21.7, 19.4, 19.3, 18.6, 18.5, 10.0. IR (KBr) 3467, 2934, 2881, 1738, 1627 cm^{-1}. MS (ESI) *m*/*z* (rel intensity) 1077 (M + Na, 100), 1055 (M + H, 30), 883 (90), 619 (50), 575 (60). HRMS (ESI) calcd for $C_{53}H_{83}O_{21}$ (M + H)$^+$: 1055.5421, found 1055.5426.

Lanatoside C-3′′′′-Isobutyrate. According to the general procedure, lanatoside C was acylated with isobutyric anhydride in the presence of DMAP. The crude residue was purified by SiO_2 column

dx.doi.org/10.1021/jo301007x | J. Org. Chem. 2012, 77, 7850−7857

chromatography (MeOH/AcOEt = 0:100−5:95) to give a mixture of the monoacylates. The product ratio was determined by the ^{1}H NMR integration of the mixture and is shown in entry 1 of Table 1. The mixture of the acylates was further purified by preparative HPLC (column: COSMOSIL 5SL-II, solvent: MeOH/$CHCl_3$ = 10/90, flow rate: 2.0 mL/min) to give lanatoside C-3′′′′-isobutyrate. White amorphous powder. $[\alpha]^{20}_D$ = +21 (*c* 0.14, $CHCl_3$/MeOH = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.65−5.60 (m, 1H), 4.93−4.77 (m, 6H), 4.44 (d, *J* = 7.3 Hz, 1H), 4.28−4.21 (m, 2H), 4.02 (br s, 1H), 3.96−3.71 (m, 4H), 3.66 (dd, *J* = 5.3 Hz, 1H), 3.57 (t, *J* = 9.4 Hz, 1H), 3.48−3.07 (m, 7H), 3.02 (br s, 1H), 2.87 (br s, 1H), 2.65 (sept, *J* = 7.0 Hz, 1H), 2.48 (br s, 1H), 2.20−1.10 (m, 44H), 2.12 (s, 3H), 0.93 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 174.7, 174.5, 171.0, 117.8, 104.1, 98.5, 98.2, 95.5, 86.0, 82.6, 82.5, 80.8, 78.3, 77.8, 76.5, 75.2, 73.7, 72.5, 69.2, 69.0, 68.2, 68.2, 66.5, 61.9, 55.5, 45.7, 41.5, 37.2, 36.8, 36.3, 35.1, 34.2, 33.3, 32.6, 30.4, 30.3, 29.8, 27.5, 26.7, 26.5, 23.6, 21.8, 21.5, 19.1, 19.0, 18.4, 18.3, 8.9. IR (KBr) 3468, 2934, 2881, 1736, 1627 cm^{-1}. MS (ESI) *m*/*z* (rel intensity) 1077 (M + Na, 100), 1055 (M + H, 65), 833 (20), 610 (25). HRMS (ESI) calcd for $C_{53}H_{83}O_{21}$ (M + H)$^+$: 1055.5421, found 1055.5429.

Lanatoside C-6′′′′-Isobutyrate. According to the general procedure, lanatoside C was acylated with isobutyric anhydride in DMF in the presence of catalyst **1**. The crude residue was purified by SiO_2 column chromatography (MeOH/AcOEt = 0:100−5:95) to give a mixture of the monoacylates. The product ratio was determined by the ^{1}H NMR integration of the mixture and is shown in entry 11 of Table 1. The mixture of the acylates was purified by SiO_2 column chromatography (eluent: MeOH/AcOEt = 0:100−5:95) to give lanatoside C 6′′′′-O-isobutyrate. White amorphous powder. $[\alpha]^{20}_D$ = +5.4 (*c* 0.092, $CHCl_3$/MeOH = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.39−5.34 (m, 1H), 4.94−4.77 (m, 4H), 4.50 (dd, *J* = 12.4, 4.1 Hz, 1H), 4.38 (d, *J* = 7.8 Hz, 1H), 4.29−4.18 (m, 3H), 4.02 (br s, 1H), 3.98−3.89 (m, 1H), 3.88−3.69 (m, 2H), 3.54 (t, *J* = 9.2 Hz, 1H), 3.45−3.16 (m, 8H), 3.12 (br s, 1H), 3.02 (br s, 1H), 2.87 (br s, 1H), 2.62 (sept, *J* = 7.0 Hz, 1H), 2.20−2.01 (m, 3H), 2.12 (s, 3H), 2.00−1.15 (m, 39H), 0.93 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.4, 176.5, 174.5, 170.0, 116.3, 105.0, 99.4, 99.0, 95.8, 84.9, 82.4, 82.1, 80.2, 79.7, 76.9, 73.9, 73.8, 73.8, 73.5, 72.6, 70.5, 70.4, 69.2, 68.1, 68.0, 66.8, 66.6, 60.0, 56.2, 45.7, 41.0, 38.9, 38.4, 36.8, 35.8, 35.2, 33.7, 32.9, 32.1, 30.7, 30.2, 30.1, 27.3, 26.9, 26.5, 24.2, 21.9, 21.5, 19.2, 18.6, 18.5, 10.0. IR (KBr) 3468, 2934, 2881, 1737, 1627 cm^{-1}. MS (ESI) *m*/*z* (rel intensity) 1077 (M + Na, 100), 1055 (M + H, 70), 610 (30), 542 (45). HRMS (ESI) calcd for $C_{53}H_{83}O_{21}$ (M + H)$^+$: 1055.5421, found 1055.5429.

Lanatoside C-4′′′′-Acetate. According to the general procedure, lanatoside C was acylated with acetic anhydride in the presence of catalyst **5**. The crude residue was purified by SiO_2 column chromatography (MeOH/AcOEt = 0:100−7:93) to give a mixture of the monoacylates. The product ratio was determined by the ^{1}H NMR integration of the mixture and is shown in entry 9 of Table 1. The mixture of the acylates was further purified by preparative HPLC (column: COSMOSIL 5SL-II, solvent: MeOH/$CHCl_3$ = 12:88, flow rate: 2.0 mL/min) to give lanatoside C-4′′′′-acetate. White amorphous powder. $[\alpha]^{20}_D$ = +16 (*c* 0.064, $CHCl_3$/MeOH = 9:1). ^{1}H NMR (400 MHz, pyridine-d_5) δ 6.27 (br s, 1H), 6.17 (br s, 1H), 5.87−5.83 (m, 1H), 5.68 (br s, 1H), 5.54 (t, *J* = 9.6 Hz, 1H), 5.52−5.38 (m, 4H), 5.33−5.24 (m, 1H), 5.19−5.11 (m, 2H), 4.96 (d, *J* = 7.8 Hz, 1H), 4.71−4.61 (m, 2H), 4.35−4.19 (m, 5H), 4.13 (dd, *J* = 11.9, 2.3 Hz, 1H), 4.09−3.95 (m, 3H), 3.80−3.64 (m, 3H), 3.55 (dd, *J* = 9.6, 2.7 Hz, 1H), 3.46 (dd, *J* = 9.6, 2.7 Hz, 1H), 2.48−2.39 (m, 2H), 2.36−2.28 (m, 1H), 2.18−1.16 (m, 25H), 2.05 (s, 3H), 2.01 (s, 3H), 1.58 (d, *J* = 6.4 Hz, 3H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.28 (d, *J* = 6.0 Hz, 3H), 1.26 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.4, 174.5, 170.7, 170.2, 116.3, 104.6, 99.4, 99.1, 95.8, 84.9, 82.4, 82.0, 79.7, 74.6, 74.3, 74.0, 73.8, 73.5, 72.6, 72.0, 70.5, 70.3, 69.3, 68.1, 68.0, 66.8, 66.5, 61.5, 56.2, 45.7, 38.9, 38.3, 36.8, 36.0, 35.1, 32.9, 32.1, 30.7, 30.2, 30.1, 27.3, 26.9, 26.5, 24.2, 21.9, 21.7, 21.5, 18.6, 18.5, 18.5, 10.0. IR (KBr) 3503, 2932, 2881, 1738 cm^{-1}. MS (ESI) *m*/*z* (rel intensity) 1049 (M + Na, 100), 1027 (M + H, 25), 610 (75), 594 (25). HRMS (ESI) calcd for $C_{51}H_{79}O_{21}$ (M + H)$^+$: 1027.5108, found 1027.5098.

General Procedure for Survey for the Reaction Condition Employing Mixed Anhydride Method (Table 2). To a solution of **6** (66 mg, 0.22 mmol) and base **I** in $CHCl_3$ (1.0 mL) was added RCOX (0.22 mmol) at room temperature under Ar atmosphere. After being stirred for 1 h, the resulting mixture was added to a solution of **2** (59 mg, 0.20 mmol), catalyst **1** (20 μmol), and base **II** in $CHCl_3$ (1.0 mL) at the temperature indicated in Table 2 under Ar atmosphere. The reaction mixture was stirred for the period indicated in Table 2 and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with AcOEt, and the organic layer was washed with aqueous 1 N HCl, water, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography to give the acylated products. The spectrum data of the product were reported previously in the literature.[5d]

General Procedure for Catalytic Regioselective Acylation of 4 by Mixed Anhydride Method (Table 3). To a solution of a carboxylic acid (11 μmol) and DIPEA (1.9 μL, 11 μmol) in $CHCl_3$ was added pivaloyl chloride (1.4 μL, 11 μmol) at room temperature under Ar atmosphere, and the mixture was stirred at room temperature for 1 h. The resulting mixture was added to a precooled solution of **4** (10 mg, 11 μmol), catalyst (1.0 μmol), and 2,4,6-collidine (2.0 μL, 15 μmol) in $CHCl_3$/THF (14:1) (1.0 mL) at −60 °C under Ar atmosphere. After being stirred at −60 °C for 168 h, the reaction mixture was quenched with methanol and diluted with AcOEt. The organic layer was washed with aqueous 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography or preparative SiO_2 TLC to give the acylated products. The product ratio was determined by the ^{1}H NMR integration of the acylates.

Lanatoside C-4′′′′-((S)-2-(Benzyloxycarbonylamino)-3-phenylpropanoate). According to the general procedure for the mixed anhydride method, lanatoside C was acylated. The crude residue was purified by SiO_2 column chromatography (MeOH/AcOEt = 0:100−5:95) to give a mixture of the monoacylates. The product ratio was determined by the ^{1}H NMR integration of the mixture and is shown in entry 1 of Table 3. The mixture of the acylates was further purified by preparative HPLC (column: COSMOSIL 5SL-II, solvent: MeOH/$CHCl_3$ = 10:90, flow rate: 2.0 mL/min) to give lanatoside C-4′′′′-((*S*)-2-(benzyloxycarbonylamino)-3-phenylpropanoate). White amorphous powder. $[\alpha]^{20}_D$ = +11 (*c* 0.13, $CHCl_3$/MeOH = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.15 (m, 10H), 5.94 (s, 1H), 5.59−5.54 (m, 1H), 5.23 (d, *J* = 6.0 Hz, 1H), 5.06 (ABq, J_{AB} = 12.1 Hz, $\Delta\upsilon_{AB}$ = 23.4 Hz, 2H), 4.94−4.76 (m, 5H), 4.74 (t, *J* = 9.6 Hz, 1H), 4.41−4.32 (m, 1H), 4.35 (d, *J* = 7.3 Hz, 1H), 4.29−4.21 (m, 2H), 4.02 (br s, 1H), 3.98−3.89 (m, 1H), 3.88−3.72 (m, 2H), 3.59 (t, *J* = 9.2 Hz, 1H), 3.45−2.98 (m, 12H), 2.90 (br s, 1H), 2.20−1.12 (m, 36H), 2.13 (s, 3H), 0.92 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.4, 174.5, 171.4, 170.7, 156.5, 138.1, 137.5, 129.6, 128.9, 128.7, 128.3, 128.0, 127.0, 116.3, 104.6, 99.4, 99.1, 95.8, 84.9, 82.4, 82.0, 79.7, 74.5, 73.8, 73.5, 72.7, 72.6, 70.5, 69.2, 68.1, 68.0, 66.8, 66.6, 65.9, 61.3, 56.2, 56.1, 45.7, 41.0, 38.9, 38.4, 37.0, 36.8, 36.0, 35.2, 32.9, 32.1, 30.7, 30.2, 30.1, 27.3, 26.9, 26.5, 24.2, 21.9, 21.7, 18.6, 18.5, 10.0. IR (KBr) 3462, 2931, 2881, 1738, 1627 cm^{-1}. MS (ESI) *m*/*z* (rel intensity) 1288 (M + Na, 50), 1266 (M + H, 25), 655 (35), 610 (100). HRMS (ESI) calcd for $C_{66}H_{92}NO_{23}$ (M + H)$^+$: 1266.6055, found 1266.6069.

Lanatoside C-4′′′′-Palmitate. According to the general procedure for the mixed anhydride method, lanatoside C was acylated. The crude residue was purified by SiO_2 column chromatography (MeOH/AcOEt = 0:100−5:95) to give a mixture of the monoacylates. The product ratio was determined by the ^{1}H NMR integration of the mixture and is shown in entry 2 of Table 3. The mixture of the acylates was further purified by preparative HPLC (column: COSMOSIL 5SL-II, solvent: MeOH/$CHCl_3$ = 9/91, flow rate: 2.0 mL/min) to give lanatoside C-4′′′′-palmitate. White amorphous powder. $[\alpha]^{20}_D$ = +28 (*c* 0.070, $CHCl_3$/MeOH = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (s, 1H),

dx.doi.org/10.1021/jo301007x | J. Org. Chem. 2012, 77, 7850−7857

5.54−5.49 (m, 1H), 4.87−4.70 (m, 5H), 4.67 (t, J = 9.6 Hz, 1H), 4.32 (d, J = 7.4 Hz, 1H), 4.22−4.14 (m, 2H), 3.95 (br s, 1H), 3.91−3.82 (m, 1H), 3.80−3.65 (m, 2H), 3.61−3.50 (m, 2H), 3.45−3.37 (m, 2H), 3.36−3.21 (m, 5H), 3.20−3.11 (m, 2H), 3.00 (br s, 1H), 2.81 (br s, 1H), 2.77 (br s, 1H), 2.59 (br s, 1H), 2.32−2.23 (m, 2H), 2.12−0.90 (m, 62H), 2.07 (s, 3H), 0.86 (s, 3H), 0.81 (t, J = 6.9 Hz, 3H), 0.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 174.5, 174.2, 171.4, 117.8, 103.7, 98.5, 98.3, 95.5, 86.0, 82.7, 82.4, 80.7, 77.7, 75.2, 75.0, 74.7, 74.4, 73.7, 72.5, 70.6, 69.2, 69.2, 68.2, 68.1, 66.5, 61.7, 55.5, 45.7, 41.5, 37.2, 36.8, 36.3, 36.2, 35.1, 34.3, 33.3, 32.6, 32.0, 30.4, 30.3, 29.8, 29.8, 29.7, 29.5, 29.5, 29.3, 29.2, 27.5, 26.7, 26.5, 25.0, 23.6, 22.8, 21.7, 21.5, 18.5, 18.3, 14.2, 9.0. IR (KBr) 3503, 2926, 2854, 1739, 1627 cm^{-1}. MS (ESI) m/z (rel intensity) 1245 (M + Na, 50), 1223 (M + H, 30), 767 (50), 610 (85), 598 (60), 542 (100). HRMS (ESI) calcd for $C_{65}H_{107}O_{21}$ (M + H)$^+$: 1223.7299, found 1223.7311.

Lanatoside C-4′′′′-Eicosapentaenoate. According to the general procedure for the mixed anhydride method, lanatoside C was acylated. The crude residue was purified by SiO_2 column chromatography (MeOH/AcOEt = 0:100−5:95) to give a mixture of the monoacylates. The product ratio was determined by the ^{1}H NMR integration of the mixture and is shown in entry 3 of Table 3. The mixture of the acylates was further purified by preparative HPLC (column: COSMOSIL 5SL-II, solvent: MeOH/$CHCl_3$ = 9/91, flow rate: 2.0 mL/min) to give lanatoside C-4′′′′-eicosapentaenoate. White amorphous powder. $[\alpha]^{20}_D$ = +23 (c 0.11, $CHCl_3$/MeOH = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.62−5.56 (m, 1H), 5.46−5.27 (m, 10H), 4.94−4.72 (m, 6H), 4.38 (d, J = 7.8 Hz, 1H), 4.29−4.21 (m, 2H), 4.02 (br s, 1H), 3.98−3.89 (m, 1H), 3.88−3.71 (m, 2H), 3.68−3.57 (m, 2H), 3.53−3.44 (m, 2H), 3.43−3.28 (m, 5H), 3.27−3.18 (m, 2H), 3.07 (br s, 1H), 2.90−2.75 (m, 10H), 2.65 (br s, 1H), 2.45−2.30 (m, 2H), 2.19−1.18 (m, 42H), 2.14 (s, 3H), 0.98 (t, J = 7.8 Hz, 3H), 0.93 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 174.5, 173.8, 171.3, 132.2, 129.2, 128.7, 128.7, 128.4, 128.3, 128.2, 128.2, 128.0, 127.1, 117.8, 103.7, 98.5, 98.3, 95.5, 86.0, 82.7, 82.4, 80.7, 77.8, 75.2, 75.0, 74.6, 74.4, 73.7, 72.5, 70.6, 69.2, 69.2, 68.2, 68.1, 66.5, 61.7, 55.5, 45.7, 41.5, 37.2, 36.8, 36.3, 36.2, 35.1, 33.7, 33.3, 32.6, 30.4, 30.3, 29.8, 29.8, 27.5, 26.7, 26.5, 25.7, 25.6, 24.8, 23.6, 21.7, 21.5, 20.7, 18.5, 18.3, 14.4, 9.0. IR (KBr) 3469, 2933, 2877, 1738, 1628 cm^{-1}. MS (ESI) m/z (rel intensity) 1291 (M + Na, 30), 1269 (M + H, 15), 616 (35), 610 (100). HRMS (ESI) calcd for $C_{69}H_{105}O_{21}$ (M + H)$^+$: 1269.7143, found 1269.7163.

Lanatoside C-4′′′′-Levulinate. According to the general procedure for the mixed anhydride method, lanatoside C was acylated. The crude residue was purified by SiO_2 column chromatography (MeOH/AcOEt = 0:100−5:95) to give a mixture of the monoacylates. The product ratio was determined by the ^{1}H NMR integration of the mixture and is shown in entry 4 of Table 3. The mixture of the acylates was further purified by preparative HPLC (column: COSMOSIL 5SL-II, solvent: MeOH/$CHCl_3$ = 10/90, flow rate: 2.0 mL/min) to give lanatoside C-4′′′′-levulinate. White amorphous powder. $[\alpha]^{20}_D$ = +22 (c 0.14, $CHCl_3$/MeOH = 9:1). ^{1}H NMR (400 MHz, acetone-d_6) δ 5.79 (s, 1H), 5.52−5.47 (m, 1H), 4.95−4.76 (m, 5H), 4.60 (t, J = 9.6 Hz, 1H), 4.50−4.36 (m, 1H), 4.47 (d, J = 7.8 Hz, 1H), 4.26−4.16 (m, 2H), 3.99−3.86 (m, 2H), 3.84−3.65 (m, 2H), 3.60−3.31 (m, 9H), 3.28−3.17 (m, 4H), 2.83−2.68 (m, 2H), 2.59−2.45 (m, 2H), 2.20−1.05 (m, 40H), 2.11 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 207.4, 177.4, 174.5, 172.3, 170.7, 116.3, 104.6, 99.4, 99.1, 95.8, 84.9, 82.4, 82.0, 79.7, 74.8, 74.2, 74.0, 73.8, 73.5, 72.6, 72.1, 70.6, 69.2, 68.1, 68.0, 66.8, 66.6, 61.4, 56.3, 56.2, 45.7, 41.0, 38.9, 38.4, 38.0, 36.8, 36.0, 35.2, 32.9, 32.1, 30.7, 30.2, 30.1, 30.1, 28.3, 27.3, 26.9, 26.5, 24.2, 21.9, 21.7, 18.6, 18.5, 10.0. IR (KBr) 3468, 2933, 2881, 1737, 1628 cm^{-1}. MS (ESI) m/z (rel intensity) 1100 (100), 1083 (M + H, 20), 610 (40), 550 (45). HRMS (ESI) calcd for $C_{54}H_{83}O_{22}$ (M + H)$^+$: 1083.5371, found 1083.5373.

Synthesis of Catalyst 5. Compound **5** was prepared according to the procedure described below.

*Ester **8**.* To a stirred solution of *N*-Boc-L-tryptophan (100 mg, 0.32 mmol), 1-naphthalenemethanol (52 mg, 0.32 mmol), and DMAP (3.9 m, 32 μmol) in dichloromethane (1.5 mL) was added EDCI (61 mg, 0.32 mmol) at room temperature. After being stirred for 30 min, the mixture was diluted with AcOEt, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by SiO_2 chromatography (AcOEt/hexane = 1:4) to give **8** as a white amorphous powder (142 mg, 99%): $[\alpha]^{20}_D$ = −19.0 (c 0.84, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 7.99−7.85 (m, 3H), 7.59−7.41 (m, 5H), 7.35 (d, J = 8.2 Hz, 1H), 7.10 (s, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.97 (t, J = 7.3 Hz, 1H), 6.92 (s, 1H), 5.54 (ABq, J = 12.4 Hz, $\Delta\upsilon_{AB}$ = 21.9 Hz, 2H), 4.37−4.25 (m, 1H), 3.22−3.00 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.7, 154.7, 136.0, 132.9, 131.0, 130.7, 128.4, 128.0, 126.9, 126.5, 126.0, 125.4, 124.8, 123.3, 123.0, 120.5, 118.0, 117.6, 111.0, 109.4, 78.0, 63.9, 54.8, 27.7, 26.8. IR (KBr) 3413, 3355, 3056, 2977, 2928, 1739, 1698, 1500, 1458 cm^{-1}. MS (FAB) m/z (rel intensity) 443 (M−H, 22), 306 (50), 153 (100). HRMS (FAB) calcd for $C_{27}H_{27}N_2O_4$ (M − H)$^-$: 443.1971, found 443.1974.

*Amine Hydrochloride **9**.* To a stirred solution of **8** (426 mg, 0.958 mmol) in AcOEt (1.0 mL) was added 4 N HCl/AcOEt (4.0 mL, 16 mmol) at 0 °C, and the mixture was gradually warmed to room temperature. After being stirred for 2 h, the mixture was concentrated in vacuo. The resulting solid was recrystallized from MeOH/Et_2O to give **9** as a colorless plates (325 mg, 89%): mp183−186 °C. $[\alpha]^{20}_D$ = +1.3 (c 1.00, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.95−7.82 (m, 3H), 7.55−7.41 (m, 5H), 7.39 (d, J = 8.4 Hz, 1H), 7.14 (t, J = 7.1 Hz, 1H), 7.04 (t, J = 7.3 Hz, 1H), 7.03 (s, 1H), 5.66 (ABq, J = 12.4 Hz, $\Delta\upsilon_{AB}$ = 54.0 Hz, 2H), 4.32 (t, J = 6.7 Hz, 1H), 3.42−3.21 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 170.5, 138.3, 135.2, 133.0, 131.6, 130.9, 129.8, 129.3, 128.2, 127.9, 127.1, 126.3, 125.5, 124.4, 122.9, 120.4, 118.8, 112.7, 107.4, 67.5, 54.8, 27.7. IR (KBr) 3509, 3455, 3421, 3272, 3050, 2894, 1737, 1509, 1493 cm^{-1}. MS (FAB) m/z (rel intensity) 345 (M − Cl, 24), 329 (18), 307 (20), 154 (100). HRMS (FAB) calcd for $C_{22}H_{21}N_2O_2$ (M − Cl)$^+$: 345.1603, found 345.1605.

*Catalyst **5**.* To a stirred suspension of (2*S*,5*S*)-1-(pyridin-4-yl)-pyrrolidine-2,5-dicarboxylic acid hydrochloride, synthesized according to the previously reported procedure[5a] (20 mg, 73 μmol), **9** (67 mg, 0.18 mmol), HOBt (24 mg, 0.18 mmol), and NMM (20 μL, 0.18 mmol) in dichloromethane (1.0 mL) was added EDCI (38 mg, 0.18 mmol) at room temperature. After being stirred for 18 h, the reaction mixture was diluted with AcOEt, washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by SiO_2 chromatography (MeOH/$CHCl_3$ = 3:97−10:90) to give a colorless solid. The solid was recrystallized from MeOH/Et_2O to give **5** as a colorless plates (53 mg, 81%): mp 193−195 °C. $[\alpha]^{20}_D$ = −38 (c 0.10, $CHCl_3$/MeOH = 9:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 2H), 8.66 (d, J = 8.2 Hz, 2H), 7.96−7.85 (m, 6H), 7.59 (d, J = 6.4 Hz, 2H), 7.54−7.41 (m, 10H), 7.34 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 2.3 Hz, 2H), 7.03 (t, J = 7.3 Hz, 2H), 6.92 (t, J = 7.3 Hz, 2H), 5.68 (d, J = 6.4 Hz, 2H), 5.54 (ABq, J_{AB} = 12.6 Hz, $\Delta\upsilon_{AB}$ = 8.8 Hz, 4H), 4.54−4.46 (m, 2H), 4.12 (d, J = 7.8 Hz, 2H), 3.20 (dd, J = 14.4, 4.4 Hz, 2H), 3.01 (dd, J = 14.4, 10.1 Hz, 2H), 1.88−1.81 (m, 2H), 1.40−1.30 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.0, 171.7, 136.7, 133.8, 131.7, 131.5, 129.6, 129.1, 127.8, 127.5, 127.1, 126.6, 125.8, 124.3, 124.0, 121.6, 119.0, 118.5, 112.0, 110.0, 107.9, 65.2, 61.6, 53.6, 29.2, 27.3. IR (KBr) 3395, 3296, 3050, 2925, 1736, 1657, 1600, 1513 cm^{-1}. MS (ESI) m/z (rel intensity) 889 (M + H, 100). HRMS (ESI) calcd for $C_{55}H_{49}N_6O_6$ (M + H)$^+$: 889.3708, found 889.3711.

dx.doi.org/10.1021/jo301007x | J. Org. Chem. 2012, 77, 7850−7857

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds and molecular modeling of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from The Ministry of Education, Culture, Sports, Science and Technology, Japan, and by Grant-in-Aid for JSPS Fellows to Y.U. and K.M.

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