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New Methods Suitable for Large-Scale Preparation of Sialoglycosides[1)]

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Facile methods applicable for large-scale preparation of sialoglycosides were developed by using Lewis acid alone or the combination of trimethylsilyl chloride and Lewis acid as the activator. Glycosylation catalyzed by zinc bromide using methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-galacto-2-nonulopyranosyl chlorid)onate as a glycosyl donor afforded predominantly α-sialoglycosides. In the reaction using methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosonate as the glycosyl donor, with tin(IV) chloride as an activator, β-sialoglycosides were obtained stereoselectively, whereas the combination of trimethylsilyl chloride and zinc triflate as an activator afforded predominantly α-sialoglycosides.

Keywords glycosylation; activator; glycosyl donor; trimethylsilyl chloride; zinc bromide; zinc triflate; tin(IV) chloride; sialoglycoside; sialic acid; liposome

The rapid clearance of circulating liposomes from the blood-steam, coupled with their high uptake into the reticuloendothelial system (RES) has thus far been an obstacle to attempts at applying them for targeting drugs to tumors.[2)] Recently, Allen *et al.*[3)] and Gabizon and Papahadjopoulos[4)] showed that the use of ganglioside GM1, having an *N*-acetylneuraminic acid (Neu5Ac) at the terminal position of the glycolipid, as a lipid component of the liposomes allowed them to avoid or delay uptake by the RES. In the course of synthetic studies of sialoglycolipids[5)] as mimicks of ganglioside GM1, which would reduce RES-trapping of liposomes, it was necessary to develop a stereoselective glycosylation applicable for large-scale synthesis of α- and β-sialoglycosides.[6,7)] For the preparation of glycosides of Neu5Ac, silver salts and mercury compounds have commonly been used as activators.[6)] We report herein new methods for the preparation of sialoglycosides with Lewis acid alone or with a combination of trimethylsilyl chloride and Lewis acid as a non-toxic, non-explosive and inexpensive catalyst.

Glycosyl donors (**1**—**3**) and glycosyl acceptors (**4a—d**) used here for the preparation of sialoglycosides are shown in Chart 1. These compounds were easily prepared according to published procedures.

First, we evaluated relatively weak Lewis acids such as $SnCl_2$, $Sn(OTf)_2$, $ZnCl_2$, $ZnBr_2$, ZnI_2 and $Zn(OTf)_2$ as activators in glycosylation of the L-serine derivative (**4a**) with methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosyl chlorid)-onate (**1**)[8)] as a commonly used glycosyl donor. The results are summarized in Table I (runs 1—7). As judged from the yield and α-stereoselectivity, $ZnBr_2$[9)] seemed to be the most suitable reagent of the Lewis acids investigated here. Thus, coupling of **1** with **4a** (2.0 eq) in dichloromethane in the presence of $ZnBr_2$ (1.0 eq) and pulverized molecular sieves 4A at room temperature for 20 h afforded the sialoglycoside (**5a**) with the α:β ratio of 79:21 in 55% yield (run 4). When 3 molar eq of $ZnBr_2$ was used as an activator, the yield of **5a** was slightly improved (run 7).

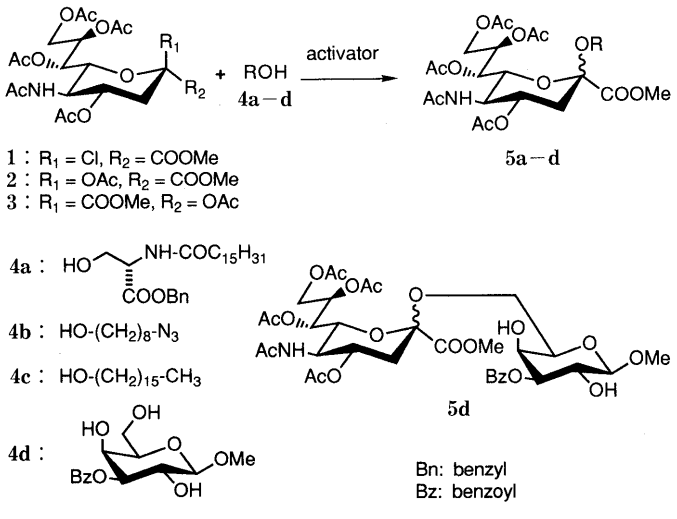

Chart 1

TABLE I. Preparation of Sialoglycosides with Lewis Acid alone or with a Combination of Trimethylsilyl Chloride and Zinc Triflate

Run	Donor	Acceptor (eq)	Activator (eq)	Solvent	Time[a)] (h)	Yield[b)] (%)	α:β[c)]
1	**1**	**4a** (2.0)	$SnCl_2$ (1.0)	CH_2Cl_2	22	57	46:54
2	**1**	**4a** (2.0)	$Sn(OTf)_2$ (1.0)	CH_2Cl_2	20	44	27:73
3	**1**	**4a** (2.0)	$ZnCl_2$ (1.0)	CH_2Cl_2	28	57	75:25
4	**1**	**4a** (2.0)	$ZnBr_2$ (1.0)	CH_2Cl_2	20	55	79:21
5	**1**	**4a** (2.0)	ZnI_2 (1.0)	CH_2Cl_2	22	50	76:24
6	**1**	**4a** (2.0)	$Zn(OTf)_2$ (1.0)	CH_2Cl_2	77	57	59:41
7	**1**	**4a** (2.0)	$ZnBr_2$ (3.0)	CH_2Cl_2	28	62	80:20
8	**1**	**4b** (2.0)	$ZnBr_2$ (1.0)	CH_2Cl_2	22	68	56:44
9	**1**	**4b** (10.0)	$ZnBr_2$ (1.0)	CH_2Cl_2	28	68	81:19
10	**1**	**4b** (2.0)	$ZnBr_2$ (1.0)	CH_3CN	22	64	70:30
11	**1**	**4b** (10.0)	$ZnBr_2$ (2.0)	CH_3CN	28	68	81:19
12	**1**	**4c** (2.0)	$ZnBr_2$ (2.0)	CH_2Cl_2	22	76	63:37
13	**1**	**4d** (2.0)	$ZnBr_2$ (2.0)	CH_2Cl_2	40	66	68:32
14	**2**	**4b** (3.0)	$ZnBr_2$ (3.7)	CH_2Cl_2	330	3[d)]	20:80
15	**2**	**4b** (3.0)	$SnCl_4$ (4.5)	CH_2Cl_2	4	59	1:>99
16	**2**	**4b** (3.0)	BF_3–Et_2O (4.5)	CH_2Cl_2	144	57	1:>99
17	**2**	**4b** (3.0)	$FeCl_3$ (3.7)	CH_2Cl_2	360	32[e)]	8:92
18	**2**	**4b** (3.0)	TMSOTf (3.7)	CH_2Cl_2	3	27	16:84
19	**2**	**4b** (3.0)	$SnCl_4$ (4.5)	CH_3CN	3.5	65	18:82
20	**2**	**4b** (3.0)	$SnCl_4$ (4.5)	Et_2O	24	15	15:85
21	**3**	**4b** (3.0)	$SnCl_4$ (4.5)	CH_2Cl_2	2.5	51	1:>99
22	**2**	**4b** (3.0)	$SnCl_4$ (1.3)	CH_2Cl_2	33	81	3:97
23	**2**	**4a** (3.0)	$SnCl_4$ (1.3)	CH_2Cl_2	4	14	1:>99
24	**2**	**4c** (3.0)	$SnCl_4$ (1.3)	CH_2Cl_2	30	67	6:94
25	**2**	**4d** (3.0)	$SnCl_4$ (1.3)	CH_2Cl_2	144	25	24:76
26	**2**	**4b** (2.0)	TMSCl–$Zn(OTf)_2$	CH_3CN	3.5	66	70:30
27	**3**	**4b** (2.0)	TMSCl–$Zn(OTf)_2$	CH_3CN	2	61	72:28
28	**2**	**4c** (2.0)	TMSCl–$Zn(OTf)_2$	Mixed[f)]	7	64	66:34

a) All reactions were carried out at room temperature. *b*) Isolated total yield. *c*) The α:β ratios were determined by ^{1}H-NMR analysis. *d*) The starting material (**2**) was recovered in 65% yield. *e*) The starting material (**2**) was recovered in 39% yield. *f*) Mixed solvent of CH_3CN–CH_2Cl_2 (3:1).

Armed with these positive results, we then investigated the reaction of **1** with one of the other alcohols (**4b—d**) using $ZnBr_2$ as an activator (runs 8—13). Glycosylation reaction of **1** and **4b** (2.0 eq) in dichloromethane in the presence of $ZnBr_2$ (1.0 eq) and pulverized molecular sieves 4A at room temperature for 22 h afforded the sialoglycoside (**5b**)[10] with the $\alpha:\beta$ ratio of 56:44 in 68% yield (run 8). The stereoselectivity was found to vary depending on the solvent and quantity of glycosyl acceptor. When 10 molar eq of glycosyl acceptor (**4b**) was used, α-stereoselectivity was enhanced although the yield of **5b** was not changed (runs 9 and 11). An α-directing effect of acetonitrile[7c] used as the solvent was observed in this glycosylation reaction, as has already been reported (run 10). Glycosylation reaction of **1** and hexadecyl alcohol (**4c**, 2.0 eq) under conditions similar to those described above resulted in the formation of **5c**[11] with the $\alpha:\beta$ ratio of 63:37 in 76% yield (run 12). Glycosylation of the HO-6 of a D-galactopyranose residue (**4d**)[12] with the Neu5Ac glycosyl donor **1** promoted by $ZnBr_2$ was found to proceed to give the known disaccharide derivative (**5d**)[13] with the $\alpha:\beta$ ratio of 68:32 in 66% yield (run 13).

The stereochemistry of the products (**5a—d**) was confirmed by proton nuclear magnetic resonance (^{1}H-NMR) spectral comparison of the chemical shifts of H-3e measured in deuteriochloroform. A lower-field shift (δ 2.52, 2.58, 2.58 and 2.57) was observed for the α-anomers (**5aα—5dα**) and a higher-field shift (δ 2.36, 2.46, 2.46 and 2.44) was observed for the β-anomers (**5aβ—5dβ**).[14]

We then investigated the reaction using methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosonate (**2**) directly as a glycosyl donor.[15] Glycosylation reaction of **2**[16] and **4b** (3.0 eq) in dichloromethane in the presence of $ZnBr_2$ (3.7 eq) and pulverized molecular sieves 4A at room temperature for 330 h afforded the sialoglycoside (**5b**) in only 3% yield along with 65% recovery of the starting material (**2**) (run 14). From this result, we suspected that stronger Lewis acids would be required for activation of the glycosyl acetate (**2**). We evaluated Lewis acids such as $SnCl_4$, BF_3–Et_2O, $FeCl_3$ and trimethylsilyl triflate (TMSOTf) in a glycosylation of **2** and **4b**. The results are summarized in Table I (runs 15—22). The combined use of $SnCl_4$ as an activator and dichloromethane as a solvent proved to be the best choice for stereoselective preparation of the β-sialoglycoside (**5bβ**). Thus, glycosylation reaction of **2** and **4b** (3.0 eq) in dichloromethane in the presence of $SnCl_4$ (1.3 eq) and pulverized molecular sieves AW-300 at room temperature for 33 h resulted in the stereoselective production of the sialoglycoside (**5b**) with the $\alpha:\beta$ ratio of 3:97 in 81% yield (run 22). Reaction of the α-anomer (**3**)[16] as a glycosyl donor gave essentially the same yield and stereoselectivity as that of the β-anomer (**2**) (runs 15 and 21). As was expected, the reaction of **2** and **4c** as a glycosyl acceptor using $SnCl_4$ (1.3 eq) stereoselectively afforded the glycoside (**5c**) with the $\alpha:\beta$ ratio of 6:94 in 67% yield (run 24), whereas the reaction using a L-serine derivative (**4a**) or D-galactopyranose derivative (**4d**) as a glycosyl acceptor resulted in the formation of the corresponding glycosides (**5a** and **5d**) in poor yields (runs 23 and 25).

We have recently developed a novel glycosylation catalyzed by the combination of trimethylsilyl chloride (TMSCl) and zinc triflate ($Zn(OTf)_2$) using glycosyl esters directly as glycosyl donors.[17] We then turned our attention to application of the promoter system to glycosylation of **2** and **4b**. When **2** was treated with **4b** (2.0 eq) in the presence of TMSCl (1.5 eq) and $Zn(OTf)_2$ (1.5 eq) in acetonitrile for 3.5 h at room temperature, the sialoglycoside (**5b**) was obtained in 66% yield with the $\alpha:\beta$ ratio of 70:30 (run 26). Reaction of the α-anomer (**3**) as a glycosyl donor gave essentially the same yield and stereoselectivity as that of the β-anomer (**2**) (run 27). No reaction occurred when $Zn(OTf)_2$ was used alone as an activator, indicating that the presence of both TMSCl and $Zn(OTf)_2$ is necessary for this glycosylation to proceed. It should be emphasized that the combination of TMSCl and a relatively weak Lewis acid such as $Zn(OTf)_2$ proved to be effective for activation of the glycosyl acetates (**2** and **3**) and the stereoselectivity was found to be changed drastically as compared to the usage of $SnCl_4$. The promoter system was also found to be sufficiently applicable to the reaction of **2** and **4c**, giving predominantly the α-glycoside, whereas a reaction using L-serine derivative (**4a**) as an acceptor resulted in recovery of the starting material. Thin layer chromatographic analysis of the reaction mixture of **2** and **4d** showed the formation of the desired disaccharide derivative (**5d**) as one of multiple products, but we could not find a condition providing **5d** in good yield because activation of glycosyl acetate with the combined use of TMSCl and $Zn(OTf)_2$ was probably accompanied with cleavage of the methyl glycoside bond in the galactose residue (**4d**).

In conclusion, facile preparation of sialoglycosides was achieved with Lewis acid alone or with a combination of trimethylsilyl chloride and Lewis acid as a non-toxic, non-explosive and inexpensive catalyst. This method should be widely applicable for the large-scale preparation of α- and β-sialoglycosides.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus, and are uncorrected. Infrared (IR) spectra were taken on a Shimadzu FTIR-4300 infrared spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian VXR-500S spectrometer (500 MHz). Chemical shifts are reported in parts per million relative to tetramethylsilane (δ units) as an internal standard. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Column chromatography was performed with Merck Silica gel 60 (230—400 mesh).

2-Benzyloxycarbonyl-2-palmitoylaminoethanol (4a) Triethylamine (8.64 g, 85.4 mmol) was added to a stirred solution of L-serine benzyl ester *p*-toluenesulfonate (15.69 g, 42.7 mmol) and palmitoyl chloride (10.56 g, 38.4 mmol) in dichloromethane (250 ml) under ice-cooling. The reaction mixture was allowed to warm to room temperature and stirring was continued for 5 h at room temperature. The reaction mixture was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crystals were washed with isopropyl ether to give **4a** (8.76 g, 53%), mp 84—85 °C. $[\alpha]_D$ +7.9° (c=1.07, $CHCl_3$). *Anal.* Calcd for $C_{26}H_{43}NO_4$: C, 72.01; H, 10.00; N, 3.23. Found: C, 72.20; H, 10.32; N, 3.45. IR (KBr): 3302, 1742, 1634, 1551, 1472 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.1 Hz, CH_3), 1.2—1.4 (24H, m, $CH_2\times12$), 1.64 (2H, quintet, CH_2), 2.26 (2H, t, J=7.6 Hz, $COCH_2$), 3.94 (1H, dd, J=3.2, 11.2 Hz, OCH_2), 4.00 (1H, dd, J=3.9, 11.2 Hz, OCH_2), 4.73 (1H, ddd, J=3.2, 3.9, 7.1 Hz, NCH), 5.22 and 5.23 (2H, ABq, J=12.2 Hz, $ArCH_2$), 6.38 (1H, d, NH), 7.3—7.4 (5H, m, ArH).

Typical Procedure for Glycosylation with $ZnBr_2$ $ZnBr_2$ (331 mg, 1.47 mmol) was added to a stirred mixture of **1** (250 mg, 0.49 mmol), **4a** (425 mg, 0.98 mmol) and molecular sieves 4A (150 mg) in dichloromethane (5 ml). The stirring was continued for 20 h at room temperature,

and the precipitates were filtered off on Celite and washed with dichloromethane. The filtrate and washings were combined, washed with water, 5% $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (50 g) with chloroform–EtOH (100 : 1) to give a 79 : 21 anomeric mixture (276 mg, 62%) of **5aα** and **5aβ** as a colorless foam. Analytical samples of **5aα** and **5aβ** were prepared by repeated silica gel (40 g) column chromatography with chloroform–EtOH (100 : 1).

Analytical data for the sialoglycosides (**5a** and **5b**) thus obtained are as follows.

5aα: A colorless foam. $[\alpha]_D$ −14.1° (c=0.78, $CHCl_3$). *Anal.* Calcd for $C_{46}H_{70}N_2O_{16}$: C, 60.91; H, 7.78; N, 3.09. Found: C, 61.03; H, 7.94; N, 2.84. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.1 Hz, CH_3), 1.2—1.4 (24H, m, $CH_2\times12$), 1.6—1.7 (2H, m, CH_2), 1.89 (1H, dd, $J_{3a,4}$=12.2 Hz, $J_{3a,3e}$=12.9 Hz, H-3a), 1.89 (3H, s, CH_3CO), 2.03 (3H, s, CH_3CO), 2.04 (3H, s, CH_3CO), 2.13 (3H, s, CH_3CO), 2.14 (3H, s, CH_3CO), 2.27 (2H, m, $COCH_2$), 2.52 (1H, dd, $J_{3e,4}$=4.6 Hz, $J_{3e,3a}$=12.9 Hz, H-3e), 3.71 (3H, s, $COOCH_3$), 3.84 (1H, dd, J=3.2, 10.0 Hz, OCH_2), 4.01 (1H, dd, J=3.4, 10.0 Hz, OCH_2), 4.08 (1H, dd, $J_{9,8}$=5.4 Hz, $J_{9,9'}$=12.5 Hz, H-9), 4.09 (1H, ddd, $J_{5,NH}$=9.5 Hz, $J_{5,4}$=9.8 Hz, $J_{5,6}$=10.7 Hz, H-5), 4.11 (1H, dd, $J_{6,7}$=1.7 Hz, $J_{6,5}$=10.7 Hz, H-6), 4.25 (1H, dd, $J_{9',8}$=2.4 Hz, $J_{9',9}$=12.5 Hz, H-9'), 4.79 (1H, ddd, J=3.2, 3.4, 8.3 Hz, NCH), 4.86 (1H, ddd, $J_{4,3e}$=4.6 Hz, $J_{4,5}$=9.8 Hz, $J_{4,3a}$=12.2 Hz, H-4), 5.12 (1H, d, $J_{NH,5}$=9.5 Hz, NH), 5.18 and 5.19 (2H, ABq, J=12.7 Hz, $ArCH_2$), 5.33 (1H, dd, $J_{7,6}$=1.7 Hz, $J_{7,8}$=8.8 Hz, H-7), 5.36 (1H, ddd, $J_{8,9'}$=2.4 Hz, $J_{8,9}$=5.4 Hz, $J_{8,7}$=8.8 Hz, H-8), 6.26 (1H, d, J=8.3 Hz, NH), 7.3—7.4 (5H, m, ArH).

5aβ: mp 85—87 °C. $[\alpha]_D$ −17.8° (c=0.96, $CHCl_3$). *Anal.* Calcd for $C_{46}H_{70}N_2O_{16}$: C, 60.91; H, 7.78; N, 3.09. Found: C, 61.05; H, 7.90; N, 3.22. IR (KBr): 2932, 2860, 1748, 1650, 1538, 1464, 1374, 1228, 1122 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.1 Hz, CH_3), 1.2—1.4 (24H, m, $CH_2\times12$), 1.64 (2H, m, CH_2), 1.84 (1H, dd, $J_{3a,4}$=12.4 Hz, $J_{3a,3e}$=12.9 Hz, H-3a), 1.84 (3H, s, CH_3CO), 1.99 (3H, s, CH_3CO), 2.04 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 2.12 (3H, s, CH_3CO), 2.27 (2H, t, J=7.6 Hz, $COCH_2$), 2.36 (1H, dd, $J_{3e,4}$=4.9 Hz, $J_{3e,3a}$=12.9 Hz, H-3e), 3.56 (1H, dd, J=2.7, 9.5 Hz, OCH_2), 3.65 (1H, dd, $J_{6,7}$=2.2 Hz, $J_{6,5}$=10.5 Hz, H-6), 3.79 (3H, s, $COOCH_3$), 3.99 (1H, dd, J=2.9, 9.5 Hz, OCH_2), 4.03 (1H, ddd, $J_{5,4}$=10.0 Hz, $J_{5,NH}$=10.3 Hz, $J_{5,6}$=10.5 Hz, H-5), 4.03 (1H, dd, $J_{9,8}$=7.8 Hz, $J_{9,9'}$=12.5 Hz, H-9), 4.72 (1H, dd, $J_{9',8}$=2.4 Hz, $J_{9',9}$=12.5 Hz, H-9'), 4.77 (1H, d, $J_{NH,5}$=10.3 Hz, NH), 4.86 (1H, ddd, J=2.7, 2.9, 8.1 Hz, NCH), 4.87 (1H, ddd, $J_{4,3e}$=4.9 Hz, $J_{4,5}$=10.0 Hz, $J_{4,3a}$=12.4 Hz, H-4), 5.16 (1H, d, J=12.5 Hz, $ArCH_2$), 5.18 (1H, ddd, $J_{8,9'}$=2.4 Hz, $J_{8,7}$=4.2 Hz, $J_{8,9}$=7.8 Hz, H-8), 5.24 (1H, dd, $J_{7,6}$=2.2 Hz, $J_{7,8}$=4.2 Hz, H-7), 5.46 (1H, d, J=12.5 Hz, $ArCH_2$), 6.57 (1H, d, J=8.1 Hz, NH), 7.3—7.5 (5H, m, ArH).

5dα: A colorless foam. $[\alpha]_D$ −7.6° (c=0.75, MeOH). [lit.[13] $[\alpha]_D$ −7° (c=1.0, $CHCl_3$)]. *Anal.* Calcd for $C_{34}H_{45}NO_{19}$: C, 52.91; H, 5.88; N, 1.82. Found: C, 52.21; H, 6.05; N, 1.69. ^{1}H-NMR (C_6D_6) δ: 1.56 (3H, s, CH_3CO), 1.59 (3H, s, CH_3CO), 1.66 (3H, s, CH_3CO), 1.96 (1H, dd, $J_{3'a,4'}$=12.5 Hz, $J_{3'a,3'e}$=12.8 Hz, H-3'a), 2.01 (3H, s, CH_3CO), 2.05 (3H, s, CH_3CO), 2.10 (1H, d, $J_{OH,2}$=3.2 Hz, HO-2), 2.64 (1H, dd, $J_{3'e,4'}$=4.5 Hz, $J_{3'e,3'a}$=12.8 Hz, H-3'e), 2.73 (1H, d, $J_{OH,4}$=6.6 Hz, HO-4), 3.31 (3H, s, CH_3O), 3.38 (3H, s, CH_3O), 3.57 (1H, t, $J_{5,6a}$=$J_{5,6b}$=6.5 Hz, H-5), 3.93 (1H, d, $J_{NH,5'}$=10.3 Hz, NH), 3.99 (2H, d, $J_{6a,5}$=$J_{6b,5}$=7.4 Hz, H-6a, H-6b), 4.07 (1H, dd, $J_{6',7'}$=2.3 Hz, $J_{6',5'}$=10.7 Hz, H-6'), 4.13 (1H, d, $J_{1,2}$=7.6 Hz, H-1), 4.21 (1H, ddd, $J_{2,OH}$=3.2 Hz, $J_{2,1}$=7.6 Hz, $J_{2,3}$=10.0 Hz, H-2), 4.29 (1H, dd, $J_{9'a,8'}$=6.9 Hz, $J_{9'a,9'b}$=12.3 Hz, H-9'a), 4.36 (1H, dd, $J_{4,3}$=3.4 Hz, $J_{4,OH}$=6.6 Hz, H-4), 4.39 (1H, ddd, $J_{5',NH}$=10.3 Hz, $J_{5',4'}$=10.4 Hz, $J_{5',6'}$=10.7 Hz, H-5'), 4.77 (1H, dd, $J_{9'b,8'}$=2.7 Hz, $J_{9'b,9'a}$=12.3 Hz, H-9'b), 4.79 (1H, ddd, $J_{4',3'e}$=4.5 Hz, $J_{4',5'}$=10.4 Hz, $J_{4',3'a}$=12.5 Hz, H-4'), 5.29 (1H, dd, $J_{3,4}$=3.4 Hz, $J_{3,2}$=10.0 Hz, H-3), 5.48 (1H, dd, $J_{7',6'}$=2.3 Hz, $J_{7',8'}$=7.4 Hz, H-7'), 5.79 (1H, ddd, $J_{8',9'b}$=2.7 Hz, $J_{8',9a}$=6.9 Hz, $J_{8',7'}$=7.4 Hz, H-8'), 7.02—7.13 (3H, m, ArH), 8.22—8.27 (2H, m, ArH).

5dβ: $[\alpha]_D$ −2.4° (c=0.70, MeOH). [lit.[13] $[\alpha]_D$ −5° (c=1.1, $CHCl_3$)]. *Anal.* Calcd for $C_{34}H_{45}NO_{19}$: C, 52.91; H, 5.88; N, 1.82. Found: C, 52.39; H, 6.04; N, 1.84. ^{1}H-NMR (C_6D_6) δ: 1.38 (3H, s, CH_3CO), 1.59 (3H, s, CH_3CO), 1.65 (3H, s, CH_3CO), 1.78 (1H, dd, $J_{3'a,4'}$=11.7 Hz, $J_{3'a,3'e}$=12.8 Hz, H-3'a), 1.90 (3H, s, CH_3CO), 1.95 (3H, s, CH_3CO), 2.28 (1H, d, $J_{OH,2}$=2.9 Hz, HO-2), 2.77 (1H, dd, $J_{3'e,4'}$=4.9 Hz, $J_{3'e,3'a}$=12.8 Hz, H-3'e), 3.31 (3H, s, CH_3O), 3.33 (3H, s, CH_3O), 3.61 (1H, dd, $J_{6a,6b}$=4.9 Hz, $J_{6a,5}$=8.5 Hz, H-6a), 3.83 (1H, dd, $J_{6b,6a}$=4.9 Hz, $J_{6b,5}$=8.5 Hz, H-6b), 4.06 (1H, br s, HO-4), 4.15—4.24 (3H, m, H-1, H-2, H-5'), 4.29 (1H, t, $J_{5,6a}$=$J_{5,6b}$=8.5 Hz, H-5), 4.49 (1H, dd, $J_{9'a,8'}$=7.3 Hz, $J_{9'a,9'b}$=12.5 Hz, H-9'a), 4.66 (1H, br s, H-4), 4.79 (1H, br d, J=10.7 Hz, H-6'), 5.23 (1H, br d, J=12.2 Hz, H-9'b), 5.40 (1H, dd, $J_{3,4}$=3.2 Hz, $J_{3,2}$=9.5 Hz, H-3), 5.73 (1H, ddd, $J_{4',3'e}$=4.9 Hz, $J_{4',5'}$=10.5 Hz, $J_{4',3'a}$=11.7 Hz, H-4'), 5.85 (1H, dd, $J_{7',6'}$=2.2 Hz, $J_{7',8'}$=3.7 Hz, H-7'), 5.93 (1H, ddd, $J_{8',9'b}$=2.2 Hz, $J_{8',7'}$=3.7 Hz, $J_{8',9'a}$=7.3 Hz, H-8'), 7.02—7.13 (3H, m, ArH), 8.22—8.19 (2H, m, ArH).

Typical Procedure for Glycosylation with $SnCl_4$ $SnCl_4$ (125 mg, 0.48 mmol) was added to a stirred mixture of **2** (202 mg, 0.38 mmol), 8-azidooctanol (**4b**, 193 mg, 1.13 mmol) and molecular sieves AW-300 (500 mg) in dichloromethane (10 ml) and stirring was continued for 33 h at room temperature. The precipitates were filtered off on Celite and washed with dichloromethane. The filtrate and washings were combined, washed with water, 5% $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (50 g) with chloroform–MeOH (100 : 1) to give a 3 : 97 anomeric mixture (197 mg, 81%) of **5bα** and **5bβ** as a colorless foam. Analytical samples of **5bα** and **5bβ** were prepared by repeated silica gel (40 g) column chromatography with chloroform–MeOH (100 : 1).

5bα: A colorless foam. $[\alpha]_D$ −15.1° (c=0.81, $CHCl_3$). *Anal.* Calcd for $C_{28}H_{44}N_4O_{13}$: C, 52.16; H, 6.88; N, 8.69. Found: C, 51.97; H, 6.77; N, 8.50. IR (KBr): 2100, 1747, 1688, 1663, 1373, 1231, 1038 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27—1.40 (8H, m, $CH_2\times4$), 1.50—1.64 (4H, m, $CH_2\times2$), 1.88 (3H, s, CH_3CO), 1.95 (1H, dd, $J_{3a,4}$=12.3 Hz, $J_{3a,3e}$=12.8 Hz, H-3a), 2.03 (3H, s, CH_3CO), 2.05 (3H, s, CH_3CO), 2.14 (3H, s, CH_3CO), 2.15 (3H, s, CH_3CO), 2.58 (1H, dd, $J_{3e,4}$=4.5 Hz, $J_{3e,3a}$=12.8 Hz, H-3e), 3.21 (1H, dt, J=6.6, 9.3 Hz, OCH_2), 3.26 (2H, t, J=6.6 Hz, CH_2N_3), 3.75 (1H, dt, J=6.6, 9.3 Hz, OCH_2), 3.80 (3H, s, $COOCH_3$), 4.06 (1H, ddd, $J_{5,NH}$=9.5 Hz, $J_{5,4}$=10.5 Hz, $J_{5,6}$=10.7 Hz, H-5), 4.08 (1H, dd, $J_{6,7}$=2.0 Hz, $J_{6,5}$=10.7 Hz, H-6), 4.10 (1H, dd, $J_{9,8}$=5.6 Hz, $J_{9,9'}$=12.5 Hz, H-9), 4.31 (1H, dd, $J_{9',8}$=2.7 Hz, $J_{9',9}$=12.5 Hz, H-9'), 4.84 (1H, ddd, $J_{4,3e}$=4.5 Hz, $J_{4,5}$=10.5 Hz, $J_{4,3a}$=12.3 Hz, H-4), 5.11 (1H, d, $J_{NH,5}$=9.5 Hz, NH), 5.33 (1H, dd, $J_{7,6}$=2.0 Hz, $J_{7,8}$=8.5 Hz, H-7), 5.40 (1H, ddd, $J_{8,9'}$=2.7 Hz, $J_{8,9}$=5.6 Hz, $J_{8,7}$=8.5 Hz, H-8).

5bβ: $[\alpha]_D$ −11.2° (c=0.73, $CHCl_3$). *Anal.* Calcd for $C_{28}H_{44}N_4O_{13}$: C, 52.16; H, 6.88; N, 8.69. Found: C, 51.93; H, 6.80; N, 8.52. IR (KBr): 2100, 1747, 1685, 1663, 1373, 1230, 1038 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26—1.42 (8H, m, $CH_2\times4$), 1.51—1.65 (4H, m, $CH_2\times2$), 1.86 (1H, dd, $J_{3a,4}$=11.4 Hz, $J_{3a,3e}$=12.9 Hz, H-3a), 1.88 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 2.03 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO), 2.14 (3H, s, CH_3CO), 2.46 (1H, dd, $J_{3e,4}$=4.9 Hz, $J_{3e,3a}$=12.9 Hz, H-3e), 3.27 (2H, t, J=6.6 Hz, CH_2N_3), 3.31 (1H, dt, J=6.6, 9.3 Hz, OCH_2), 3.47 (1H, dt, J=6.6, 9.3 Hz, OCH_2), 3.80 (3H, s, $COOCH_3$), 3.92 (1H, dd, $J_{6,7}$=2.2 Hz, $J_{6,5}$=10.5 Hz, H-6), 4.11 (1H, ddd, $J_{5,4}$=10.5 Hz, $J_{5,6}$=10.5 Hz, $J_{5,NH}$=10.7 Hz, H-5), 4.12 (1H, dd, $J_{9,8}$=7.8 Hz, $J_{9,9'}$=12.5 Hz, H-9), 4.80 (1H, dd, $J_{9',8}$=2.4 Hz, $J_{9',9}$=12.5 Hz, H-9'), 5.19 (1H, ddd, $J_{8,9'}$=2.4 Hz, $J_{8,7}$=3.5 Hz, $J_{8,9}$=7.8 Hz, H-8), 5.23 (1H, d, $J_{NH,5}$=10.7 Hz, NH), 5.25 (1H, ddd, $J_{4,3e}$=4.9 Hz, $J_{4,5}$=10.5 Hz, $J_{4,3a}$=11.4 Hz, H-4), 5.39 (1H, dd, $J_{7,6}$=2.2 Hz, $J_{7,8}$=3.5 Hz, H-7).

Typical Procedure for Glycosylation with Combined Use of TMSCl and $Zn(OTf)_2$ TMSCl (61 mg, 0.56 mmol) was added to a stirred solution of **2** (200 mg, 0.38 mmol), hexadecyl alcohol (**4c**, 182 mg, 0.75 mmol) and $Zn(OTf)_2$ (204 mg, 0.56 mmol) in acetonitrile (15 ml) and dichloromethane (5 ml). After being stirred for 7 h at room temperature, the reaction mixture was diluted with AcOEt, washed with water, 5% $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (50 g) with chloroform–MeOH (100 : 1) to give a 66 : 34 anomeric mixture (172 mg, 64%) of **5cα** and **5cβ** as a colorless foam. Analytical samples of **5cα** and **5cβ** were prepared by repeated silica gel (40 g) column chromatography with chloroform–MeOH (100 : 1).

5cα: A colorless foam. $[\alpha]_D$ −14.6° (c=0.81, $CHCl_3$). IR (KBr): 1751, 1659, 1360, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz, CH_3), 1.16—1.37 (26H, m, $CH_2\times13$), 1.48—1.57 (2H, m, CH_2), 1.88 (3H, s, CH_3CO), 1.95 (1H, dd, $J_{3a,4}$=12.7 Hz, $J_{3a,3e}$=12.9 Hz, H-3a), 2.03 (3H, s, CH_3CO), 2.04 (3H, s, CH_3CO), 2.14 (3H, s, CH_3CO), 2.15 (3H, s, CH_3CO), 2.58 (1H, dd, $J_{3e,4}$=4.6 Hz, $J_{3e,3a}$=12.9 Hz, H-3e), 3.20 (1H, dt, J=6.6, 9.3 Hz, OCH_2), 3.75 (1H, dt, J=6.6, 9.3 Hz, OCH_2), 3.79 (3H, s, $COOCH_3$), 4.03—4.14 (3H, m, H-5, H-6, H-9), 4.31 (1H, dd, $J_{9',8}$=2.7 Hz, $J_{9',9}$=12.5 Hz, H-9'), 4.83 (1H, ddd, $J_{4,3e}$=4.6 Hz, $J_{4,5}$=9.5 Hz, $J_{4,3a}$=12.7 Hz, H-4), 5.16 (1H, d, $J_{NH,5}$=9.0 Hz, NH), 5.33 (1H, dd, $J_{7,6}$=1.7 Hz, $J_{7,8}$=8.3 Hz, H-7), 5.39 (1H, ddd, $J_{8,9'}$=2.7 Hz, $J_{8,9}$=5.4 Hz, $J_{8,7}$=8.3 Hz, H-8).

5cβ: $[\alpha]_D$ −11.6° (c=0.88, $CHCl_3$). IR (KBr): 1747, 1661, 1371, 1224 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz, CH_3), 1.20—1.37 (26H, m, $CH_2\times13$), 1.53—1.60 (2H, m, CH_2), 1.86 (1H, dd,

$J_{3a,4}=11.7$ Hz, $J_{3a,3e}=13.0$ Hz, H-3a), 1.89 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 2.03 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO), 2.15 (3H, s, CH_3CO), 2.46 (1H, dd, $J_{3e,4}=5.1$ Hz, $J_{3e,3a}=13.0$ Hz, H-3e), 3.30 (1H, dt, $J=6.8$, 9.3 Hz, OCH_2), 3.45 (1H, dt, $J=6.8$, 9.3 Hz, OCH_2), 3.80 (3H, s, $COOCH_3$), 3.92 (1H, dd, $J_{6,7}=2.2$ Hz, $J_{6,5}=10.5$ Hz, H-6), 4.12 (1H, ddd, $J_{5,NH}=10.3$ Hz, $J_{5,6}=10.5$ Hz, $J_{5,4}=10.7$ Hz, H-5), 4.13 (1H, dd, $J_{9,8}=7.6$ Hz, $J_{9,9'}=12.5$ Hz, H-9), 4.79 (1H, dd, $J_{9',8}=2.4$ Hz, $J_{9',9}=12.5$ Hz, H-9'), 5.18 (1H, ddd, $J_{8,9'}=2.4$ Hz, $J_{8,7}=3.8$ Hz, $J_{8,9}=7.6$ Hz, H-8), 5.23 (1H, d, $J_{NH,5}=10.3$ Hz, NH), 5.25 (1H, ddd, $J_{4,3e}=5.1$ Hz, $J_{4,5}=10.7$ Hz, $J_{4,3a}=11.7$ Hz, H-4), 5.40 (1H, dd, $J_{7,6}=2.2$ Hz, $J_{7,8}=3.8$ Hz, H-7).

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