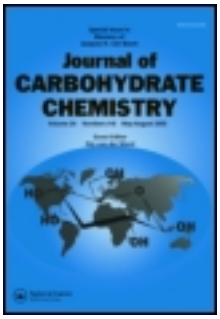

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Efficient Conversion of a 1,6-Anhydro Chitobiose Derivative into the Corresponding Tetradecyl β-Glycoside Derivative by Means of Participation of a Neighboring Tetradecanamide Group

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EFFICIENT CONVERSION OF A 1,6-ANHYDRO CHITOBIOSE DERIVATIVE INTO THE CORRESPONDING TETRADECYL β-GLYCOSIDE DERIVATIVE BY MEANS OF PARTICIPATION OF A NEIGHBORING TETRADECANAMIDE GROUP

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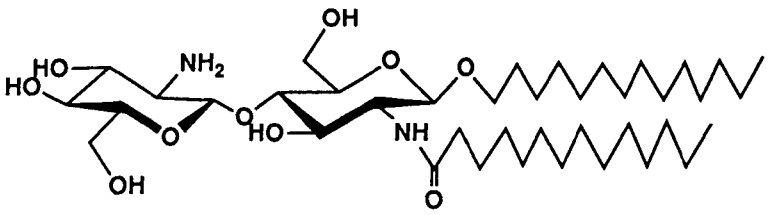
ABSTRACT

In the course of our studies on the synthesis of amphiphilic chitoheptaose derivatives carrying binary long hydrocarbon chains at the reducing sugar, tetradecyl 4-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-2-deoxy-2-tetradecanamido-β-D-glucopyranoside was prepared as a model. For general applicability, the 1,6-anhydro-2-deoxy-2-tetradecanamido-β-D-glucopyranosyl moiety was employed as a precursor of the reducing end. Acetolysis of the 1,6-anhydro ring using triethylsilyl triflate gave an oxazoline intermediate as a major product, accompanied by α-glycosyl acetate as a by-product. Immediate treatment of the mixture with 1-tetradecanol and protic acid followed by a separation work-up efficiently led to tetradecyl β-glycoside derivative.

INTRODUCTION

Chitin, one of the abundant polysaccharides, and its deacetylated derivative, chitosan, have attracted much attention from the view point of their diverse biological possibilities.[1] Small fragments of chitin such as *N*-acetylchitohexaose and larger

oligosaccharides of this type as well as their deacetylated compounds are also interesting because of their biological activities in both mammals and plants. For example, chitohexaose and its *N*-peracetylated derivative show a growth-inhibitory effect against solid tumors implanted in mice,[2] while *N*-acetylchitooligosaccharides of more than dp 6 induce phytoalexin formation in rice cells.[3] Unexpectedly, glycolipid type derivatives of chitooligosaccharide of dp 2-4 possessing a long fatty *N*-acyl group at the reducing D-glucosamine moiety were recently found to have immunostimulating and antitumor activities.[4] Because of this biological relevance, we planned to introduce binary hydrophobic tails into the reducing end of the originally bioactive chitoheptaose, mimicking phospholipids of cell membranes. One hydrophobic group was to be introduced as an *N*-acyl group, while the other as an aglycon of a glycoside. Prior to synthesis of the heptasaccharide derivative, a general way to introduce different types of hydrophobic groups into the terminal monosaccharide moiety had to be established. This paper describes the synthesis of tetradecyl 4-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-2-deoxy-2-tetradecanamido-β-D-glucopyranoside (**1**) as a disaccharidic model compound, which includes an efficient conversion of 1,6-anhydro-2-deoxy-2-tetradecanamido-β-D-glucopyranose moiety, a precursor of the reducing end, into the corresponding tetradecyl β-glycopyranoside moiety.



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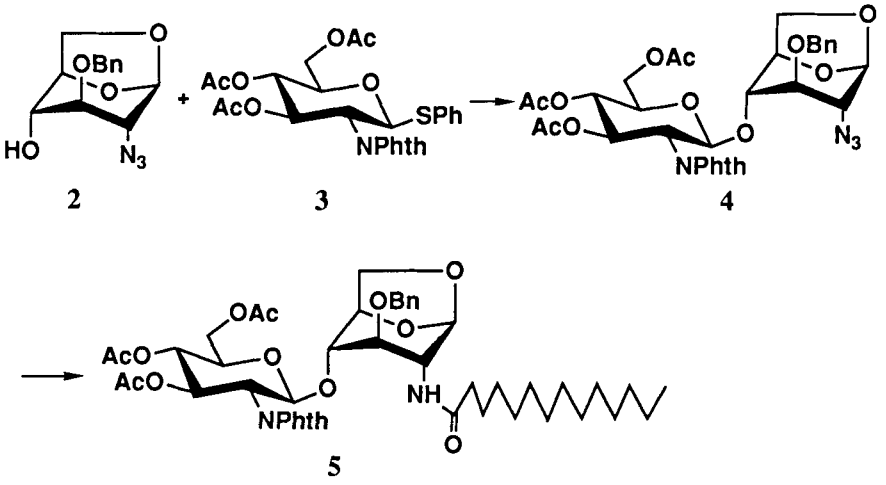
RESULTS AND DISCUSSION

1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**2**)[5] was glycosylated at the 4-position with phenyl 3,4,6-tri-*O*-acetyl-1,2-dideoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**3**)[6] activated by *N*-iodosuccinimide and a catalytic amount of trifluoromethanesulfonic acid, giving 1,6-anhydrodisaccharide derivative (**4**) in good yield. The azido group of **4** was selectively reduced with hydrogen sulfide in pyridine-triethylamine mixture and the resulting amino group was immediately treated with tetradecanoyl chloride in pyridine for *N*-acylation to give 4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-

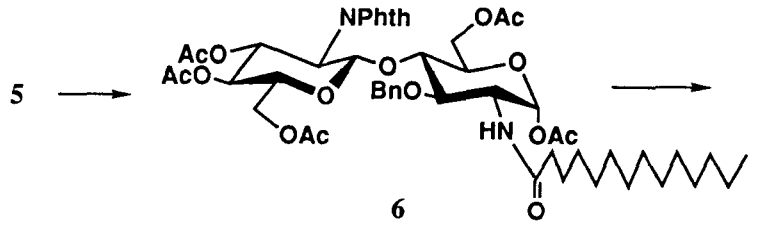


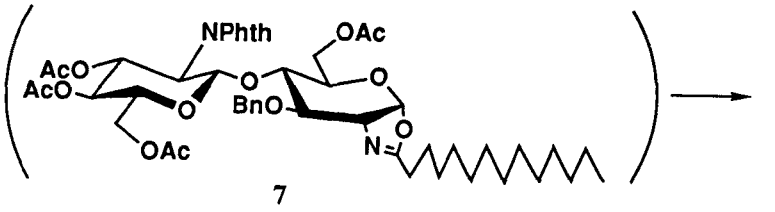
2 3 4

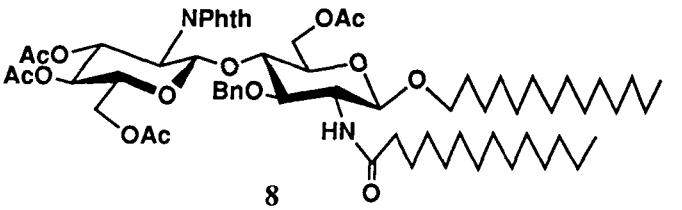
5

2-phthalimido-β-D-glucopyranosyl)-1,6-anhydro-3-*O*-benzyl-2-deoxy-2-tetradecanamido-β-D-glucopyranose (**5**) in 96% yield as crystals.

The initial attempt to convert the 1,6-anhydro derivative **5** into the corresponding tetradecanyl β-glycoside derivative **8** was conducted in three steps: i.e., 1) acetolysis of the 1,6-anhydro ring into 1,6-diacetate, 2) tentative formation of an oxazoline intermediate, and 3) coupling with 1-tetradecanol for β-glycoside formation as shown on the next page. Acetolysis was carried out as follows. When 20 equivalents of trifluoroacetic acid was employed as catalyst, the reaction proceeded very sluggishly, giving α-glycosyl acetate **6** ($J_{1,2}$ = 3.5 Hz in ^{1}H NMR spectrum) in only 43% yield after 3 days. On the other hand, 5 equivalents of boron trifluoride diethyl etherate remarkably improved the acetolysis reaction, which was complete within 10 minutes giving **6** in 61% yield. Compound **6** was then treated with trimethylsilyl triflate at 50 °C for 1 hour for conversion into the oxazoline intermediate **7**,[7] which, without isolation, was soon condensed with 1-tetradecanol in the presence of a catalytic amount of (+)-10-camphorsulfonic acid, giving tetradecanyl 6-*O*-acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3-*O*-benzyl-2-deoxy-2-tetradecanamido-β-D-glucopyranoside (**8**) in 74% yield from **6**. Thus, the overall yield of **8** from **5** *via* acetolysis with BF_3-Et_2O was 45%. At this stage, we noticed a paper reported by B. Fraser-Reid et al.[8] about a mild acetolysis procedure of 1,6-anhydro sugars using triethylsilyl triflate as catalyst. Applying this catalyst to acetolysis of **5** at 0 °C→room temperature showed that **5** underwent cleavage of its anhydro ring within 30 min, giving the oxazoline derivative **7** as the major product and the glycosyl acetate **6** as the minor product. After neutralization with triethylamine, the mixture was subjected to



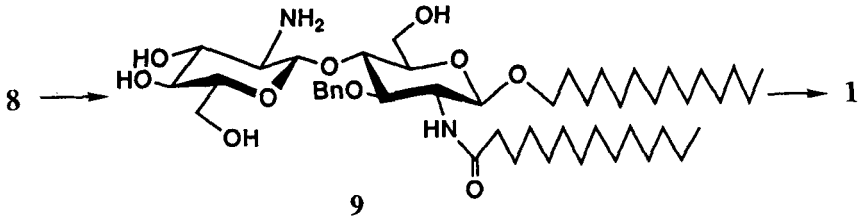




treatment with 1-tetradecanol in the presence of (+)-10-camphorsulfonic acid and subsequent work-up to give **8** in 60% overall yield from **5**. The intermediate **6** was also obtained in 22% yield. Therefore, a one-pot synthesis employing triethylsilyl triflate proved to be a more efficient way for conversion of **5** into **8**.

Compound **8** then underwent step-wise deprotections. A successive treatment of **8** with sodium methoxide in methanol at room temperature and then with ethylenediamine in 1-butanol at 90 °C completed de-*O*-acetylation and de-*N*-phthaloylation, leaving the tetradecanamido group unaffected. The product, tetradecyl 4-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-3-*O*-benzyl-2-deoxy-2-tetradecanamido-β-D-glucopyranoside (**9**), had extremely poor solubility in most solvents, making the ^{1}H NMR spectrum measurement difficult. Debenzylation of **9** was successful by catalytic hydrogenation with palladium hydroxide in a large volume of acetic acid. The solubility of the resulting **1** with a free amino group at the 2'-position was also very poor in most solvents but its ^{1}H NMR spectrum could be recorded using a solution of $CDCl_3$-CD_3COOD-D_2O (3:3:1 v/v) as the NMR solvent. For purification of **1**, it was converted into its hydrochloride salt.

Hydrochloric acid was added in small portions to a suspension of **1** in chloroform-methanol, giving **hydrochloride salt of 1** in 51% yield, which was recrystallizable from a large quantity of methanol. This hydrochloride salt was essentially insoluble in protic, aprotic, and even dipolar aprotic solvents although slightly soluble in a chloroform-methanol mixture.



9

EXPERIMENTAL

General methods. Melting points were determined with a Laboratory Devices MEL-TEMPT II apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-1000 polarimeter, using a 10-cm micro cell. IR spectra were recorded with a JASCO FT/IR-300E spectrophotometer. ^{1}H NMR spectra were recorded at 200 MHz or 400 MHz with Bruker AC-200 or Bruker AM-400 spectrometers for solutions in $CDCl_3$ unless otherwise specified. Column chromatography was performed on Silica Gel 60 (70-230 mesh, E. Merck) with the solvent systems specified. Solvent extracts were dried over anhyd Na_2SO_4, and solutions were concentrated under diminished pressure below 50 °C. Analytical samples were dried at 50-60 °C over P_2O_5 for 4-5 h *in vacuo*.

4-*O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranose (4). To a solution of compounds **2** (3.31 g, 11.94 mmol), **3** (5.26 g, 9.96 mmol), and *N*-iodosuccinimide (5.60 g, 24.91 mmol) in dichloromethane (80 mL) was added dropwise a dichloromethane solution (13.56 mL) saturated with trifluoromethanesulfonic acid at -8 °C under an argon atomosphere in the presence of molecular sieves 4A (13 g). The reaction mixture was kept at room temperature for another 30 min, poured into saturated aqueous $NaHCO_3$, and extracted with chloroform. The extract was successively washed with aqueous sodium thiosulfate, sodium hydrogencarbonate, and brine, dried, and concentrated. The resulting residue was chromatographed with toluene-ethyl acetate (5:1 v/v) as eluent to give **4** (6.7 g, 96%) as an amorphous powder: $[\alpha]_D^{22}$ +34.2° (*c* 1.09, $CHCl_3$); IR (KBr) 2102 (N_3), 1749 (OAc), and 1716 cm^{-1} (NPhth); ^{1}H NMR (400 MHz)

δ 3.08 (bs, 1H, H-2), 3.69 (dd, 1H, J= , H-6a), 3.73 (bs, 1H, H-3), 3.80-3.84 (m, 2H, H-4, H-5'), 4.04 (bd, 1H, H-6b), 4.17 (dd, 1H, $J_{6'a,6'b}$=12,3 Hz, $J_{5',6'a}$=2.3 Hz, H-6'a), 4.26 (dd, 1H, $J_{5',6'b}$=4.6 Hz, H-6'b), 4.40 (dd, 1H, $J_{1',2'}$=8.5 Hz, $J_{2',3'}$=10.7 Hz, H-2'), 4.45 (bd, 1H, H-5), 4.61 (m, 2H, $PhCH_2$), 5.20 (t, 1H, $J_{3',4'}$=$J_{4',5'}$=10.0 Hz, H-4'), 5.26 (s, 1H, H-1), 5.70 (d, 1H, H-1'), 5.71(dd, 1H, H-3').

Anal. Calcd for $C_{33}H_{34}N_4O_{13}$ (694.65): C, 57.06; H, 4.93; N, 8.07. Found: C, 56.86; H,4.90; N, 7.86.

4-*O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-1,6-anhydro-3-*O*-benzyl-2-deoxy-2-tetradecanamido-β-D-glucopyranose (5). Hydrogen sulfide gas was slowly bubbled for 30 min into a solution of **4** (2.00 g, 2.87 mmol) in pyridine-triethylamine (7:3 v/v, 10 mL) and the resulting mixture was kept at room temperature overnight in a capped flask. After concentration of the mixture, the residual product was chromatographed on silica gel with toluene-ethyl acetate (1:5 v/v) as eluent to give the intermediate 2-amino derivative (1.76 g, 92%), which showed no IR absorption around 2100 cm^{-1} due to the azido group. The resulting 2-amino compound (1.66 g, 2.48 mmol) was dissolved in dry pyridine (10 mL) and the solution cooled in an ice bath. Tetradecanoyl chloride (0.95 mL, 3.49 mmol) was added to the solution and the mixture was stirred at ambient temperature for 30 min. After addition of methanol (1 mL), the mixture was diluted with chloroform, washed with water, dried, and concentrated. The residue was chromatographed with toluene-ethyl acetate (2:1 v/v) to give **5** (2.09 g, 96%): mp 64-66 °C; $[\alpha]_D^{27}$ -58.6° (*c* 3.36, $CHCl_3$); IR (KBr) 3421 (NH), 1753 (OAc), 1718 (NPhth), 1674 (NHCO), and 1506 cm^{-1} (NHCO); ^1H NMR (200 MHz) δ 0.88 (m, 3H, CH_3), 1.27 (s, 22H, CH_2), 1.89, 2.04, 2.09 (s, each 3H, OAc), 2.27 (m, 2H, $NHCOCH_2$), 3.53-3.59 (m, 2H, H-3, H-6'a), 3.74-3.82 (m, 2H, H-4, H-5'), 4.05 (dd, 1H, $J_{5,6a}$=2.1 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.14-4.20 (m, 3H, H-2, H-5, H-6b), 4.33 (dd, 1H, $J_{5',6'b}$=4.3 Hz, $J_{6'a,6'b}$=12.4 Hz, H-6'b), 4.34 (dd, 1H, $J_{1',2'}$=8.6 Hz, $J_{2',3'}$=10.6 Hz, H-2'), 4.59 (m, 2H, $PhCH_2$), 4.99 (s, 1H, H-1), 5.15 (dd, 1H, $J_{3',4'}$=9.1 Hz, $J_{4',5'}$=9.9 Hz, H-4'), 5.37 (d, 1H, H-1'), 5.75 (bd, 1H, NH), 5.91(dd, 1H, H-3').

Anal. Calcd for $C_{47}H_{62}N_2O_{14}$ (879.01): C, 64.22; H, 7.11; N, 3.19. Found: C, 64.43; H, 7.18; N, 3.13.

1,6-Di-*O*-acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3-*O*-benzyl-2-deoxy-2-tetradecanamido-α-D-glucopyranose (6). *Method A* Trifluoroacetic acid (0.82 mL, 10.6 mmol) was added at 0 °C under an argon atmosphere to a solution of **5** (500 mg, 0.56 mmol) in acetic anhydride (20 mL). The mixture was kept at room temperature for 3 days and concentrated. The resulting

residue was chromatographed with toluene-ethyl acetate (4:1 v/v) to give **6** (240 mg, 43%): mp 169-170 °C; $[\alpha]_D^{25}$ +49° (*c* 0.36, $CHCl_3$); IR (KBr) 1750 (OAc), 1714 (NPhth), 1651 (NHCO), and 1532 cm^{-1} (NHCO); ^1H NMR (200 MHz) δ 0.88 (t, 3H, CH_3), 1.25 (s, 22H, CH_2), 1.83-2.12 (m, 17H, $NHCOCH_2$, OAc x 5), 3.60-3.72 (m, 4H), 3.91-4.04 (m, 2H), 4.14-4.30 (m, 3H), 4.33 (dd, 1H, $J_{1',2'}$=8.4 Hz, $J_{2',3'}$=10.5 Hz, H-2'), 4.76 (m, 2H, $PhCH_2$), 4.92 (bd, 1H, NH), 5.15 (dd, 1H, $J_{3',4'}$=9.5 Hz, $J_{4',5'}$=9.8 Hz, H-4'), 5.54 (d, 1H, H-1'), 5.76 (dd, 1H, H-3'), 6.05 (d, 1H, $J_{1,2}$=3.5 Hz, H-1).

Method B Boron trifluoride diethyl etherate (0.14 mL, 1.13 mmol) was added at 0 °C under an argon atmosphere to a solution of **5** (200 mg, 0.23 mmol) in acetic anhydride (2 mL) and the mixture was kept at 0 °C for 10 min. After addition of triethylamine (1 mL), the mixture was diluted with toluene and concentrated to dryness. The resulting residue was chromatographed as described in method A, giving **6** (136 mg, 61%).

Anal. Calcd for $C_{51}H_{68}N_2O_{17}$ (981.10): C, 62.44; H, 6.99; N, 2.86. Found: C, 62.25; H, 7.00; N, 2.84.

Tetradecanyl 6-*O*-Acetyl-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3-*O*-benzyl-2-deoxy-2-tetradecanamido-β-D-glucopyranoside (8). *Method A (from 6)* Trimethylsilyl triflate (0.07 mL, 0.36 mmol) was added at 0 °C under an argon atmosphere to a solution of **6** (340 mg, 0.35 mmol) in 1,2-dichloroethane (5 mL) and the mixture was stirred at 50 °C for 1 h. After addition of triethylamine (0.5 mL), the mixture was placed on a short column of silica gel and eluted with toluene-ethyl acetate (3:1 v/v). The eluate was concentrated to give the crude oxazoline intermediate (**7**), ^1H NMR (400 MHz) δ 5.86 (d, 1H, $J_{1,2}$=7.5 Hz, H-1), which was immediately used for the next glycosidation reaction without further purification. A solution of **7**, 1-tetradecanol (1.11 g, 5.19 mmol), and (+)-10-camphorsulfonic acid (8 mg, 0.034 mmol) in 1,2-dichloroethane was heated at 90 °C for 30 min with stirring under an argon atmosphere and diluted with chloroform. The mixture was successively washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated to dryness. The resulting residue was chromatographed with toluene-ethyl acetate (3:1 v/v), giving **8** (292 mg, 74% from **6**) which was recrystallized from methanol: mp 149-150 °C; $[\alpha]_D^{26}$ +1.2° (*c* 1.15, $CHCl_3$); IR (KBr) 1747 (OAc), 1714 (NPhth), 1647 (NHCO), 1536 cm-1 (NHCO); ^1H NMR (400 MHz) δ 0.88 (m, 6H, CH_3), 1.25 (s, 46H, CH_2), 1.84, 1.95, 2.00, 2.01 (s, each 3H, OAc), 2.03-2.05 (m, 2H, $NHCOCH_2$), 3.24 (m, 1H, one of OCH_2), 3.42-3.48 (m, 2H, H-2, H-5), 3.63-3.71 (m, 2H, H-5', one of OCH_2), 3.81-3.87 (m, 2H, H-4, H-6a), 3.97 (dd, 1H, $J_{5',6'a}$=ca 1Hz, $J_{6'a,6'b}$=12.2 Hz, H-6'a), 4.07 (t, 1H, $J_{2,3}$=$J_{3,4}$=7.5 Hz, H-3), 4.22 (dd, 1H, $J_{5',6'a}$=4.4 Hz, H-6'b), 4.25-4.31 (m, 2H, H-2', H-6b), 4.68 (d, 1H, $J_{1,2}$=6.4 Hz, H-1), 4.75 (m, 2H,

$PhCH_2$), 5.13 (dd, 1H, $J_{3',4'}$=9.4 Hz, $J_{4',5'}$=9.8 Hz, H-4'), 5.50 (d, 1H, $J_{1',2'}$=8.4 Hz, H-1'), 5.61 (bd, 1H, NH), 5.78 (dd, 1H, $J_{2',3'}$=10.6 Hz, H-3')

Anal. Calcd for $C_{63}H_{94}N_2O_{16}$ (1135.44): C, 66.64; H,8.34; N, 2.47. Found: C, 66.45; H, 8.34; N, 2.46.

Method B (from 5) Triethylsilyl triflate (0.18 mL, 0.79 mmol) was added at 0 °C under argon atmosphere to a solution of **5** (583 mg, 0.66 mmol) in acetic anhydride (5 mL) and the mixture was kept at room temperature for 30 min. After addition of triethylamine (1 mL), the mixture was co-evaporated with toluene to give **7** as a major product and **6** as a minor one. The mixture was dissolved in 1,2-dichloroethane (10 mL) and treated with 1-tetradecanol (1.0 g, 4.66 mmol) and (+)-10-camphorsulfonic acid (10 mg, 0.043 mmol) as described in Method A. A similar subsequent work-up and chromatographic purification gave **8** (447 mg, 59% from **5**) and **6** (169 mg, 22% from **5**).

Tetradecanyl 4-*O*-(2-Amino-2-deoxy-β-D-glucopyranosyl)-3-*O*-benzyl-2-deoxy-2-tetradecanamido-β-D-glucopyranoside (9). To a suspension of **8** (531 mg, 0.467 mmol) in methanol (15 mL) was added methanolic sodium methoxide (28%, 0.03 mL) and the mixture was stirred at room temperature for 4.5 h under an argon atmosphere. The resulting clear solution was neutralized with Amberlite IR-120B (H^+, 2 mL), filtered, and concentrated. The residue was suspended in a mixture of 1-butanol (15 mL) and ethylenediamine (1 mL) and the suspension was heated at 90 °C with stirring under an argon atmosphere. The mixture was concentrated and then co-evaporated with toluene to give **9**, which was recrystallized from a large volume of 2-propanol, yielding **9** (390 mg, 99%): mp 200-201 °C; $[\alpha]_D^{28}$ -2.60° {*c* 0.17, $CHCl_3$-CH_3OH (1:1 v/v)}; IR (KBr): around 3283 (NH_2, OH), 1648 (NHCO), 1556 cm^{-1} (NHCO); ^1H NMR spectrum could not be recorded due to the poor solubility of **9**.

Anal. Calcd for $C_{47}H_{84}N_2O_{10}\bullet 0.5H_2O$ (846.20): C, 66.71; H, 10.12; N, 3.31. Found: C, 66.83; H, 10.11; N, 3.56.

Tetradecyl 4-*O*-(2-Amino-2-deoxy-β-D-glucopyranosyl)-2-deoxy-2-tetradecanamido-β-D-glucopyranoside (1) and its hydrochloride. A solution of **9** (326 mg, 0.38 mmol) in acetic acid (30 mL) was shaken in H_2 for 8 h with palladium hydroxide on carbon (Aldrich). After dilution with chloroform-methanol, the mixture was filtered and concentrated to give **1**: mp 200 °C (dec); IR (KBr) around 3269 (NH_2, OH), 1654 (NHCO), 1550 (NHCO); ^1H NMR (400 MHz, $CDCl_3$-CD_3COOD-D_2O) δ 0.88 (t, 6H, CH_3), 1.26 (s, 46H, CH_2), 2.02-2.07 (m, 2H, $NHCOCH_2$), 3.21-3.26 (m, 1H, H-2'), 3.40-3.92 (m, 13H), 4.68 (d, 1H, $J_{1,2}$=8.3 Hz, H-1), 4.96 (d, 1H, $J_{1',2'}$=8.4 Hz, H-1'). To a suspension of **1** in a large volume (ca. 50 mL) of chloroform-methanol (1:1) was added 0.5 M aqueous HCl in small portions until the mixture became a clear solution.

After evaporation of the solvents, the resulting residue was recrystalized from a large volume of methanol, giving **hydrochloride of 1** (153 mg, 51%): mp 176 °C (dec).

Anal. Calcd for $C_{40}H_{79}N_2O_{10}Cl$ (783.53): C, 61.32; H, 10.16; N, 3.58. Found: C, 61.21; H, 10.35; N,3.51.

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