Carbohydrate Research 355 (2012) 6–12

Contents lists available at SciVerse ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Synthesis of glycoglycerolipid of 1,2-dipalmitoyl-3-(*N*-palmitoyl-6′-amino-6′-deoxy-α-D-glucosyl)-*sn*-glycerol and its analogues, inhibitors of human Myt1-kinase

Yihua Sun, Jun Zhang, Chunxia Li *, Huashi Guan, Guangli Yu

Key Laboratory of Marine Drugs, Ministry of Education of China, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, PR China

ARTICLE INFO

Article history:
Received 20 February 2012
Received in revised form 5 April 2012
Accepted 6 April 2012
Available online 26 April 2012

Keywords:
Glycoglycerolipid
Glycosylation
α-Selectivity
Myt1-kinase inhibitor

ABSTRACT

A glycoglycerolipid **1a** isolated from a marine alga showed inhibition to Myt1 kinase with IC_{50} of 0.12 μg/mL. We synthesized **1a** and its seven analogues (**1b–h**) in an efficient method with high stereoselectivity. The process employed trichloroacetimidate donor **4b** at low substrate concentration to achieve high α-selectivity (α/β = 33:1) in glycosylation reaction. The present synthesis provided various acyl derivatives required for the study on the structure–activity relationship later.

1. Introduction

Glycoglycerolipids isolated from marine organisms have recently shown a wide spectrum of biological activities, including antitumor, anti-HIV-1 infection, and anti-inflammatory activities.[1–4] The 6-deoxy-6-aminoglycoglycerolipids, rarely occurred as glycoglycerolipids in nature, exhibit unique bioactivities, such as antibacterial, Myt1 kinase inhibitory, and antileishmanial activities.[5–8] Among the bioactive aminoglycoglycerolipids, glycolipid **1a** (Fig. 1), which was isolated from a marine alga with high inhibitory activity on the enzyme Myt1-kinase (IC_{50} 0.12 μg/mL),[6] attracts our great interest.

The human Myt1-kinase is an important regulator of the G2/M transition in the cell cycle. Myt1 specifically mediates phosphorylation at Thr-14 and Tyr-15 of Cdc2-kinase activity and the inhibition of phosphorylation of Cdc2 is important for timing the entry into mitosis. Various studies have shown that premature activation of Cdc2 would lead to mitotic dysfunction and apoptosis.[9] Inhibition of Myt1-kinase is predicted to cause premature activation of Cdc2.[10,11] Therefore inhibitors of Myt1-kinase are supposed to kill rapidly proliferating cells and interfere with cell cycle checkpoints. Such inhibitors could represent an extension to conventional chemotherapy and overcome drug resistance.

With the aim to search for potential Myt1-kinase inhibitors, glycoglycerolipid **1a** has been synthesized by our group.[12] Previous studies have shown that the minor structural changes of lipophilic acyl chain of glycolipids exert positive effect on the antitumor activity of glycolipids.[13] To ascertain the influence of acyl chains on the inhibitory activity of Myt1-kinase, we synthesized a series of analogues **1b–h** (Fig. 1) of **1a**. The structures of compounds **1b–h** are different from the natural compound **1a** mainly in the length (**b–f**), branch (**g**), and aromaticity (**h**) of the acyl chains, which are homogenous at C6′, C1, and C2. Although the synthetic method of compound **1a** has been reported,[12,14] the procedure was tedious and the stereoselectivity of glycosylation was still unsatisfied. Here we report a concise and high stereoselective method for the synthesis of these compounds for further structure–activity relationship research.

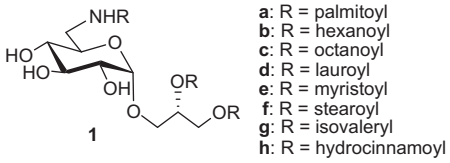


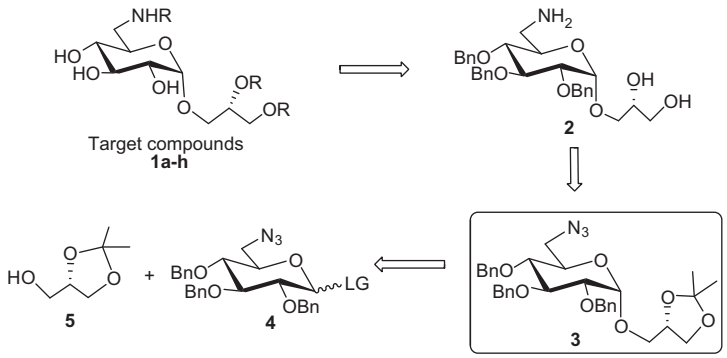
Figure 1. Structures of natural aminoglycoglycerolipid **1a** and its analogues **1b–h**.

2. Results and discussion

Our synthetic strategy is depicted in Scheme 1. It is noteworthy that compounds **1a–h** have four common structural features, which contain 6′-amino group, homogeneous acyl chains at C6′,

* Corresponding author. Tel.: +86 532 82032030; fax: +86 532 82033054.
E-mail address: lchunxia@ouc.edu.cn (C. Li).

0008-6215/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.carres.2012.04.005



Scheme 1. Retrosynthetic analysis.

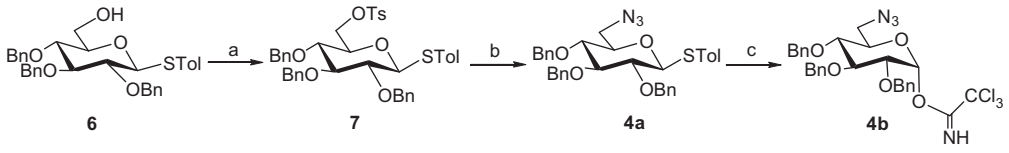
C1, and C2 positions, α glycosidic linkage bond and *S*-chiral center. Considering the homogeneous acyl chains ligated at C6′, C1, and C2, precursor **2** was reasonably designed first. The structure of **2** would enable us to acylate the C6′ amino and C1, C2 hydroxyl groups with corresponding acyl chloride simultaneously. Thus a properly protected glycosyl glycerol derivative **3** was envisaged as a key intermediate, whose C6′ was linked with azide as a latent amino group and C1, C2 hydroxyl groups were protected with acetonide. To get this key intermediate **3**, we assumed that an appropriate glycosyl donor **4** with the 6′-azido group and non-participating benzyl group at C2′ could couple with (*S*)-1,2-isopropylideneglycerol **5** to construct the α-glycosidic bond.

The initial effort was to build up the donor **4** as shown in Scheme 2. Thioglycoside **6** with the 6-hydroxyl free was synthesized in five steps from glucose penta-acetate according to the literature procedures.[15] Treatment of **6** with *p*-toluene sulfonyl chloride produced compound **7**, which was immediately reacted with sodium azide in DMF to yield the thioglycoside **4a** as the first donor. Removal of the *p*-tolylthio group using *N*-bromosuccinimide (NBS) in acetone-water, followed by treatment with trichloroacetonitrile (CCl_3CN) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) gave trichloroacetimidate **4b** as the second donor.

With the donors **4a** and **4b** available, glycosylation of (*S*)-isopropylideneglycerol **5** with the donors was then carefully examined. The results are summarized in Table 1. The main challenge in the glycosylation was to efficiently construct the α-configuration glycosidic bond. Firstly, the glycosylation of (*S*)-isopropylideneglycerol with donor **4a** was carried out in the presence of *N*-iodosuccinimide (NIS)–trimethylsilyl trifluoromethanesulfonate (TMSOTf) in absolute ether (entry **1**). This reaction was completed in 4 h and gave a mixture of α-glycoside **3** and β-glycoside **8** and their C2-epimers. The ratio of α/β (5:1) was determined by the ^1H NMR spectrum. Under such coupling conditions, we observed the isopropylidene migration which resulted in the glycoside products with undesired C2-racemization. Intramolecular migration of the isopropylidene group before glycosylation readily occurred under Lewis acids.[16] Danishefsky reported that the glycosylation of glycosyl fluoride with **5** in the presence of 2,6-di-*tert*-butylpyridine (DTBP) can prevent the racemization.[17] Here the hindered base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was employed. When **4a** was dissolved in Et_2O, followed by adding NIS, DTBMP (1 equiv), **5,** and TMSOTf (0.6 equiv) in turn, anomeric mixture of glycosides **3** and **8** was produced after 72 h without racemization. Meanwhile, the anomeric selectivity was raised to 9:1 (entry **2**). Obviously, DTBMP served as an addictive prolonged the reaction time but improved the α-selectivity. We supposed that DTBMP can effectively suppress Lewis acid promoters to make the coupling reaction occur in a mild condition.

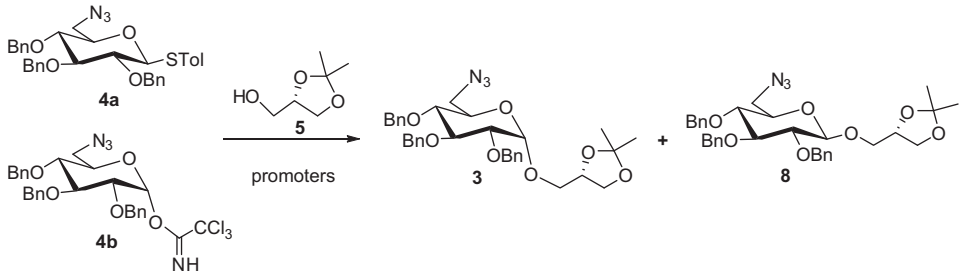
To further improve the stereoselectivity and efficiency of glycosylation, we paid attention to the Schmidt method which usually worked well for the synthesis of α-glycoside with good yield.[18] The glycosylation of (*S*)-isopropylideneglycerol with trichloroacetimidate donor **4b** was subsequently investigated (Table 1, entries **3–5**). Compared to the thioglycoside **4a**, this acid-catalyzed reaction proceeded quickly without the racemization of the (*S*)-isopropylideneglycerol residue. We found this process, which employed chemically active imidate donor **4b** with low substrate concentration, can achieve good α-selectivity in glycosylation. A high stereoselectivity (α/β = 33:1) could be achieved when the concentration of **4b** was 20 mM (entry **5**). The trace amount of β anomer can be isolated easily by silica gel column chromatography in the next step. When the concentration of **4b** was enhanced to 40 mM and 80 mM, the stereoselectivity would decline to α/β 8:1 (entry **4**) and α/β 4:1 (entry **3**), respectively. The concentration of the reaction mixture influenced anomeric selectivity and the reason was presumably explained that mild conditions were beneficial for 1,2-*cis* glycosylation.[19] However, this high stereoselectivity with low concentration effect for imidate donor **4b** was just opposite to the study of using chemically stable thioglycoside donors in appropriate CH_2Cl_2/nitrile solvent mixture.[20]

With the key intermediate **3** in hand, we accessed the final compounds through four steps (Scheme 3). Hydrolysis of the isopropylidene protecting group with TsOH in methanol provided **9** in 93% yield. Then reduction of the azido group by Staudinger reaction yielded the amino derivative **2**. Introduction of acyl chains on C1, C2, and C6′–NH_2 of **2** by condensation with corresponding acyl chloride in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) gave **10a–h** in 66–92% yield. Then removal of the benzyl by hydrogenolysis using $H_2/Pd(OH)_2$ generated the final compounds **1a–h**. All structures of the synthetic compounds were identified



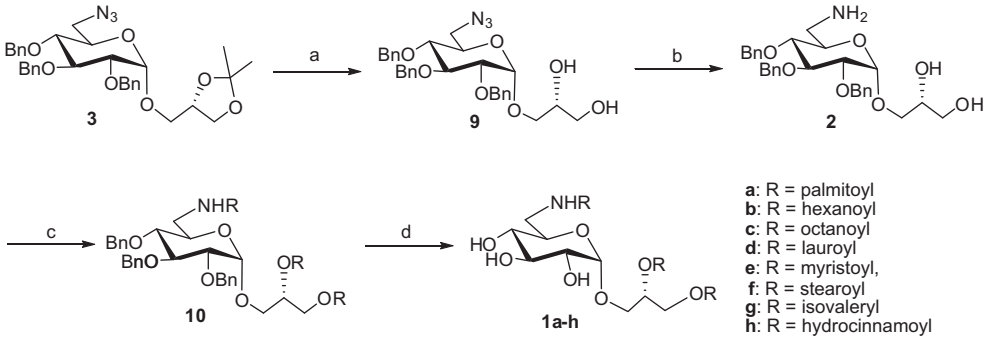
Scheme 2. Synthesis of the glycosyl donors. Reagents and conditions: (a) CH_2Cl_2, Et_3N, DMPA, TsCl, 95%; (b) NaN_3, DMF, 65 °C, 88%; (c) NBS, acetone/water (9:1); then DBU, $CNCCl_3$, CH_2Cl_2, 76% over two steps.

Table 1
Glycosylation of **4a** and **4b** with **5**[a]



Entry	Donor	Promoter (equiv)	Temp	Time (h)	Yield (%)	Ratio (α/β)[b]	C2-chirality[c]
1	**4a**	NIS–TMSOTf (1.5–0.6)	rt	4	86	5:1[d]	R
2[e]	**4a**	NIS–TMSOTf (1.5–0.6)	rt	72	85	9:1	NR
3[f]	**4b**	TMSOTf (0.2)	0 °C	0.5	87	4:1	NR
4[g]	**4b**	TMSOTf (0.2)	0 °C	0.5	87	8:1	NR
5[h]	**4b**	TMSOTf (0.2)	0 °C	0.5	88	33:1	NR

[a] All reactions were carried out in absolute ether with 1.2 equiv acceptor.
[b] Determined by 600 MHz ^{1}H NMR.
[c] R = Racemation, NR = No racemization.
[d] C-2 epimers were not shown.
[e] 1 equiv DTBMP was added.
[f] Concentration of **4b** was 80 mM.
[g] Concentration of **4b** was 40 mM.
[h] Concentration of **4b** was 20 mM.



Scheme 3. Synthesis of the target compounds **1a**–**h**. (a) TsOH, MeOH, 93%; (b) PPh_3, THF–H_2O, 96%; (c) acyl chloride, Py, DMAP; (d) $Pd(OH)_2$/C, H_2, THF/*i*-PrOH (9:1).

by ^{1}H, ^{13}C NMR, and MS. And the data of **1a** were in accord with the data of the natural product reported before.[6,12]

3. Conclusion

The natural aminoglycoglycerolipid **1a** and its analogues were synthesized in an efficient method with high stereoselectivity. The glycosylation reaction employed trichloroacetimidate donor **4b** at low substrate concentration (20 mM) can achieve high α-configuration selectivity (α/β = 33:1). The present synthesis also provided various acyl derivatives of glycolipid **1a** required for the studies on the structure–activity relationship and on the mode of action. A detailed SAR study of these analogues will be reported later.

4. Experimental

4.1. General methods

Solvents were purified in a conventional manner. Thin layer chromatography (TLC) was performed on precoated HSGF254 plates (Yantai, China). Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao, China). Optical rotation was determined with a Perkin–Elmer Model 241 MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were taken on a JEOL JNM-ECP 600 spectrometer with tetramethylsilane (Me_4Si) as the internal standard, and chemical shifts were recorded as δ values. Mass spectra were recorded on a Global Q-TOF mass spectrometer and IonSpec 4.7 T FTMS (MALDI/DHB).

4.2. *p*-Tolyl-2,3,4-tri-*O*-benzyl-6-*O*-*p*-tosyl-1-thio-β-D-glucopyranoside (7)

To a mixture of **6** (1.1 g, 2.0 mmol) and TsCl (1.5 g, 8.0 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (0.55 mL, 4.0 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 5 h, and then washed with aq HCl (1 M) and brine. The organic phase was collected, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (8:1 petroleum ether–EtOAc) to provide **7** (1.32 g, 95%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06–7.80 (m, 23H, Ar) , 4.88 (d, 1H, *J* 11.0 Hz, PhCH), 4.87 (d, 1H, *J* 10.4 Hz, PhCH), 4.81 (d, 1H, *J* 11.0 Hz, PhCH), 4.80 (d, 1H, *J* 11.0 Hz, PhCH), 4.68 (d, 1H, *J* 10.4 Hz, PhCH), 4.52 (d, 1H, *J* 10.7 Hz, PhCH), 4.50 (d, 1H, *J* 9.8 Hz, H-1), 4.25 (dd, 1H, *J* 10.4, 1.6 Hz, H-6′), 4.17(dd, 1H, *J* 10.4, 4.4 Hz, H-6), 3.64 (t, 1H, *J* 8.8 Hz, H-3), 3.48 (t, 1H, *J* 8.3 Hz, H-4), 3.45 (ddd, 1H, *J* 9.9,

4.4, 1.7 Hz, H-5), 3.39 (dd, 1H, *J* 9.7, 8.9 Hz, H-2), 2.40 (s, 3H, $ArCH_3$), 2.33 (s, 3H, $ArCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 21.8, 68.6, 75.3, 75.6, 76.0, 76.6, 77.0, 80.7, 86.7, 87.6, 127.9–130.1, 133.0, 133.1, 133.2, 137.7, 138.1, 138.2, 138.4, 145.1; HR-ESI-MS *m*/*z* Calcd for $C_{41}H_{43}O_7S_2$ 711.2445 $[M+H]^+$, $C_{41}H_{42}O_7NaS_2$ 733.2264 $[M+Na]^+$. Found 711.2452 $[M+H]^+$, 733.2271 $[M+Na]^+$.

4.3. *p*-Tolyl-6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-1-thio-β-D-glucopyranoside (4a)

A mixture of **7** (1.0 g, 1.4 mmol) and sodium azide (0.46 g, 7.0 mmol) in dry DMF (15 mL) was stirred at 60 °C overnight. After the reaction was completed, the solvent was removed in vacuo and the residue was dissolved in EtOAc. The excess of sodium azide and sodium tosylate was removed by filtration. The filtrate was evaporated and purified by silica gel column (12:1 petroleum ether–EtOAc) to afford **4a** (0.73 g, 88%) as a white solid; $[\alpha]_D^{22} = +21.8$ (*c* 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.11–7.49 (m, 19H, Ar), 4.58–4.93 (m, 6H, 3× $PhCH_2$), 4.73 (d, 1H, *J* 9.9 Hz, H-1), 3.68 (t, 1H, *J* 8.8 Hz, H-3), 3.52 (dd, 1H, *J* 13.2, 2.2 Hz, H-6), 3.45–3.50 (m, 2H, H-2, H-4), 3.40–3.43 (m, 1H, H-5), 3.33 (dd, 1H, *J* 13.2, 5.5 Hz, H-6′), 2.34 (s, 3H, $ArCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 51.6, 75.4, 75.6, 76.0, 78.3 (2C), 81.0, 86.8, 88.2, 128.0–128.8, 130.0, 133.6, 137.9, 138.2, 138.4; LR-ESI-MS *m*/*z* Calcd for $[M+Na]^+$ 604.2. Found 604.3.

4.4. 6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucosyl trichloro acetimidate (4b)

To a stirred solution of **4a** (1.2 g, 2.0 mmol) in acetone (36 mL) and H_2O (4 mL) at ambient temperature was added NBS (1.1 g, 6.0 mmol). After 5 min, the reaction was quenched with saturated $NaHCO_3$ and the mixture concentrated. The crude intermediate was diluted with $CHCl_3$ (150 mL) and washed with satd aq $NaHCO_3$ (100 mL), brine (2 × 100 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography to afford white solid (0.87 g). To a stirred solution of the white solid were added CCl_3CN (1.1 mL, 11.0 mmol) and DBU (137 μL, 0.92 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 4 h, the solution was concentrated and the residue was purified by silica gel column chromatography (10:1 petroleum ether–EtOAc) to afford **4b** (0.97 g, 76%) as a syrup; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.62 (s, 1H, NH), 7.24–7.34 (m, 15H, Ph), 6.50 (d, 1H, *J* 4.4 Hz, H-1), 4.60–4.99 (m, 6H, 3× $PhCH_2$), 4.05 (t, 1H, *J* 9.8 Hz, H-4), 4.01 (ddd, 1H, *J* 9.9, 4.4, 2.2 Hz, H-5), 3.74 (dd, 1H, *J* 9.9, 3.3 Hz, H-2), 3.60 (t, 1H, *J* 8.8 Hz, H-3), 3.53 (dd, 1H, *J* 13.2, 2.2 Hz, H-6), 3.37 (dd, 1H, *J* 13.2, 4.4 Hz, H-6′); ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.1, 72.8, 73.2, 75.7, 75.9, 79.6, 81.3, 91.4, 94.0, 94.1, 128.2–128.8, 137.9, 138.0, 138.6, 161.4; HR-ESI-MS *m*/*z* Calcd for $C_{29}H_{29}O_5N_4Cl_3Na$ 641.1096 $[M+Na]^+$. Found 641.1078.

4.5. 3-*O*-(6′-Azido-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-1,2-isopropylidene -*sn*-glycerol (3)

4.5.1. For donor 4a (entry 2)

A mixture of the glycosyl donor **4a** (0.41 g, 0.70 mmol) and activated 4 Å molecular sieves was stirred in dry Et_2O (40 mL) at room temperature under an N_2 atmosphere, then NIS (0.23 g, 1.05 mmol) was added. After stirring for 10 min, DTBMP (143 mmg, 3.8 mmol) was added, followed by addition of acceptor (*S*)-1,2-isopropylideneglycerol (100 μL, 0.84 mmol) and TMSOTf (150 μL, 0.42 mmol). The reaction mixture was stirred at room temperature under an N_2 atmosphere for 72 h, when TLC showed that the reaction was completed. The mixture was quenched by addition of Et_3N, filtered through a pad of Celite. The filtrate was concentrated by diminished pressure and the residue was dissolved in CH_2Cl_2. The solution was washed with 10% $Na_2S_2O_3$, followed by satd aq $NaHCO_3$. The organic layer was dried over Na_2SO_4, then the solvent was removed in vacuo, and the residue was purified by column chromatography (8:1 petroleum ether–EtOAc) to afford a mixture of **3** and **8** (0.36 g, 85%, α/β = 9:1) as a syrup; ^1H NMR ($CDCl_3$, 600 MHz): δ H-1 for **3**: 4.86 (d, *J* 3.8 Hz), δ H-1 for **8**: 4.46 (d, *J* 7.7 Hz).

4.5.2. For donor 4b (entry 5)

A solution of trichloroacetimidate **4b** (60.0 mg, 0.097 mmol) and (*S*)-1,2-isopropylideneglycerol **5** (15 μL, 0.116 mmol) in dry Et_2O (4.9 mL) was added to freshly dried powdered 4 Å MS and cooled to 0 °C. TMSOTf (3.9 μL, 0.019 mmol) was added to the solution, and the mixture was stirred at 0 °C for 0.5 h. The mixture was diluted with EtOAc (50 mL) and filtered through Celite. The organic layer was washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel (8:1 petroleum ether–EtOAc) to furnish **3** and **8** (49.7 mg, 88%, α/β = 33:1) as a colorless oil; for α anomer (**3**): $[\alpha]_D^{22} = +58.0$ (*c* 0.50, $CHCl_3$), lit.[13] +58.5 (*c* 11.96, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.21–7.35 (m, 15H, –Ar); 4.55–5.0 (m, 6H, 3× $PhCH_2$), 4.86 (d, 1H, *J* 3.8 Hz, H-1), 4.33–4.35 (m, 1H, H_{sn-2}), 4.07(dd, 1H, *J* 8.2, 6.0 Hz, $H_{sn-3'}$), 3.96 (t, 1H, *J* 9.4 Hz, H-3), 3.80–3.84 (m, 1H, H-5), 3.74 (dd, 1H, *J* 8.2, 6.0 Hz, H_{sn-3}), 3.63 (dd, 1H, *J* 11.0, 6.0 Hz, $H_{sn-1'}$), 3.53–3.57 (m, 2H, H-2, H_{sn-1}), 3.42–3.47 (m, 2H, H-4, H-6′), 3.33 (dd, 1H, *J* 13.2, 5.5 Hz, H-6), 1.37 (s, 3H, $-CH_3$), 1.43 (s, 3H, $-CH_3$); HR-ESI-MS *m*/*z* Calcd for $C_{33}H_{39}O_7N_3Na$ 612.2680 $[M+Na]^+$. Found 612.2671.

4.6. 3-*O*-(6′-Azido-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (9)

TsOH (0.32 g, 1.70 mmol) was added to a stirred solution of **3** (0.50 g, 0.85 mmol) in MeOH (20 mL). After stirring for 2 h at ambient temperature, the solution was concentrated and dissolved in CH_2Cl_2. The organic layer was washed with satd aq $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and concentrated. Purification was achieved by silica gel column chromatography (2:1 petroleum ether–EtOAc) to give **9** (0.27 g, 93%) as a colorless waxy substance; $[\alpha]_D^{22} = +44.2$ (*c* 0.75, $CHCl_3$), lit.[13] +35.7 (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.25–7.36 (m, 15H, $-C_6H_5$), 4.57–4.97 (m, 6H, 3× $PhCH_2$), 4.73 (d, 1H, *J* 3.8 Hz, H-1), 3.95 (t, 1H, *J* 9.4 Hz, H-3), 3.84–3.89 (m, 2H, H_{sn-1}, H_{sn-2}), 3.80–3.83 (m, 1H, H-5), 3.74 (dd, 1H, *J* 11.6, 4.4 Hz, H_{sn-3}), 3.64 (dd, 1H, *J* 11.5, 4.4 Hz, $H_{sn-3'}$), 3.56 (dd, 1H, *J* 9.9, 3.8 Hz, H-2), 3.40–3.47 (m, 3H, H-4, H-6, $H_{sn-1'}$), 3.33 (dd, 1H, *J* 12.7, 5.5 Hz, H-6′); HR-ESI-MS *m*/*z* Calcd for $C_{30}H_{36}O_7N_3$ 550.2548 $[M+H]^+$, $C_{30}H_{35}O_7N_3Na$ 572.2367 $[M+Na]^+$. Found 550.2537 $[M+H]^+$, 572.2357 $[M+Na]^+$.

4.7. 3-*O*-(6′-Amino-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (2)

To a solution of **9** (0.60 g, 1.08 mmol) in THF (20 mL) and water (0.21 mL) was added PPh_3 (0.57 g, 2.16 mmol). The reaction mixture was heated at 50 °C for 5 h and then cooled to room temperature. The mixture was evaporated under diminished pressure, and the residue was purified by gel silica column chromatography (10:1 CH_2Cl_2–MeOH) to give **2** (0.55 g, 96%) as a colorless waxy substance; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.24–7.34 (m, 15H, $-C_6H_5$), 4.55–4.96 (m, 6H, 3× $PhCH_2$), 4.73 (d, 1H, *J* 3.7 Hz, H-1), 3.93 (t, 1H, *J* 9.2 Hz, H-3), 3.86–3.89 (m, 1H, H_{sn-2}), 3.69–3.73 (m, 2H, H_{sn-3}, $H_{sn-3'}$), 3.62–3.67 (m, 2H, H-5, H_{sn-1}), 3.50 (dd, 1H, *J* 9.6, 3.7 Hz, H-2), 3.45 (dd, 1H, *J* 10.1, 6.4 Hz, $H_{sn-1'}$), 3.20–3.26 (m, 3H, H-4, $-NH_2$), 2.97 (dd, 1H, *J* 12.8, 2.3 Hz, H-6), 2.61 (dd, 1H, *J* 12.8, 8.3 Hz, H-6′); ^{13}C NMR (150 MHz, $CDCl_3$) δ 42.4, 63.0, 70.1, 70.2, 71.7, 73.6, 75.2, 75.9, 79.4, 80.2, 82.3, 97.5, 128.2–128.6, 138.0,

138.8; HR-ESI-MS *m*/*z* Calcd for $C_{30}H_{38}O_7N$ 524.2643 $[M+H]^+$. Found 524.2634.

4.8. General procedure for 10a–h formation

To a solution of compound **2** (80 mg, 0.15 mmol) in dry pyridine (4 mL), a catalytic amount of DMAP and acyl chloride (6 equiv) were added. The reaction mixture was stirred at room temperature for 4 h, and then was diluted with EtOAc (15 mL) and washed with satd aq NH_4Cl (15 mL). The organic phase was dried over $MgSO_4$, filtrated, and concentrated. Purification by flash chromatography (petroleum ether–EtOAc) yielded the corresponding compounds **10a–h** (66–92%) as a colorless syrup or white solid.

4.8.1. 1,2-Dipalmitoyl-3-*O*-(*N* -palmitoyl-6′-amino-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (10a, 76%)

^1H NMR ($CDCl_3$, 600 MHz): δ 7.26–7.35 (m, 15H, $-C_6H_5$), 5.66 (dd, 1H, *J* 7.3, 4.1 Hz, –NH–CO–), 5.21–5.23 (m, 1H, H_{sn-2}), 4.61–4.97 (m, 6H, 3× $PhCH_2$), 4.69 (d, 1H, *J* 3.3 Hz, H-1), 4.39 (dd, 1H, *J* 3.8, 12.1 Hz, H_{sn-3}), 4.18 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-3'}$), 3.95 (t, 1H, *J* 8.8 Hz, H-3), 3.75–3.78 (m, 1H, H-5), 3.65–3.70 (m, 2H, H-6, H_{sn-1}), 3.57 (dd, 1H, *J* 5.5, 11.0 Hz, $H_{sn-1'}$), 3.47 (dd, 1H, *J* 3.8, 9.9 Hz, H-2), 3.32–3.35 (m, 1H, H-6′), 3.27 (t, 1H, *J* 9.4 Hz, H-4), 2.28–2.34 (m, 4H, 2× $-CH_2$–COO–), 2.11 (t, 2H, *J* 7.1 Hz, –NHCO–CH_2–), 1.57–1.64 (m, 6H, 3× $-CO-CH_2-CH_2-$), 1.21–1.33 (m, 72H, 3× $-CH_2-CH_2(CH_2)_{12}-CH_3$), 0.87 (t, 9H, *J* 6.6 Hz, 3× $-CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 22.9, 25.0, 25.1, 26.0, 29.3–29.9, 32.1, 34.3, 34.5, 37.0, 39.8, 62.7, 66.8, 69.8, 70.1, 73.4, 75.5, 76.0, 78.9, 80.3, 81.7, 99.8, 128.1–128.7, 138.1, 138.4, 138.7, 173.4, 173.6, 179.0; HR-ESI-MS *m*/*z* Calcd for $C_{78}H_{128}O_{10}N$ 1238.9533 $[M+H]^+$. Found 1238.9549.

4.8.2. 1,2-Dihexanoyl-3-*O*-(*N* -hexanoyl-6′-amino-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (10b, 81%)

^1H NMR ($CDCl_3$, 600 MHz): δ 7.26–7.34 (m, 15H, $-C_6H_5$), 5.65 (dd, 1H, *J* 4.4, 7.7 Hz, –NH–CO–), 5.20–5.23 (m, 1H, H_{sn-2}), 4.62–4.97 (m, 6H, 3× $PhCH_2$), 4.69 (d, 1H, *J* 3.3 Hz, H-1), 4.39 (dd, 1H, *J* 3.9, 12.1 Hz, H_{sn-3}), 4.18 (dd, 1H, *J* 6.1, 11.6 Hz, $H_{sn-3'}$), 3.95 (t, 1H, *J* 9.4 Hz, H-3), 3.71–3.76 (m, 1H, H-5), 3.65–3.70 (m, 2H, H-6, H_{sn-1}), 3.57 (dd, 1H, *J* 5.5, 11.0 Hz, $H_{sn-1'}$), 3.47 (dd, 1H, *J* 3.3, 9.3 Hz, H-2), 3.33–3.36 (m, 1H, H-6′), 3.27 (t, 1H, *J* 9.4 Hz, H-4), 2.28–2.31 (m, 4H, 2× $-CH_2$–COO–), 2.11 (t, 2H, *J* 6.6 Hz, –NHCO–CH_2–), 1.57–1.62 (m, 6H, 3× $-CO-CH_2-CH_2-$), 1.26–1.31 (m, 12H, 3× $-CH_2-CH_2(CH_2)_2-CH_3$), 0.88 (m, 9H, 3× $-CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 14.2, 22.5, 22.6, 24.8, 25.7, 31.4–31.7, 34.3, 34.4, 37.0, 39.7, 62.6, 66.8, 69.8, 70.1, 73.4, 75.5, 76.0, 78.8, 80.3, 81.7, 97.8, 128.0–128.7, 138.1, 138.4, 138.8, 173.3, 173.4, 173.6; HR-ESI-MS *m*/*z* Calcd for $C_{48}H_{68}O_{10}N$ 818.4838 $[M+H]^+$. Found 818.4863.

4.8.3. 1,2-Dioctanoyl-3-*O*-(*N* -octanoyl-6′-amino-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (10c, 86%)

^1H NMR ($CDCl_3$, 600 MHz): δ 7.26–7.34 (m, 15H, $-C_6H_5$), 5.65 (dd, 1H, *J* 3.9, 7.1 Hz, –NH–CO–), 5.20–5.23 (m, 1H, H_{sn-2}), 4.62–4.97 (m, 6H, 3× $PhCH_2$), 4.69 (d, 1H, *J* 3.3 Hz, H-1), 4.39 (dd, 1H, *J* 3.8, 12.1 Hz, H_{sn-3}), 4.18 (dd, 1H, *J* 6.0, 12.1 Hz, $H_{sn-3'}$), 3.95 (t, 1H, *J* 9.3 Hz, H-3), 3.75–3.78 (m, 1H, H-5), 3.65–3.70 (m, 2H, H-6, H_{sn-1}), 3.57 (dd, 1H, *J* 5.5, 11.0 Hz, $H_{sn-1'}$), 3.47 (dd, 1H, *J* 3.3, 9.4 Hz, H-2), 3.33–3.35 (m, 1H, H-6′), 3.27 (t, 1H, *J* 9.9 Hz, H-4), 2.28–2.33 (m, 4H, 2× $-CH_2$–COO–), 2.11 (t, 2H, *J* 7.1 Hz, –NHCO–CH_2–), 1.59–1.64 (m, 6H, 3× $-CO-CH_2-CH_2-$), 1.21–1.33 (m, 24H, 3× $-CH_2-CH_2(CH_2)_4-CH_3$), 0.87 (t, 9H, *J* 7.1 Hz, 3× $-CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 22.8, 25.1, 26.0, 29.1–29.4, 31.9, 34.3, 34.5, 37.0, 39.7, 62.6, 66.8, 69.8, 70.0, 73.4, 75.5, 76.0, 78.8, 80.3, 81.7, 97.8, 128.3–128.7, 138.1, 138.4, 138.7, 173.2, 173.4, 173.6; HR-ESI-MS *m*/*z* Calcd for $C_{54}H_{80}O_{10}N$ 902.5777 $[M+H]^+$. Found 902.5788.

4.8.4. 1,2-Dilauroyl-3-*O*-(*N* -lauroyl-6′-amino-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (10d, 92%)

^1H NMR ($CDCl_3$, 600 MHz): δ 7.26–7.35 (m, 15H, $-C_6H_5$), 5.67 (dd, 1H, *J* 4.4, 7.7 Hz, –NH–CO–), 5.21–5.23 (m, 1H, H_{sn-2}), 4.61–4.97 (m, 6H, 3× $PhCH_2$), 4.69 (d, 1H, *J* 3.3 Hz, H-1), 4.39 (dd, 1H, *J* 3.8, 12.0 Hz, H_{sn-3}), 4.18 (dd, 1H, *J* 6.6, 12.1 Hz, $H_{sn-3'}$), 3.95 (t, 1H, *J* 9.3 Hz, H-3), 3.75–3.78 (m, 1H, H-5), 3.65–3.70 (m, 2H, H-6, H_{sn-1}), 3.57 (dd, 1H, *J* 5.5, 10.4 Hz, $H_{sn-1'}$), 3.47 (dd, 1H, *J* 3.8, 9.9 Hz, H-2), 3.32–3.35 (m, 1H, H-6′), 3.27 (t, 1H, *J* 9.4 Hz, H-4), 2.28–2.34 (m, 4H, 2× $-CH_2$–COO–), 2.11 (t, 2H, *J* 7.1 Hz, –NHCO–CH_2–), 1.57–1.64 (m, 6H, 3× $-CO-CH_2-CH_2-$), 1.21–1.33 (m, 48H, 3× $-CH_2-CH_2(CH_2)_8-CH_3$), 0.87 (t, 9H, *J* 7.1 Hz, 3× $-CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 22.9, 25.1, 26.0, 29.4–29.8, 32.1, 34.3, 34.5, 37.0, 39.7, 62.7, 66.8, 69.8, 70.1, 73.4, 75.5, 76.0, 78.8, 80.3, 81.7, 97.8, 128.0–128.7, 138.1, 138.4, 138.8, 173.3, 173.4, 173.6; HR-ESI-MS *m*/*z* Calcd for $C_{66}H_{104}O_{10}N$ 1070.7655 $[M+H]^+$. Found 1070.7647.

4.8.5. 1,2-Dimyristoyl-3-*O*-(*N* -myristoyl-6′-amino-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (10e, 83%)

^1H NMR ($CDCl_3$, 600 MHz): δ 7.26–7.35 (m, 15H, $-C_6H_5$), 5.66 (dd, 1H, *J* 3.8, 7.1 Hz, –NH–CO–), 5.20–5.23 (m, 1H, H_{sn-2}), 4.61–4.97 (m, 6H, 3× $PhCH_2$), 4.69 (d, 1H, *J* 3.3 Hz, H-1), 4.39 (dd, 1H, *J* 3.8, 12.0 Hz, H_{sn-3}), 4.18 (dd, 1H, *J* 6.1, 11.5 Hz, $H_{sn-3'}$), 3.95 (t, 1H, *J* 8.8 Hz, H-3), 3.75–3.78 (m, 1H, H-5), 3.65–3.70 (m, 2H, H-6, H_{sn-1}), 3.57 (dd, 1H, *J* 4.9, 10.4 Hz, $H_{sn-1'}$), 3.47 (dd, 1H, *J* 3.8, 9.9 Hz, H-2), 3.32–3.35 (m, 1H, H-6′), 3.27 (t, 1H, *J* 9.4 Hz, H-4), 2.28–2.35 (m, 4H, 2× $-CH_2$–COO–), 2.11 (t, 2H, *J* 7.7 Hz, –NHCO–CH_2–), 1.57–1.64 (m, 6H, 3× $-CO-CH_2-CH_2-$), 1.21–1.33 (m, 60H, 3× $-CH_2-CH_2(CH_2)_{10}-CH_3$), 0.87 (t, 9H, *J* 6.6 Hz, 3× $-CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 22.9, 25.1, 26.0, 29.4–29.9, 32.1, 34.3, 34.5, 37.0, 39.8, 62.7, 66.8, 69.8, 70.1, 73.4, 75.5, 76.0, 78.8, 80.3, 81.7, 99.8, 128.1–128.6, 138.1, 138.3, 138.7, 173.4, 173.6, 178.4; HR-ESI-MS *m*/*z* Calcd for $C_{72}H_{116}O_{10}N$ 1154.8594 $[M+H]^+$. Found 1154.8600.

4.8.6. 1,2-Distearoyl-3-*O*-(*N* -stearoyl-6′-amino-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (10f, 66%)

^1H NMR ($CDCl_3$, 600 MHz): δ 7.26–7.35 (m, 15H, $-C_6H_5$), 5.66 (dd, 1H, *J* 3.8, 7.1 Hz, –NH–CO–), 5.21–5.23 (m, 1H, H_{sn-2}), 4.61–4.97 (m, 6H, 3× $PhCH_2$), 4.69 (d, 1H, *J* 3.3 Hz, H-1), 4.39 (dd, 1H, *J* 3.3, 11.5 Hz, H_{sn-3}), 4.18 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-3'}$), 3.95 (t, 1H, *J* 9.4 Hz, H-3), 3.75–3.78 (m, 1H, H-5), 3.65–3.70 (m, 2H, H-6, H_{sn-1}), 3.57 (dd, 1H, *J* 5.5, 11.0 Hz, $H_{sn-1'}$), 3.47 (dd, 1H, *J* 3.3, 9.9 Hz, H-2), 3.32–3.35 (m, 1H, H-6′), 3.27 (t, 1H, *J* 9.3 Hz, H-4), 2.28–2.34 (m, 4H, 2× $-CH_2$–COO–), 2.11 (t, 2H, *J* 7.1 Hz, –NHCO–CH_2–), 1.57–1.64 (m, 6H, 3× $-CO-CH_2-CH_2-$), 1.21–1.33 (m, 84H, 3× $-CH_2-CH_2(CH_2)_{14}-CH_3$), 0.87 (t, 9H, *J* 6.6 Hz, 3× $-CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 22.9, 25.1, 26.0, 29.4–29.9, 32.2, 34.1, 34.3, 34.5, 37.0, 39.7, 62.7, 66.8, 69.8, 70.1, 73.4, 75.5, 76.0, 78.8, 80.3, 81.7, 97.8, 128.1–128.7, 138.1, 138.4, 138.8, 173.4, 173.6, 178.3; LR-APCI-MS: *m*/*z* Calcd for $C_{84}H_{140}NO_{10}$ 1323.0 $[M+H]^+$. Found 1323.0.

4.8.7. 1,2-Diisovaleryl-3-*O*-(*N* -isovaleryl-6′-amino-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (10g, 78%)

^1H NMR ($CDCl_3$, 600 MHz): δ 7.26–7.34 (m, 15H, $-C_6H_5$), 5.63 (dd, 1H, *J* 3.3, 7.2 Hz, –NH–CO–), 5.21–5.24 (m, 1H, H_{sn-2}), 4.61–4.96 (m, 6H, 3× $PhCH_2$), 4.69 (d, 1H, *J* 3.3 Hz, H-1), 4.40 (dd, 1H, *J* 3.9, 12.1 Hz, H_{sn-3}), 4.18 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-3'}$), 3.95 (t, 1H, *J* 8.8 Hz, H-3), 3.72–3.76 (m, 1H, H-5), 3.65–3.71 (m, 2H, H-6, H_{sn-1}), 3.57 (dd, 1H, *J* 5.5, 11.0 Hz, $H_{sn-1'}$), 3.46 (dd, 1H, *J* 3.3, 9.9 Hz, H-2), 3.35–3.39 (m, 1H, H-6′), 3.27 (t, 1H, *J* 9.4 Hz, H-4),

1.95–2.19 (m, 9H, 3× –CO–$CH_2CH(CH_3)_2$), 0.92–0.95 (m, 18H, 3× –CO–$CH_2CH(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.5, 22.6, 22.8, 25.8, 25.9, 26.3, 39.7, 43.3, 43.5, 46.3, 62.6, 66.8, 69.8, 70.0, 73.4, 75.4, 75.9, 78.9, 80.3, 81.7, 97.8, 128.2–128.7, 138.1, 138.4, 138.7, 172.6, 172.8; HR-ESI-MS *m*/*z* Calcd for $C_{45}H_{62}O_{10}N$ 776.4368 $[M+H]^+$. Found 776.4375.

4.8.8. 1,2-Dihydrocinnamoyl-3-*O*-(*N*-hydrocinnamoyl-6′-amino-2′,3′,4′-tri-*O*-benzyl-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (10h, 77%)

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.10–7.34(m, 30H, –C_6H_5), 5.55 (dd, 1H, *J* 3.8, 7.1 Hz, –NH–CO–), 5.15–5.17 (m, 1H, H_{sn-2}), 4.56–4.96 (m, 6H, 3× $PhCH_2$), 4.61 (d, 1H, *J* 2.8 Hz, H-1), 4.34 (dd, 1H, *J* 3.8, 12.1 Hz, H_{sn-3}), 4.14 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-3'}$), 3.90 (t, 1H, *J* 9.4 Hz, H-3), 3.72–3.77 (m, 1H, H-5), 3.58–3.60 (m, 2H, H-6, H_{sn-1}), 3.46 (dd, 1H, *J* 5.0, 11.0 Hz, $H_{sn-1'}$), 3.38 (dd, 1H, *J* 3.8, 9.9 Hz, H-2), 3.24–3.27 (m, 1H, H-6′), 3.14 (t, 1H, *J* 8.8 Hz, H-4), 2.40–2.95 (m, 12H, 3× –$COCH_2CH_2$–); ^{13}C NMR (150 MHz, $CDCl_3$) δ 31.0, 31.8, 35.7, 35.9, 38.5, 39.6, 62.8, 66.7, 69.7, 70.3, 73.3, 75.4, 75.9, 78.6, 80.2, 81.7, 97.8, 127.8–128.7, 138.1, 138.4, 138.8, 140.4, 140.5, 141.0, 172.2, 172.4, 172.5; HR-ESI-MS *m*/*z* Calcd for $C_{57}H_{62}O_{10}N$ 920.4368 $[M+H]^+$. Found 920.4385.

4.9. General procedure for 1a–h formation

A solution of **10a–h** (100 mg) in 20 mL THF/*i*-PrOH (9:1) was treated with 10% palladium hydroxide (100 mg) and stirred at ambient temperature under hydrogen atmosphere for 6 h. After filtration the solvent was evaporated and the residue was purified by column chromatography (CH_2Cl_2–MeOH) to afford **1a–h** (84–90%) as a colorless syrup or waxy solid.

4.9.1. 1,2-Dipalmitoyl-3-*O*-(*N*-palmitoyl-6′-amino-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (1a, 86%)

$[\alpha]_D^{22} = +9.5$ (*c* 0.75, $CHCl_3$), lit.[13] +12.4 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.95 (dd, 1H, *J* 7.7, 4.4 Hz, –NH–CO–), 5.22–5.24 (m, 1H, H_{sn-2}), 4.81 (d, 1H, *J* 3.8 Hz, H-1), 4.39 (dd, 1H, *J* 3.8, 11.5 Hz, H_{sn-1}), 4.13 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-1'}$), 4.01–4.05 (m, 1H, H-5), 3.79 (dd, 1H, *J* 4.9, 11.0 Hz, H_{sn-3}), 3.75 (t, 1H, *J* 9.3 Hz, H-3), 3.63 (dd, 1H, *J* 6.1, 11.0 Hz, $H_{sn-3'}$), 3.58 (dd, 1H, *J* 3.8, 9.5 Hz, H-2), 3.49 (dd, 1H, *J* 3.9, 11.1 Hz, H-6), 3.11 (t, 1H, *J* 9.4 Hz, H-4), 3.03–3.05 (m, 1H, H-6′), 2.24–2.31 (m, 6H, 3× –CH_2–CO–), 1.60–1.65 (m, 6H, 3× –CO–CH_2–CH_2–), 1.26–1.30 (m, 72H, 3× –CH_2–$CH_2(CH_2)_{12}$–CH_3), 0.87 (t, 9H, *J* 7.2 Hz, 3× –CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 22.9, 25.1, 25.9, 29.6–29.9, 32.2, 34.3, 34.5, 36.7, 40.0, 62.4, 67.1, 70.1, 70.3, 71.4, 72.6, 73.4, 99.7, 173.4, 173.7, 175.9; LR-APCI-MS *m*/*z* 968.9 $[M+H]^+$; HR-MALDI-MS *m*/*z* Calcd for $C_{57}H_{109}O_{10}NNa$ 990.7949 $[M+Na]^+$. Found 990.7922.

4.9.2. 1,2-Dihexanoyl-3-*O*-(*N*-hexanoyl-6′-amino-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (1b, 84%)

$[\alpha]_D^{22} = +13.0$ (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.06 (dd, 1H, *J* 6.1, 5.0 Hz, –NH–CO–), 5.16–5.18 (m, 1H, H_{sn-2}), 4.74 (d, 1H, *J* 2.2 Hz, H-1), 4.31 (dd, 1H, *J* 3.9, 12.1 Hz, H_{sn-1}), 4.08 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-1'}$), 3.82–3.85 (m, 1H, H-5), 3.71 (dd, 1H, *J* 3.8, 9.9 Hz, H_{sn-3}), 3.67 (t, 1H, *J* 9.9 Hz, H-3), 3.57 (dd, 1H, *J* 5.5, 10.4 Hz, $H_{sn-3'}$), 3.51 (dd, 1H, *J* 3.8, 9.4 Hz, H-2), 3.41 (dd, 1H, *J* 5.0, 11.0 Hz, H-6), 3.06–3.09 (m, 2H, H-4, H-6′), 2.13–2.26 (m, 6H, 3× –CH_2–CO–), 1.54 (m, 6H, 3× –CO–CH_2–CH_2–), 1.17–1.25 (m, 12H, 3× –CH_2–$CH_2(CH_2)_2$–CH_3), 0.83 (t, 9H, *J* 7.1 Hz, 3× –CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 22.8, 25.0, 25.9, 29.1–29.5, 31.8, 34.3, 34.5, 36.6, 40.1, 62.5, 66.8, 70.1, 70.6, 71.2, 72.4, 73.3, 99.6, 173.4, 173.7, 175.6; LR-ESI-MS *m*/*z* 548.2 $[M+H]^+$; HR-ESI-MS *m*/*z* Calcd for $C_{27}H_{50}O_{10}N$ 548.3435 $[M+H]^+$. Found 548.3447.

4.9.3. 1,2-Dioctanoyl-3-*O*-(*N*-octanoyl-6′-amino-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (1c, 90%)

$[\alpha]_D^{22} = +15.9$ (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.96 (dd, 1H, *J* 7.7, 4.4 Hz, –NH–CO–), 5.23–5.25 (m, 1H, H_{sn-2}), 4.81 (d, 1H, *J* 2.8 Hz, H-1), 4.39 (dd, 1H, *J* 3.8, 12.1 Hz, H_{sn-1}), 4.15 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-1'}$), 3.86–3.91 (m, 1H, H-5), 3.77 (dd, 1H, *J* 5.0, 11.0 Hz, H_{sn-3}), 3.74 (t, 1H, *J* 9.4 Hz, H-3), 3.63 (dd, 1H, *J* 5.5, 10.4 Hz, $H_{sn-3'}$), 3.58 (dd, 1H, *J* 3.8, 9.4 Hz, H-2), 3.50 (dd, 1H, *J* 3.8, 10.1 Hz, H-6), 3.13–3.18 (m, 2H, H-4, H-6′), 2.21–2.32 (m, 6H, 3× –CH_2–CO–), 1.61 (m, 6H, 3× –CO–CH_2–CH_2–), 1.24–1.30 (m, 24H, 3× –CH_2–$CH_2(CH_2)_4$–CH_3), 0.88 (t, 9H, *J* 7.7 Hz, 3× –CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 22.8, 25.0, 25.9, 29.1–29.5, 31.8, 34.3, 34.5, 36.6, 40.1, 62.5, 66.8, 70.1, 70.6, 71.2, 72.4, 73.3, 99.6, 173.4, 173.7, 175.6; LR-ESI-MS *m*/*z* 632.5 $[M+H]^+$, 654.5 $[M+Na]^+$; HR-ESI-MS *m*/*z* Calcd for $C_{33}H_{62}O_{10}N$ 632.4374 $[M+H]^+$, $C_{33}H_{61}O_{10}NNa$ 654.4193 $[M+Na]^+$. Found 632.4387 $[M+H]^+$, 654.4206 $[M+Na]^+$.

4.9.4. 1,2-Dilauroyl-3-*O*-(*N*-lauroyl-6′-amino-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (1d, 86%)

$[\alpha]_D^{22} = +10.5$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.27 (dd, 1H, *J* 7.7, 4.9 Hz, –NH–CO–), 5.22–5.24 (m, 1H, H_{sn-2}), 4.81 (d, 1H, *J* 3.8 Hz, H-1), 4.39 (dd, 1H, *J* 3.3, 11.6 Hz, H_{sn-1}), 4.14 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-1'}$), 3.88–3.92 (m, 1H, H-5), 3.78 (dd, 1H, *J* 5.5, 11.0 Hz, H_{sn-3}), 3.74 (t, 1H, *J* 9.4 Hz, H-3), 3.63 (dd, 1H, *J* 5.5, 11.0 Hz, $H_{sn-3'}$), 3.58 (dd, 1H, *J* 3.8, 9.4 Hz, H-2), 3.48 (dd, 1H, *J* 3.8, 10.1 Hz, H-6), 3.13–3.16 (m, 2H, H-4, H-6′), 2.22–2.32 (m, 6H, 3× –CH_2–CO–), 1.61 (m, 6H, 3× –CO–CH_2–CH_2–), 1.24–1.31 (m, 48H, 3× –CH_2–$CH_2(CH_2)_8$–CH_3), 0.88 (t, 9H, *J* 6.6 Hz, 3× –CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 22.7, 24.9, 25.8, 29.2–30.0, 32.0, 34.2, 34.3, 36.5, 39.9, 62.4, 66.7, 70.2, 70.5, 71.1, 72.4, 73.2, 99.6, 173.3, 173.5, 175.5; LR-ESI-MS *m*/*z* 800.7 $[M+H]^+$; HR-ESI-MS *m*/*z* Calcd for $C_{45}H_{86}O_{10}N$ 800.6252 $[M+H]^+$. Found 800.6270.

4.9.5. 1,2-Dimyristoyl-3-*O*-(*N*-myristoyl-6′-amino-6′-deoxy-α-D-glucopyranosyl)-*sn*-glycerol (1e, 85%)

$[\alpha]_D^{22} = +6.2$ (*c* 3.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.00 (dd, 1H, *J* 8.2, 4.9 Hz, –NH–CO–), 5.23–5.25 (m, 1H, H_{sn-2}), 4.81 (d, 1H, *J* 3.8 Hz, H-1), 4.39 (dd, 1H, *J* 3.8, 11.5 Hz, H_{sn-1}), 4.13 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-1'}$), 3.97–4.01 (m, 1H, H-5), 3.78 (dd, 1H, *J* 4.4, 11.0 Hz, H_{sn-3}), 3.75 (t, 1H, *J* 9.3 Hz, H-3), 3.63 (dd, 1H, *J* 6.0, 11.0 Hz, $H_{sn-3'}$), 3.58 (dd, 1H, *J* 3.8, 9.5 Hz, H-2), 3.49 (dd, 1H, *J* 4.4, 9.9 Hz, H-6), 3.12 (t, 1H, *J* 9.9 Hz, H-4), 3.04 (dd, 1H, *J* 7.4, 14.9 Hz, H-6′), 2.24–2.34 (m, 6H, 3× –CH_2–CO–), 1.61–1.66 (m, 6H, 3× –CO–CH_2–CH_2–), 1.26–1.30 (m, 60H, 3× –CH_2–$CH_2(CH_2)_{10}$–CH_3), 0.88 (t, 9H, *J* 7.2 Hz, 3× –CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 22.9, 25.0, 25.1, 25.9, 29.4–29.9, 32.2, 34.2, 34.3, 34.5, 36.7, 40.0, 62.4, 67.1, 70.1, 70.4, 71.3, 72.5, 73.3, 99.7, 173.5, 173.7, 176.0; LR-ESI-MS *m*/*z* 884.9 $[M+H]^+$; HR-ESI-MS *m*/*z* Calcd for $C_{51}H_{98}O_{10}N$ 884.7191 $[M+H]^+$. Found 884.7210.

4.9.6. 1,2-Distearoyl-3-*O*-(*N*-stearoyl-6′-amino-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (1f, 88%)

$[\alpha]_D^{22} = +5.6$ (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.89 (dd, 1H, *J* 8.7, 5.5 Hz, –NH–CO–), 5.22–5.25 (m, 1H, H_{sn-2}), 4.81 (d, 1H, *J* 3.8 Hz, H-1), 4.39 (dd, 1H, *J* 3.8, 12.1 Hz, H_{sn-1}), 4.13 (dd, 1H, *J* 6.1, 12.1 Hz, $H_{sn-1'}$), 3.97–4.01 (m, 1H, H-5), 3.78 (dd, 1H, *J* 4.9, 11.0 Hz, H_{sn-3}), 3.75 (t, 1H, *J* 9.3 Hz, H-3), 3.63 (dd, 1H, *J* 6.5, 11.5 Hz, $H_{sn-3'}$), 3.58 (dd, 1H, *J* 3.8, 9.9 Hz, H-2), 3.49 (dd, 1H, *J* 3.8, 10.4 Hz, H-6), 3.12 (t, 1H, *J* 9.9 Hz, H-4), 3.07 (m, 1H, H-6′), 2.24–2.34 (m, 6H, 3× –CH_2 –CO–), 1.61–1.66 (m, 6H, 3× –CO–CH_2–CH_2–), 1.26–1.30 (m, 84H, 3× –CH_2–$CH_2(CH_2)_{14}$–CH_3), 0.87 (t, 9H, *J* 6.6 Hz, 3× –CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 22.9, 25.0, 25.1, 25.9, 29.4–29.9, 32.2, 34.2, 34.3, 34.5, 36.7, 40.0, 62.4, 67.1, 70.1, 70.4, 71.3, 72.5, 73.3, 99.7, 173.5, 173.7, 176.0;

LR-APCI-MS *m*/*z* 1052.9 $[M+H]^+$; HR-MALDI-MS *m*/*z* Calcd for $C_{63}H_{121}O_{10}NNa$ 1074.8888 $[M+Na]^+$. Found 1074.8889.

4.9.7. 1,2-Diisovaleryl-3-*O*-(*N*-isovaleryl-6′-amino-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (1g, 88%)

$[\alpha]_D^{22} = +16.5$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 6.25 (dd, 1H, *J* 6.6, 5.0 Hz, –NH–CO–), 5.24–5.26 (m, 1H, H_{sn-2}), 4.81 (d, 1H, *J* 3.8 Hz, H-1), 4.40 (dd, 1H, *J* 3.3, 11.6 Hz, H_{sn-1}), 4.16 (dd, 1H, *J* 6.1, 11.6 Hz, $H_{sn-1'}$), 3.83–3.89 (m, 1H, H-5), 3.78 (dd, 1H, *J* 4.9, 10.4 Hz, H_{sn-3}), 3.74 (t, 1H, *J* 8.8 Hz, H-3), 3.63 (dd, 1H, *J* 5.5, 11.0 Hz, $H_{sn-3'}$), 3.58 (dd, 1H, *J* 3.8, 9.9 Hz, H-2), 3.48 (dd, 1H, *J* 3.8, 10.1 Hz, H-6), 3.15–3.22 (m, 2H, H-4, H-6′), 2.07–2.21 (m, 9H, 3× –CO–$CH_2CH(CH_3)_2$), 0.93–0.96 (m, 18H, –CO–$CH_2CH(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.6–22.7, 25.8, 25.9, 26.3, 40.1, 43.3, 43.5, 45.9, 62.5, 66.8, 70.0, 70.8, 71.2, 72.4, 73.3, 99.6, 172.7, 173.1, 174.9; LR-ESI-MS *m*/*z* 506.2 $[M+H]^+$, 528.2 $[M+Na]^+$; HR-ESI-MS *m*/*z* Calcd for $C_{24}H_{44}O_{10}N$ 506.2965 $[M+H]^+$. Found 506.2974.

4.9.8. 1,2-Dihydrocinnamoyl-3-*O*-(*N*-hydrocinnamoyl-6′-amino-6′-deoxy-α-D-glucosyl)-*sn*-glycerol (1h, 87%)

$[\alpha]_D^{22} = +18.0$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.15–7.27 (m, 15H, C_6H_5), 6.04 (dd, 1H, *J* 7.2, 5.0 Hz, –NH–CO–), 5.17–5.19 (m, 1H, H_{sn-2}), 4.70 (d, 1H, *J* 3.8 Hz, H-1), 4.31 (dd, 1H, *J* 6.1, 12.1 Hz, H_{sn-1}), 4.09 (dd, 1H, *J* 5.5, 12.1 Hz, $H_{sn-1'}$), 3.82–3.85 (m, 1H, H-5), 3.69 (dd, 1H, *J* 8.8 Hz, H-3), 3.64 (dd, 1H, *J* 4.9, 11.0 Hz, H_{sn-3}), 3.47–3.50 (m, 2H, $H_{sn-3'}$, H-2), 3.38 (m, 1H, H-6), 2.98–3.06 (m, 2H, H-4, H-6′), 2.88–2.96 (m, 6H, 3× –CH_2–CO–), 2.52–2.62 (m, 6H, 3× –CO–CH_2–CH_2–C_6H_5); ^{13}C NMR (150 MHz, $CDCl_3$) δ 30.9, 31.7, 35.7, 35.8, 38.3, 40.0, 62.7, 66.7, 70.3, 70.4, 71.1, 72.3, 73.2, 99.5, 126.5–128.9, 140.4–140.6, 172.6, 172.8, 174.5; LR-ESI-MS *m*/*z* 650.3 $[M+H]^+$, 672.3 $[M+Na]^+$; HR-ESI-MS *m*/*z* Calcd for $C_{36}H_{44}O_{10}N$ 650.2965 $[M+H]^+$, $C_{36}H_{43}O_{10}N$ Na 672.2785 $[M+Na]^+$. Found 650.2969 $[M+H]^+$, 672.2787 $[M+Na]^+$.

Acknowledgements

This work was supported in parts by the National Natural Science Foundation of China (No. 81072574), program for New Century Excellent Talents in University (NCET-08-0506), Special Fund for Marine Scientific Research in the Public Interest (No. 201005024) and PCSIRT (No. IRT09444).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012.04.005.

References

1. Kikuchi, H.; Tsukitani, Y.; Shimizu, I.; Kobayashi, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 552–556.
2. Loya, S.; Reshef, V.; Mizrachi, E.; Silberstein, C.; Rachamim, Y.; Carmeli, S.; Hizi, A. *J. Nat. Prod.* **1998**, *61*, 891–895.
3. Nagatsu, A.; Murakami, N.; Ikemoto, K.; Hashimoto, M.; Murakami, N.; Sakakibara, J.; Tokuda, H.; Nishino, H.; Iwashima, A.; Yazawa, K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1619–1622.
4. Morimoto, T.; Nagatsu, A.; Murakami, N.; Sakakibara, J.; Tokuda, H.; Nishino, H.; Iwashima, A. *Phytochemistry* **1995**, *40*, 1433–1437.
5. Dai, J. Q.; Zhu, Q. X.; Zhao, C. Y.; Yang, L.; Li, Y. *Phytochemistry* **2001**, *58*, 1305–1309.
6. Zhou, B.; Tang, S.; Johnson, R. K.; Mattern, M. P.; Lazo, J. S.; Sharlow, E. R.; Harich, K.; Kingston, D. G. I. *Tetrahedron* **2005**, *61*, 883–887.
7. Andersen, R. J.; Scafati, O. T. *J. Nat. Prod.* **2005**, *68*, 1428–1430.
8. Gupta, P.; Yadav, D. K.; Maurya, K. B.; Palit, G.; Maurya, R. *J. Nat. Prod.* **2007**, *70*, 1410–1416.
9. Squire, C. J.; Dickson, J. M.; Ivanovic, I.; Baker, E. N. *Structure* **2005**, *13*, 541–550.
10. Liu, F.; Stanton, J. J.; Wu, Z.; Piwnica-Worms, H. *Mol. Cell. Biol.* **1997**, 571–583.
11. Liu, F.; Rothblum-Oviatt, C.; Ryan, Ch. E.; Piwnica-Worms, H. *Mol. Cell. Biol.* **1999**, 5113–5123.
12. Wu, H. J.; Li, C. X.; Song, G. P.; Li, Y. X. *Chin. J. Chem.* **2008**, *26*, 1641–1646.
13. Colombo, D.; Franchini, L.; Toma, L.; Ronchetti, F.; Tanaka, R.; Takayasu, J.; Nishino, H.; Tokuda, H. *Eur. J. Med. Chem.* **2006**, *41*, 1456–1463.
14. Gollner, C.; Philipp, C.; Dobner, B.; Sippl, W.; Schmidt, M. *Carbohydr. Res.* **2009**, *344*, 1628–1631.
15. France, R. R.; Compton, R. G.; Davis, B. G.; Fairbanks, A. J.; Rees, N. V.; Wadhawan, J. D. *Org. Biomol. Chem.* **2004**, *2*, 2195–2202.
16. David, A. M.; Ruthven, N. A. H.; Ronald, N. M. *Chem. Phys. Lip.* **1987**, *43*, 113–127.
17. Gordon, D. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 659–663.
18. Hanashima, A.; Mizushina, Y.; Yamazaki, T.; Ohata, K.; Takahashi, S.; Koshino, H.; Sahara, S.; Sakaguchi, K.; Sugawara, F. *Tetrahedron Lett.* **2000**, *41*, 4403–4407.
19. Demchenko, A. V. *Curr. Org. Chem.* **2003**, *7*, 35–79.
20. Chao, C. S.; Li, C. W.; Chen, M. C.; Chang, S. Sheng; Mong, K.-K. T. *Chem. Eur. J.* **2009**, *15*, 10972–10982.