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ARTICLE TYPE

Synthesis of ganglioside Hp-s1

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A simple protocol for the synthesis of a ganglioside Hp-s1 (**1**) starting from commercial available phytosphingosine, sialic acid, and D-glucose is described. This synthesis involved glycosylation reaction of phytosphingosine derived acceptor with highly active benzyl protected glucosyl donor, second glycosylation of glucosyl acceptor with sialyl donor followed by Staudinger reaction, amidation, and global deprotection as key steps.

Introduction

Ganglioside is a well-known glycosphingolipid where one or more sialic acids linked on the sugar chain. Being part of tissues, body fluids and nervous system, ganglioside plays important role in biological system[1] and also behaves as scavengers in body to repair and regenerate the neurons to suppress neuronal diseases.[2] Gangliosides have been found as inhibitory agents towards Alzheimer's disease, Parkinson's diseases, Guillain-Barré syndrome, Huntington's disease and studied well in stem cell biology.[3] In biological system, synthesis of such molecules take place primarily in the endoplasmic reticulum and the sequential addition of carbohydrate moieties on the existing acceptor lipid take place in Golgi apparatus.[4] Recent studies revealed that on the cell surface, gangliosides are involved in the cell-cell recognition[5], cell differentiation[6], and signal transduction.[7] Marine invertebrates are the major source for gangliosides extraction and these extracts had shown neuritogenic activity toward the rat pheochromocytoma cell line PC-12 in the presence of nerve growth factor.

Recently, it is observed that ganglioside Hp-s1 (**1**) shows superior neuritogenic activity (34%) then that of mammalian ganglioside GM1 (25.4%).[8] At the same time, GM1 have more complex structure and there are synthetic difficulties for the preparation of this molecule.[9] Due to multidimensional importance of ganglioside, recently the synthesis of these molecules have attracted much attention, though few gangliosides i.e. M5, HLG-2, and LLG-3 have been synthesized by various groups.[10] Recently, Ye and co-workers have also reported stereoselective synthesis of trisaccharide moiety of ganglioside HLG-2.[11]

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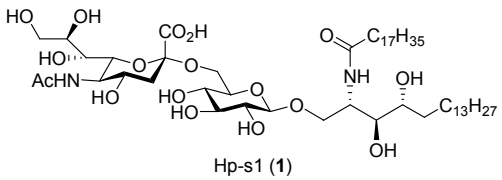
Ganglioside Hp-s1 (**1**) (Fig. 1), isolated from the ovary of the sea urchin *Diadema setosum* or the sperm of the sea urchin *Hemicentrotus pulcherrimus*.[12] The structure of ganglioside Hp-s1 possesses Neu5Ac α2→6Glcβ1→1Cer. The synthesis and bioassay of ganglioside Hp-s1 (**1**) has received much less attention from the scientific community. Recently, Tsai *et al* synthesized analogue of ganglioside Hp-s1, which has one carbon less than Hp-s1 in the carbon chain of phytosphingosine segment and found that this analogue of ganglioside Hp-s1 exhibits neuritogenic activity toward the human neuroblastoma cell line SH-SY5Y in absence of nerve growth factor (NGF).[13] Due to less availability of ganglioside from natural sources, in continuation of our long ongoing research program on carbohydrate chemistry,[14] we have selected ganglioside Hp-s1 as our target molecule and report the first total synthesis of ganglioside Hp-s1 (**1**) from commercially available sialic acid, D-glucose, phytosphingosine, and D-lyxose.



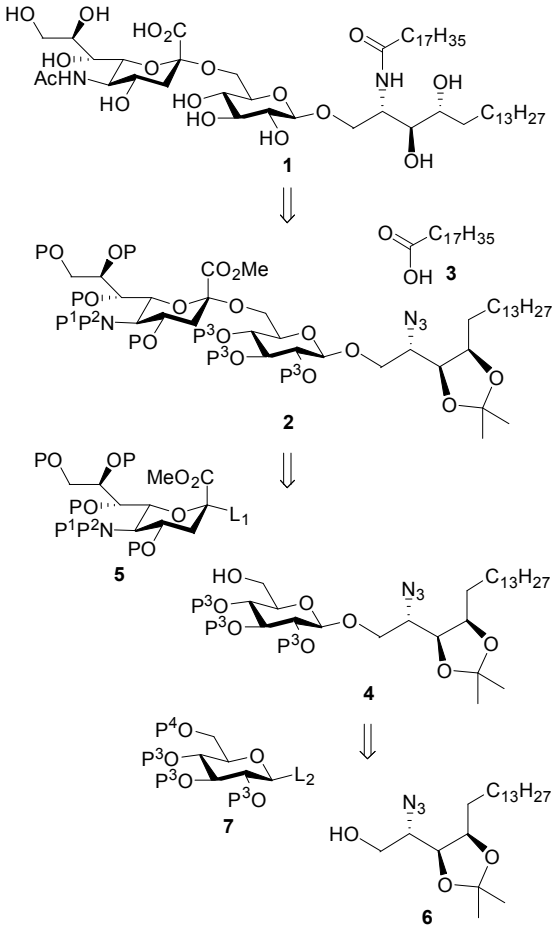
Hp-s1 (**1**)

Fig. 1 The structure of ganglioside Hp-s1 (1).

Results and Discussion

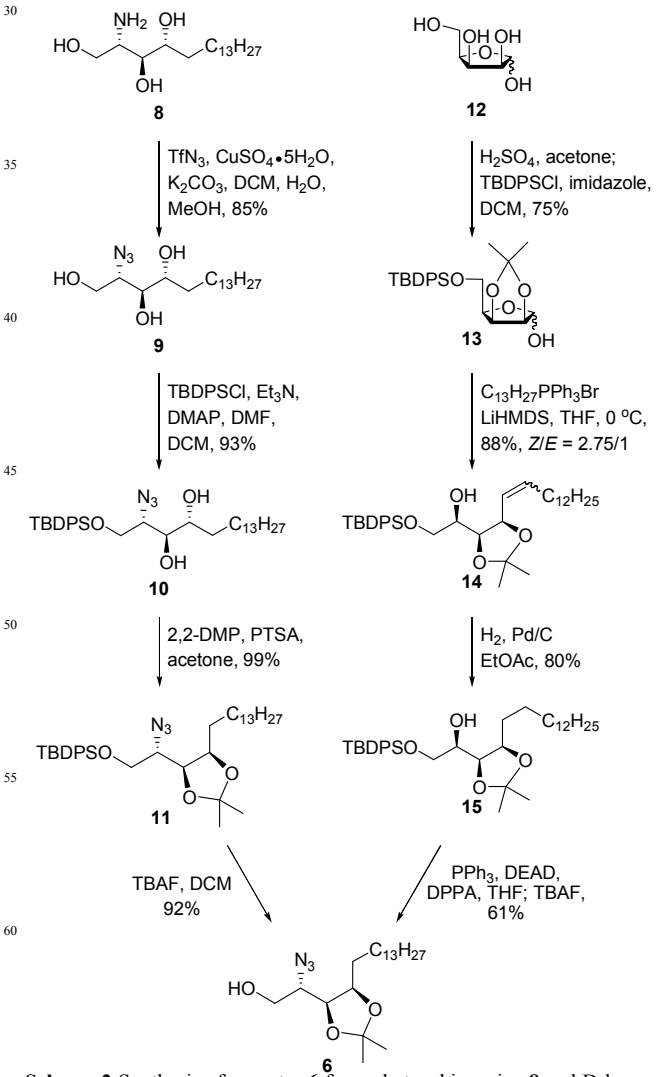
The structure of ganglioside composite with two major segments *i.e.* glycan part and ceramide part. The literature survey reveals that there are several approaches are accessible to connect these two segments. Mostly, two major approach have been used for this purpose i.e. i) pre-incorporation of phytosphingosine at the reducing end of the glycan chain followed by assembly of the ceramide structure (non-reducing end to reducing end),[13] ii)

glycosylation of ceramide part with the full-length glycan part which yields a ganglioside framework (reducing end to non-reducing end) directly.[15] It has been observed that, reducing end to non-reducing end approach could offer high efficiency for small ganglioside syntheses. Accordingly, our retrosynthetic strategy for the synthesis of **1** can follow the sequences as shown in Scheme 1. The target compound **1** can be obtained from compound **2** through Staudinger reaction, followed by amide bond formation with **3** and global deprotection. Compound **2** can be prepared via the glycosylation of sialyl donor **5** and glycosyl acceptor **4**. The glycosylation between glucosyl donor **7** and phytosphingosine derived acceptor **6** can provide glycosyl acceptor **4**.



Scheme 1 Retrosynthesis of ganglioside Hp-s1 (1).

As our retrosynthetic strategy shows, initially our aim was to synthesize the phytosphingosine derived acceptor **6** and glucosyl donor **7**. In this regard, first we have turned our attention towards the synthesis of acceptor **6** (Scheme 2). We envisaged that the acceptor **6** can be prepared from commercially available phytosphingosine **8** and D-lyxose **12**. Since, both starting materials contain all the requisite chiral centers which are necessitated for the acceptor **6**, therefore, we have selected these commercially available chemicals for the synthesis of **6**. Accordingly, phytosphingosine **8**[14a-b,16] was treated with triflyl azide (TfN_3) in the presence K_2CO_3 and catalytic amount of copper sulfate pentahydrate which produced 2-azido



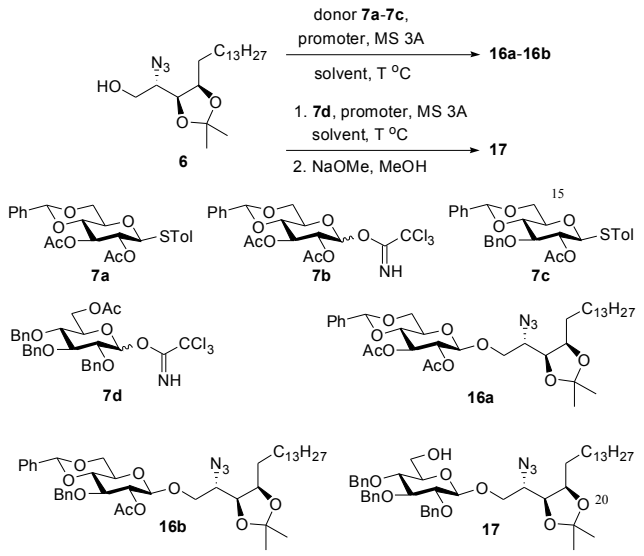
Scheme 2 Synthesis of acceptor **6** from phytosphingosine **8** and D-lyxose **12**.

phytosphingosine **9** in 85% yield.[17] The protection of primary alcohol functionality of **9** was carried out using *t*-butylchlorodiphenylsilane (TBDPSCl), triethylamine, and 4-di methylaminopyridine (DMAP) to furnish diol **10** in 93% yield.[18] The secondary alcohol group of diol **10** was protected by using 2,2-dimethoxypropane (2,2-DMP) and catalytic amount of *p*-toluenesulfonic acid (PTSA) followed by TBAF cleavage of silane group which provided the phytosphingosine derived acceptor **6** in excellent yield for two steps (Path A, Scheme 2).[17]

Since, phytosphingosine **8** is an expensive compound, we have also found an alternative approach for the synthesis of **6** where we start this synthesis from cheaper compound D-lyxose **12**. In this alternative strategy (Path B, Scheme 2) the acetonide protection of C_2-C_3 diol of D-lyxose **12**, followed by TBDPS protection of primary alcohol produced hemiacetal **13** in 75% yield in one-pot operation. Hemiacetal **13** was then treated with Wittig salt ($C_{13}H_{27}PPh_3Br$) in the presence of more hindered base LiHMDS at 0 °C, provided olefin **14** in good yield.[14c,19] Compound **15** was obtained by hydrogenation of olefin **14** using Pd/C and hydrogen gas. C-2 epimerization of mono-ol **15** was

achieved under Mitsunobu conditions and the TBAF removal of silane group provided phytosphingosine derived acceptor **6** in good yield in one-pot synthesis.[16b] It is worth mentioning here that the Wittig salt ($C_{13}H_{27}PPh_3Br$) used in this alternative path is little expensive.

Table 1 Optimization condition for glycosylation of acceptor **6** with various donors **7a**-**7d**.



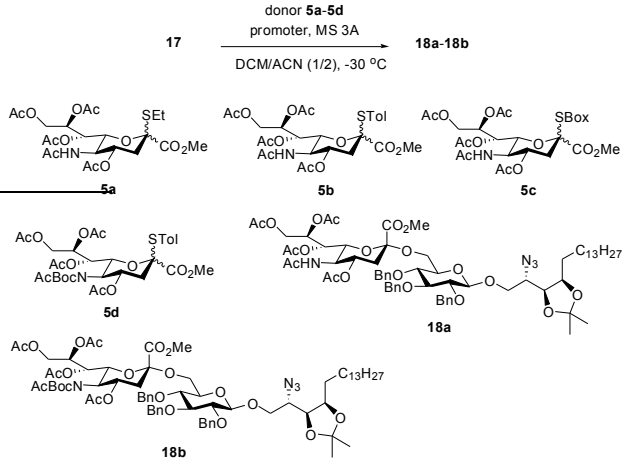
entry	donor	promoter	solvent	T (°C)	product (yield, β/α)
1	**7a**[a]	NIS/TfOH	DCM	-20	**16a** (38%, β only)
2	**7b**[a]	TMSOTf	DCM	-20	**16a** (36%, β only)
3	**7c**[a]	NIS/TfOH	DCM	-20	**16b** (46%, β only)
4	**7d**[b]	TMSOTf	DCM/ACN (1/2)	-30	**17** (48%, 2.0/1)
5	**7d**[b]	TMSOTf	DCM/ACN (1/2)	-30 °C to rt	**17** (54%, 2.0/1)
6	**7d**[c]	TMSOTf	DCM/ACN (1/2)	rt	**17** (60%, 1.0/1)
7	**7d**[c]	TMSOTf	DCM/ACN (1/2)	0 °C to rt	**17** (66%, 1.5/1)
8	**7d**[c]	TMSOTf	DCM/ACN (1/2)	-30 °C to rt	**17** (82%, 3.2/1)

[a]1.3 equiv, [b]2.0 equiv, [c]2.5 equiv.

The glucosyl acceptors **7a**-**7d** were synthesized following the literature procedures.[20] Once we have the segment **6** and **7** in our hand, now our target was to couple them. For this, in order to achieve high yield and selectivity, we have optimized the best condition of glycosylation[21] of acceptor **6** with various donors **7a**-**7d**. At first, the application of anchimeric assistance in these reactions of glucosyl donors **7a**-**7c** with acceptor **6** has been optimized. In the beginning, thioglucoside donor **7a**[20a] was reacted with acceptor **6** in the presence of NIS/TfOH at DCM at -20 °C furnished the β-stereoisomer **16a** in 38% yield (entry 1, table 1). To enhance to chemical yield of **16a,** imidate donor **7b**[20b, 22] was treated with acceptor **6** in the presence of TMSOTf which provided only β stereoisomer in 36% yield (entry 2, table 1). Next, similar reaction of thioglucoside **7c**[20c] having benzyl group at C3 position was carried out with acceptor **6,** produced compound **16b** in 46% yield (entry 3, table 1). In the above entries the low chemical yield of **16a** may be due to the less reactivity of donor's **7a**-**7c**. Anchimeric assistance could not provide higher yield of the compounds **16a** and **16b**. Since, the glycosylation of disarmed **7a-c** than **7d** therefore less reactive donors reacted with acceptor **6** provided **16a** and **16b** in lower yield.

To increase the yield and selectivity, we turned our attention to study the solvent effect using **7d**[20d] as our glucosyl donor. In this regard, imidate **7d** was allowed to react with acceptor **6** in the presence of TMSOTf provided corresponding glycosylated products (α-isomer and β-isomer) which contains acetyl group at C-6 position of glucosyl donor.[23] However, the glycosylated products (α-isomer and β-isomer) and acceptor **6** have the similar polarity on TLC, which caused difficulty in separation via column chromatography. Fortunately, we could separate the product **17** (β-isomer), α-isomer and acceptor **6** after deacetylation through column chromatography. Interestingly, we obtained a compound **17** as a mixture of stereoisomers (β:α = 2:1) at -30 °C in 48% yield (entry 4, table 1). Next, we tried to improve the yield and selectivity over β:α mixture. Variation in the temperature from -30 °C to room temperature in the similar reaction improved the yield of compound **17** to 54% with no change in stereoselectivity (entry 5, table 1). Other entries (entry 6 and 7, table 1) with changes in the temperature does not provided expected yield of compound **17** with β:α ratio. Finally, glycosylation reaction of imidate donor **7d** (2.5 equiv.) and acceptor **6** (1 equiv.) were carried out in the presence of TMSOTf and 3 Å molecular sieves in DCM/ACN solvent at -30 °C to room temperature (entry 8, table 1), gave corresponding compound **17** in 82% overall yield for two steps.

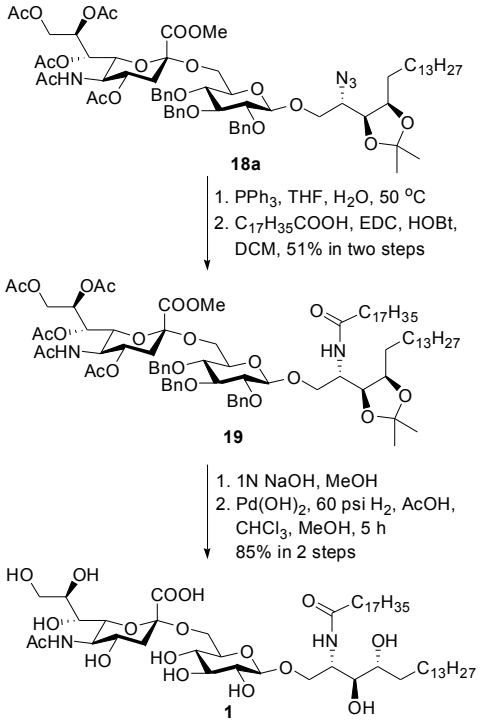
Table 2 Optimization condition for glycosylation of acceptor **17** with various donors **5a**-**5d**.



entry	donor	promoter	Product (yield, αβ/ββ)
1	**5a**	NIS/TfOH	**18a** (86%, 2.7/1)
2	**5b**	NIS/TfOH	**18a** (84%, 3.9/1)
3	**5c**	AgOTf	**18a** (29%, 2.6/1)
4	**5d**	NIS/TfOH	**18b** (54%, 1.6/1)
5	**5d**	NIS/TMSOTf	**18b** (77%, 2.0/1)

Next we have synthesized various sialyl donors (**5a**-**5d**) according to the procedures available in the literature.[24-27] Then, we performed the glycosylation between various sialyl donors (**5a**-**5d**) and glycosyl acceptor **17** using different promoters as shown in Table 2. Accordingly, first, sialyl donor **5a**[24] was treated with acceptor **17** in the presence of *N*-iodosuccinimide

(NIS) and trifluoromethanesulfonic acid (TfOH) using DCM and ACN solvent system at -30 °C, provided the compound **18a** in 86% yield (αβ/ββ = 2.7/1, entry 1, table 2). Similarly, sialyl donor **5b**[25] on treatment with acceptor **17** in the presence of NIS and TfOH under same reaction conditions furnished compound **18a** in 84% yield (αβ/ββ = 3.9/1, entry 2, table 2). When AgOTf was used for glycosylation reaction between sialyl donor **5c**[26] with acceptor **17** in similar condition (entry 3, table 2), we obtained compound **18a** in comparatively less yield (29%) with bad selectivity. Previously, sialyl donor **5d** was found to be a suitable donar for glycosylation reaction resulting high selectivity with good yields.[27] However, when we treated sialyl donor **5d**[27] with acceptor **17** under the influence of NIS and TfOH, provided the corresponding compound **18b** in 54% yield (αβ/ββ = 1.6/1, entry 4, table 2). Change of promoter from NIS/TfOH to NIS/TMSOTf for glycosylation reaction between sialyl donor **5d** with acceptor **17**, afforded **18b** in 77% yield (αβ/ββ = 2.0/1, entry 5, table 2).



Scheme 3 Finalizing synthesis of target molecule 1.

Now, we have subjected the compound **18a** for sequential Staudinger reaction and amide bond formation as shown in Scheme 3, which provided **19** in 51% overall yield for two steps. The deprotection of acetyl, benzyl, and acetonide groups of compound **19** provided the target molecule ganglioside Hp-s1 (**1**) in 85% yield.

Conclusions

We have developed first synthesis of ganglioside Hp-s1 (**1**) in overall yield of 21.5% and 9.6% starting from phytosphingosine or D-lyxose respectively in ten steps. In the assembly of the glycan part, Neu5Acα2→6Glcβ1→1Cer, the three chiral carbons of the ceramide part were each efficiently established in a stereoselective manner from commercially available phytosphingosine and D-lyxose. The final connection of the glycan and ceramide parts was accomplished with relatively high yield. This short and efficient route described here for the synthesis of ganglioside Hp-s1 is expected to provide access to other structurally related glycolipids for exploring their neuritogenic activities and other biological properties.

Experimental Section

General Information

Some reactions were conducted in flame-dried glassware, under nitrogen atmosphere. Dichloromethane, tetrahydrofuran, *N,N*-dimethylformamide were purified and dried from a safe purification system containing activated Al_2O_3. All reagents obtained from commercial sources were used without purification, unless otherwise mentioned. Phytosphingosine was purchased from Tokyo Chemical Industry Co. Ltd, Japan and D-lyxose was purchased from Carbosynth China Ltd, China. Flash column chromatography was carried out on Silica Gel 60 (230-400 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F254 (0.25mm, E. Merck); detection was executed by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$ (0.5 g), $(NH_4)_6Mo_7O_{24}$ (24 g) and H_2SO_4 (28 mL) in water (500 mL) and subsequent heating on a hot plate. Optical rotations were measured at 589 nm (Na) at ~ 27 °C, ^{1}H, ^{13}C NMR, DEPT, ^{1}H-^{1}HCOSY, ^{1}H-^{13}C COSY, and NOESY spectra were recorded with 400 and 600 MHz instruments. Chemical shifts are in ppm from Me_4Si generated from the $CDCl_3$ lock signal at δ 7.26. IR spectra were taken with a FT-IR spectrometer using KBr plates. Mass spectra were analyzed on Orbitrap instrument with an ESI source.

***(2S,3S,4R)*-2-Azido-octadecan-1,3,4-triol (9).** A mixture solution of NaN_3 (2.04 g, 31.50 mmol), DCM (5 mL) and water (5 mL) was cooled at 0 °C and Tf_2O (1.10 mL, 6.30 mmol) was added dropwise over 20 min. After the reaction mixture was stirred for 3 h, the mixture was extracted with DCM (2 × 8 mL). The combined organic layer was washed with saturated $NaHCO_3$ (16 mL) formed a combined organic layer which contains TfN_3. To a suspension of phytosphingosine (1.00 g, 3.15 mmol), K_2CO_3 (2.14 g, 15.75 mmol) and $CuSO_4$•$5H_2O$ (16 mg, 0.01 mmol) in a mixture of methanol (4 mL) and water (3 mL) were added the combined organic layer which contained TfN_3. The reaction mixture was stirred for 12 h. After reaction was completed, the resulting solution was concentrated to remove the organic solvent under vacuum. The mixture was extracted with EtOAc (2 × 24 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized with EtOH to give the triol **9** (917 mg) in 85% yield as white solid. R_f 0.50 (EtOAc/Hex = 1/1); $[\alpha]^{26}_D$ +4.5 (*c* 0.85, MeOH); mp 97 °C; IR (KBr) *v* 3343, 2918, 2848, 2118, 1463 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 3.92 (dd, *J* = 10.8, 3.0 Hz, 1H, H-1a), 3.75 (dd, *J* = 10.8, 7.8 Hz, 1H, H-1b), 3.59 (ddd, *J* = 7.8, 4.2, 3.0 Hz, 1H, H-2), 3.54-3.50 (m, 2H, H-3, H-4), 1.70-1.66 (m, 1H, H-5a), 1.57-1.54 (m, 1H, H-5b), 1.41-1.25 (m, 24H, CH_2), 0.89 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (150

MHz, CD_3OD) δ 76.0 (CH), 72.8 (CH), 66.7 (CH), 62.5 (CH_2), 33.9 (CH_2), 33.1 (CH_2), 30.8 (CH_2 × 8), 30.5 (CH_2), 26.7 (CH_2), 23.7 (CH_2), 14.5 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{18}H_{37}O_3N_3Na$ 366.2727, found 366.2723.

***(2S,3S,4R)*-2-Azido-1-*O*-*tert*-butyldiphenylsilyl-octadecan-1,3,4-triol (10).** To a solution of 2-azido phytosphingosine **9** (100 mg, 0.29 mmol) in DCM (1.4 mL) and DMF (0.3 mL) were added Et_3N (0.10 mL, 0.73 mmol), DMAP (1 mg, 0.01 mmol) and TBDPSCl (93 μL, 0.35 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h, and then diluted with EtOAc (10 mL). The organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the compound **10** (155.7 mg) in 93% yield as colorless oil. R_f 0.53 (EtOAc/Hex = 1/4); $[\alpha]^{26}_D$ +16.4 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v* 3425, 2926, 2855, 2099, 1466, 1428, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 4H, ArH), 7.47-7.38 (m, 6H, ArH), 4.03 (dd, *J* = 10.8, 4.2 Hz, 1H, H-1a), 3.92 (dd, *J* = 10.8, 6.0 Hz, 1H, H-1b), 3.70-3.66 (m, 2H, H-3, H-4), 3.57 (ddd, *J* = 6.0, 4.2, 4.2 Hz, 1H, H-2), 1.57 (bs, 2H, OH), 1.56-1.40 (m, 2H, H-5a, H-5b), 1.26 (bs, 23H, CH_2), 1.08 (s, 9H, CH_3), 0.88 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6 (CH × 4), 132.5 (C), 132.4 (C), 130.0 (CH × 2), 127.9 (CH × 3), 74.1 (CH), 72.3 (CH), 64.1 (CH_2), 63.4 (CH), 31.9 (CH_2), 31.8 (CH_2), 29.7 (CH_2 × 3), 29.6 (CH_2 × 3), 29.3 (CH_2 × 3), 26.7 (CH_3 × 3), 25.6 (CH_2), 22.7 (CH_2), 19.1 (C), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{34}H_{55}O_3N_3NaSi$ 604.3905, found 604.3912.

***(2S,3S,4R)*-2-Azido-1-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-octadecan-1,3,4-triol (11).** To a solution of the diol **10** (155 mg, 0.27 mmol) in acetone (8 mL) were added 2,2-dimethoxypropane (338 μL, 2.70 mmol) and PTSA (6 mg, 0.03 mmol). The reaction mixture was stirred for 3 h at room temperature and neutralized with Et_3N at 0 °C. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the product (166 mg) in 99% yield as colorless oil. R_f 0.61 (EtOAc/Hex = 1/20); $[\alpha]^{26}_D$ +11.9 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v* 2957, 2927, 2855, 2099, 1465, 1428, 1113 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.74-7.70 (m, 4H, ArH), 7.45-7.38 (m, 6H, ArH), 4.12 (ddd, *J* = 9.6, 4.8, 2.4 Hz, 1H, H-4), 4.03 (dd, *J* = 10.8, 2.4 Hz, 1H, H-1a), 3.94 (dd, *J* = 10.2, 6.0 Hz, 1H, H-3), 3.84 (dd, *J* = 10.8, 6.6 Hz, 1H, H-1b), 3.42 (ddd, *J* = 9.6, 6.6, 2.4 Hz, 1H, H-2), 1.62-1.47 (m, 2H, CH_2), 1.38-1.26 (m, 30H, CH_2, CH_3), 1.08 (s, 9H, CH_3), 0.88 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.7 (CH × 4), 133.0 (C), 132.9 (C), 129.8 (CH), 129.7 (CH), 127.7 (CH × 4), 108.1 (C), 77.8 (CH), 75.2 (CH), 65.3 (CH_2), 61.7 (CH), 31.9 (CH_2), 29.7 (CH_2 × 6), 29.6 (CH_2 × 2), 29.4 (CH_2 × 2), 28.1 (CH_3), 26.7 (CH_3 × 3), 26.4 (CH_2), 25.7 (CH_3), 22.7 (CH_2), 19.1 (C), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{37}H_{59}O_3N_3NaSi$ 644.4218, found 644.4213.

5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-D-lyxofuranose (13). To a solution of D-lyxose **12** (200 mg, 1.33 mmol) in acetone (2 mL) were added H_2SO_4 (7.0 μL, 0.13 mmol) at 0 °C. The reaction mixture was warmed to room temperature and kept stirring until a clear solution was achieved. Then imidazole (362 mg) dissolved in dichloromethane (2 mL) and *tert*-butylchlorodiphenylsilane (388 μL) was added to the clear solution at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. After completion, the reaction mixture was concentrated under reduced pressure to afford a residue. The residue was diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a residue. The residue was purified by column chromatography on silica gel to give the product **13** (426 mg, 75%) as colorless oil. R_f 0.58 (EtOAc/Hex = 1/3); $[\alpha]^{26}_D$ +2.83 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v* 3473, 3072, 3050, 2937, 2890, 2859, 1468, 1428, 1377, 1210, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73-7.67 (m, 4H, ArH), 7.44-7.35 (m, 6H, ArH), 5.37 (d, *J* = 1.6 Hz, 1H, H-1), 4.75 (dd, *J* = 5.6, 3.2 Hz, 1H, H-3), 4.59 (d, *J* = 6.4 Hz, 1H, H-2), 4.32 (ddd, *J* = 10.0, 6.4, 4.0 Hz, 1H, H-4), 3.99 (dd, *J* = 10.8, 5.6 Hz, 1H, H-5a), 3.90 (dd, *J* = 10.4, 6.4 Hz, 1H, H-5b), 2.31 (bs, 1H, OH), 1.35 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.06 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.64 (CH × 2), 135.58 (CH × 2), 133.4 (C × 2), 129.58 (CH), 129.57 (CH), 127.6 (CH × 2), 127.5 (CH × 2), 112.3 (C), 101.2 (CH), 85.4 (CH), 80.8 (CH), 79.7 (CH), 62.0 (CH_2), 26.7 (CH_3 × 3), 25.9 (CH_3), 25.0 (CH_3), 19.2 (C); HRMS (ESI, M+Na^+) calcd for $C_{24}H_{32}O_5NaSi$ 451.1911, found 451.1907.

***(2R,3S,4R)*-1-*tert*-Butyldiphenylsilyl-3,4-*O*-isopropylideneoctadec-5-ene-1,2,3,4-tetraol (14).** To a solution of hemiacetal **13** (275 mg, 0.64 mmol) and tridecanyltriphenylphosphonium bromide (1.35 g, 2.57 mmol) in anhydrous THF (2.8 mL) was cooled down to 0 °C under nitrogen. A 1 M solution of lithium hexamethyldisilylamide in THF (2.6 mL, 2.57 mmol) was slowly added to the mixture and the reaction solution was kept stirring for overnight at 0 °C. After completion of the reaction, water (10 mL) was added to quench the reaction and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a residue. The residue was purified by column chromatography to afford the olefin **14** (336 mg, 88%, Z/E=2.75/1). R_f 0.49 (EtOAc/Hex = 1/9); $[\alpha]^{27}_D$ -5.7 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v* 3523, 2927, 2855, 1465, 1428, 1374, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H, ArH), 7.45-7.34 (m, 6H, ArH), 5.70-5.57 (m, 2H, CH=CH), 4.50 (dd, *J* = 8.0, 6.8 Hz, 1H, H-4), 4.26 (dd, *J* = 6.8, 3.6 Hz, 1H, H-3), 3.71-3.61 (m, 3H, H-1a, H-1b, H-2), 2.44 (d, *J* = 6.0 Hz, 1H, 2-OH), 2.05-1.95 (m, 2H, CH_2), 1.50 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.34-1.22 (m, 20H, CH_2), 1.06 (s, 9H, CH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (CH), 135.6 (CH × 2), 135.5 (CH × 2), 133.2 (C), 133.1 (C), 129.8 (CH), 129.7 (CH), 127.72 (CH × 2), 127.68 (CH × 2), 125.4 (CH), 108.2 (C), 78.9 (CH), 77.0 (CH), 70.0 (CH), 64.7 (CH_2), 32.2 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 2), 29.62 (CH_2), 29.58 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 27.2 (CH_3), 26.8 (CH_3 × 3), 24.9 (CH_3), 22.7 (CH_2), 19.2 (C), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{37}H_{58}O_4NaSi$ 617.3997, found 617.4010.

***(2R,3S,4R)*-1-*O*-*tert*-Butyldiphenylsilyl-3,4-*O*-isopropylidene-**

octadecan-1,2,3,4-tetraol (15). A mixture of olefin **14** (310 mg, 0.52 mmol), 10% palladium on charcoal (62 mg) and ethyl acetate (3.1 mL) was stirred under hydrogen gas at room temperature for 8 h. The Pd/C was removed through celite. The filtrate was concentrated to give the residue. The residue was purified by column chromatography on silica gel to afford compound **15** (248 mg, 80%) as colorless oil. R_f 0.45 (EtOAc/Hex = 1/10); $[\alpha]^{27}_D$ -11.47 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v* 3687, 2927, 2855, 1465, 1428, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H, ArH), 7.45-7.36 (m, 6H, ArH), 4.18 (dd, *J* = 6.8, 2.8 Hz, 1H, H-3), 4.12 (ddd, *J* = 9.6, 6.4, 3.6 Hz, 1H, H-4), 3.74-3.63 (m, 3H, H-1a, H-1b, H-2), 2.37 (d, *J* = 5.6 Hz, 1H, OH), 1.76-1.68 (m, 1H, CH_2), 1.56-1.43 (m, 5H, CH_2, CH_3), 1.37 (s, 3H, CH_3), 1.32-1.23 (m, 23H, CH_2), 1.06 (s, 9H, CH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (CH × 2), 135.5 (CH × 2), 133.2 (C × 2), 129.8 (CH), 129.7 (CH), 127.72 (CH × 2), 127.69 (CH × 2), 107.7 (C), 77.4 (CH), 76.4 (CH), 69.8 (CH), 65.1 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2 × 3), 29.64 (CH_2 × 2), 29.61 (CH_2), 29.59 (CH_2), 29.56 (CH_2), 29.4 (CH_2), 27.3 (CH_3), 26.8 (CH_3 × 3), 26.7 (CH_2), 25.1 (CH_3), 22.7 (CH_2), 19.2 (C), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{37}H_{60}O_4NaSi$ 619.4153, found 619.4131.

***(2S,3S,4R)*-2-Azido-3,4-*O*-isopropylidene-octadecan-1,3,4-triol (6).** *Method A:* To a solution of the azide **11** (166 mg, 0.27 mmol) in THF (12 mL) was added TBAF (540 μL, 0.54 mmol, 1 M) at 30 °C for 1 h. The reaction mixture was diluted with water and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the alcohol **6** (94 mg) in 92% yield as white solid. *Method B:* To a stirring solution of alcohol **15** (185 mg, 0.31 mmol) and triphenylphosphine (244 mg, 0.93 mmol) in anhydrous tetrahydrofuran (2 mL) at 0 °C were slowly added diisopropyl azodicarboxylate (DIAD, 183 μL, 0.93 mmol) and diphenyl phosphonyl azide (DPPA, 214 μL, 0.93 mmol). After stirring for 3 h at room temperature, the solvent was removed in vacuo. The residue was dissolved in tetrahydrofuran (2 mL). The mixture solution was treated with tetra-n-butylammonium fluoride (1 M in tetrahydrofuran, 2.5 mL, 2.48 mmol, TBAF) and stirred for overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford **6** (73 mg, 61%) as a white solid. R_f 0.55 (EtOAc/Hex = 1/4); $[\alpha]^{25}_D$ +23.70 (*c* 1.0, CH_2Cl_2); mp 33 °C; IR (CH_2Cl_2) *v* 3425, 2990, 2925, 2854, 2098, 1461, 1372, 1247, 1219, 1170, 1066 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.18 (ddd, *J* = 9.6, 6.0, 4.2 Hz, 1H, H-4), 4.01-3.96 (m, 2H, H-1a, H-3), 3.87 (dd, *J* = 11.4, 5.4 Hz, 1H, H-1b), 3.47 (ddd, *J* = 9.6, 5.4, 4.2 Hz, 1H, H-2), 1.64-1.53 (m, 3H, H-5a, H-5b, CH_2), 1.43 (s, 3H, CH_3), 1.40-1.26 (m, 27H, CH_2, CH_3), 0.88 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 108.4 (C), 77.1 (CH), 76.7 (CH), 63.9 (CH_2), 61.1 (CH), 31.9 (CH_2), 29.7 (CH_2 × 3), 29.6 (CH_2 × 4), 29.5 (CH_2 ×1), 29.4 (CH_2 × 2), 28.0 (CH_3), 26.5 (CH_2), 25.5 (CH_3), 22.7 (CH_2), 14.1 (CH_3); HRMS (APCI, M+H^+) calcd for $C_{21}H_{42}N_3O_3$ 356.3159, found 356.3171.

***(2S,3S,4R)*-2-Azido-1-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-3,4-*O*-isopropylidene-octadecan-1,3,4-triol (16a).** *Method A:* A solution of thioglucoside **7a** (115 mg, 0.25 mmol) and primary alcohol **6** (73 mg, 0.19 mmol) in DCM (2 mL) was stirred for 1 h at room temperature with activated 4 Å molecular sieves (188 mg). After cooling to -20 °C, NIS (110 mg, 0.49 mmol) and TfOH (7.0 μL, 0.08 mmol) were added and reaction mixture was stirred for 2 h. When the reaction was completed, molecular sieves was removed by filtration through celite. The filtrate was extracted with aqueous $Na_2S_2O_3$ (15 mL) and brine (15 mL), and the organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. It was purified by column chromatography on silica gel to give the desired product **16a** (52 mg, 38%) as white solid. *Method B:* A solution of imidate **7b** (70 mg, 0.14 mmol) and primary alcohol **6** (42 mg, 0.11 mmol) in DCM (1 mL) was stirred for 30 min at room temperature with activated 3 Å molecular sieves (70 mg). After cooling to -20 °C, TMSOTf (2.0 μL, 0.01 mmol) was added. When the reaction was completed, molecular sieves was removed by filtration through celite. The filtrate was extracted with DCM (3 × 15 mL), and the organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. It was purified by column chromatography on silica gel to give the compound **16a** (27 mg, 36%) as white solid. R_f 0.30 (EtOAc/Hex = 1/6); $[\alpha]^{22}_D$ -33.4 (c 1.0, CH_2Cl_2); mp 81 °C; IR (CH_2Cl_2) *v* 2924, 2854, 2100, 1755, 1639, 1458, 1317, 1238, 1218, 1176, 1099, 1064, 1032 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H, Ar-H), 7.37-7.35 (m, 3H, Ar-H), 5.51 (s, 1H, CHPh), 5.32 (t, *J* = 9.6 Hz, 1H, H-3'), 5.07 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2'), 4.69 (d, *J* = 7.8 Hz, 1H, H-1'), 4.38 (dd, *J* = 10.8, 5.4 Hz, 1H, H-6a'), 4.14 (ddd, *J* = 9.6, 5.4, 5.4 Hz, 1H, H-4), 4.06 (dd, *J* = 10.8, 7.2 Hz, 1H, H-1a), 3.94 (dd, *J* = 10.8, 3.0 Hz, 1H, H-1b), 3.87-3.81 (m, 2H, H-3, H-6b'), 3.76 (t, *J* = 9.6 Hz, 1H, H-4'), 3.56 (ddd, *J* = 9.6, 9.6, 5.4 Hz, 1H, H-5'), 3.01 (ddd, *J* = 10.2, 7.2, 3.0 Hz, 1H, H-2), 2.07 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.59-1.52 (m, 2H, H-5a, H-5b), 1.41 (s, 3H, CH_3), 1.37-1.26 (m, 27H, CH_3, CH_2), 0.88 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2 (C), 169.5 (C), 136.7 (C), 129.1 (CH), 128.2 (CH × 2), 126.1 (CH × 2), 108.3 (C), 101.5 (CH), 100.9 (CH), 78.1 (CH), 77.7 (CH), 75.3 (CH), 72.2 (CH), 71.8 (CH), 70.3 (CH_2), 68.5 (CH_2), 66.4 (CH), 59.4 (CH), 31.9 (CH_2), 29.7 (CH_2 × 3), 29.6 (CH_2 × 4), 29.5 (CH_2), 29.3 (CH_2 × 2), 28.2 (CH_3), 26.4 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 20.8 (CH_3 × 2), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{38}H_{59}O_{10}N_3Na$ 740.4093, found 740.4112.

***(2S,3S,4R)*-2-Azido-1-*O*-(2-*O*-acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-3,4-*O*-isopropylidene-octadec-1,3,4-triol (16b).** A solution of thioglucoside **7c** (166 mg, 0.34 mmol) and primary alcohol **6** (100 mg, 0.26 mmol) in DCM (3 mL) was stirred for 1 h at room temperature with activated 4 Å molecular sieves (266 mg). After cooling to -20 °C, NIS (153 mg, 0.68 mmol) and TfOH (9.0 μL, 0.10 mmol) were added and reaction mixture was stirred for 2 h. When the reaction was completed, molecular sieves was removed by filtration through celite. The filtrate was extracted with aqueous $Na_2S_2O_3$ (15 mL) and brine (15 mL), and the organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel to give the desired product **16b** (92 mg, 46%) as white solid. R_f 0.35 (EtOAc/Hex = 1/8); $[\alpha]^{22}_D$ -11.2 (*c* 1.0, CH_2Cl_2); mp 65 °C; IR (CH_2Cl_2) *v* 2924,

2853, 2099, 1753, 1456, 1428, 1312, 1174, 1098, 1067, 1030 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.51-7.50 (m, 2H, Ar-H), 7.42-7.38 (m, 3H, Ar-H), 7.33-7.31 (m, 2H, Ar-H), 7.23-7.27 (m, 3H, Ar-H), 5.59 (s, 3H, CHPh), 5.09 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2'), 4.88 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.68 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.57 (d, *J* = 7.8 Hz, 1H, H-1'), 4.38 (dd, *J* = 10.2, 4.8 Hz, 1H, H-6a'), 4.13 (ddd, *J* = 9.6, 5.4, 5.4 Hz, 1H, H-4), 4.03 (dd, *J* = 10.8, 7.2 Hz, 1H, H-1a), 3.91 (dd, *J* = 10.8, 2.4 Hz, 1H, H-1b), 3.87-3.80 (m, 3H, H-3, H-4', H-6b'), 3.74 (t, *J* = 9.0 Hz, 1H, H-3'), 3.51-3.44 (m, 2H, H-2, H-5'), 2.01 (s, 3H, CH_3), 1.60-1.49 (m, 2H, H-5a, H-5b), 1.40 (s, 3H, CH_3), 1.37-1.26 (m, 27H, CH_3, CH_2), 0.88 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3 (C), 138.1 (C), 137.1 (C), 129.0 (CH), 128.3 (CH × 4), 127.8 (CH × 2), 127.7 (CH), 126.0 (CH × 2), 108.2 (C), 101.2 (CH), 101.1 (CH), 81.4 (CH), 78.4 (CH), 77.7 (CH), 75.3 (CH), 74.0 (CH_2), 72.4 (CH), 69.8 (CH_2), 68.6 (CH_2), 66.3 (CH), 59.5 (CH), 31.9 (CH_2), 29.7 (CH_2 × 3), 29.6 (CH_2 × 4), 29.3 (CH_2 × 3), 28.2 (CH_3), 26.5 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 20.9 (CH_3), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{43}H_{63}O_9N_3Na$ 788.4457, found 788.4475.

***(2S,3S,4R)*-2-Azido-1-*O*-(2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)-3,4-*O*-isopropylidene-octadec-1,3,4-triol (17).** A solution of imidate **7d** (790 mg, 1.28 mmol) and primary alcohol **6** (196 mg, 0.51 mmol) in the mixture of DCM and ACN (DCM/ACN = 1/2, 10 mL) was stirred for 30 min at room temperature with activated 3Å molecular sieves (196 mg). After cooling to -30 °C, TMSOTf (34 μL, 0.18 mmol) was slowly added. The reaction mixture was stirred at this temperature for 5 min and then warmed to room temperature. When the reaction was completed, molecular sieves was removed by filtration through celite. The filtrate was extracted with DCM (3 × 15 mL) and water (15 mL). The organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by column chromatography on silica gel to give mixture of spots of α-isomer, β-isomer, and acceptor **6**. Separation of theses α-isomer, β–isomers and acceptor **6** were difficult in column chromatography. However, to a solution of the spots mixture in MeOH (4.5 mL) was added sodium methoxide (22 mg, 0.41 mmol) and stirred for 12 h. The solvent was removed, and the residue was purified by column chromatography on silica gel to afford **17** (344 mg, 82%, β/α=3.2/1) as a colorless oil. R_f 0.63 (EtOAc/Hex = 1/4); $[\alpha]^{22}_D$ +22.5 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v* 3467, 2922, 2851, 2099, 1496, 1456, 1361, 1259, 1217, 1147, 1083, 1030 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36-7.27 (m, 15H, ArH), 4.93 (d, *J* = 10.8 Hz, 1H, CH_2Ph), 4.93 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 4.85 (d, *J* = 10.8 Hz, 1H, CH_2Ph), 4.82 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 4.63 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 4.49 (d, *J* = 7.8 Hz, 1H, H-1'), 4.17-4.13 (m, 1H, H-4), 4.08 (dd, *J* = 10.2, 7.2 Hz, 1H, H-1a), 4.00 (dd, *J* = 10.8, 3.0 Hz, 1H, H-1b), 3.90 (dd, *J* = 9.6, 5.4 Hz, 1H, H-3), 3.86 (dd, *J* = 12.0, 2.4 Hz, 1H, H-6a'), 3.70-3.66 (m, 2H, H-3', H-6b'), 3.55 (t, *J* = 9.6 Hz, 1H, H-4'), 3.50-3.46 (m, 2H, H-2, H-2'), 3.40-3.37 (m, 1H, H-5'), 1.64-1.51 (m, 4H, CH_2), 1.40 (s, 3H, CH_3), 1.37-1.26 (m, 27H, CH_2, CH_3), 0.88 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4 (C × 2), 137.9 (C), 128.5 (CH × 2), 128.4 (CH × 4), 128.1 (CH × 2), 127.9 (CH × 3), 127.8 (CH × 2), 127.7 (CH), 127.6 (CH), 108.7 (C), 103.4 (CH), 84.5 (CH), 82.5 (CH), 77.8 (CH), 77.6 (CH), 75.7 (CH_2), 75.4 (CH), 75.1 (CH), 75.0 (CH_2), 59.7 (CH), 31.9 (CH_2), 29.7 (CH_2 × 5), 29.6 (CH_2 × 6), 29.4 (CH_2), 29.3 (CH_2), 28.2 (CH_3), 26.6 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{48}H_{69}O_8N_3Na$ 838.4977, found 838.4981.

(Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→1)-(2S,3S,4R)-2-azido-3,4-*O*-isopropylidene-octadecan-1,3,4-triol (18a). *Method A:* A solution of donor **5a** (56 mg, 0.09 mmol) and primary alcohol **17** (63 mg, 0.08 mmol) in DCM/ACN (1/2 ratio, 10 mL) was stirred for 1 h at room temperature with activated 3 Å molecular sieves (180 mg). After cooling to -30 °C, NIS (52 mg, 0.23 mmol) and TfOH (3 μL, 0.04 mmol) were added and reaction mixture was stirred for 2 h. When the reaction was completed, molecular sieves was removed by filtration through celite. The filtrate was extracted with aqueous $Na_2S_2O_3$ (10 mL) and brine (10 mL), and the organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to *vacuo*. The residue was purified by column chromatography on silica gel to give the desired product **18a** (86 mg, 86%, αβ/ββ=2.7/1) as white solid. *Method B:* A solution of donor **5b** (43 mg, 0.07 mmol) and primary alcohol **17** (53 mg, 0.06 mmol) in a mixture of DCM and ACN (1/2 ratio, 0.90 mL) was stirred for 1 h at room temperature with activated 3 Å molecular sieves (140 mg). After cooling to -30 °C, NIS (40 mg, 0.18 mmol) and TfOH (4 μL, 0.04 mmol) were added and reaction mixture was stirred for 2 h. When the reaction was completed, molecular sieves was removed by filtration through celite. The filtrate was extracted with aqueous $Na_2S_2O_3$ (10 mL) and brine (10 mL), and the organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to *vacuo*. The residue was purified by column chromatography on silica gel to give the desired product **18a** (69 mg, 84%, αβ/ββ=3.2/1) as white solid. *Method C:* A solution of donor **5c** (63 mg, 0.10 mmol) and primary alcohol **17** (68 mg, 0.08 mmol) in DCM/ACN (1/2 ratio, 11 mL) was stirred for 1 h at room temperature with activated 3 Å molecular sieves (200 mg). After cooling to -30 °C, AgOTf (86 mg, 0.33 mmol) were added and reaction mixture was stirred for 21 h. When the reaction was completed, molecular sieves was removed by filtration through celite. The filtrate was extracted with aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and the organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to *vacuo*. The residue was purified by column chromatography on silica gel to give the desired product **18a** (31 mg, 29%, αβ/ββ=2.6/1) as white solid. R_f 0.69 (EtOAc/Hex = 5/1); $[\alpha]^{24}_D$ +1.8 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v* 3033, 2925, 2854, 2099, 1748, 1666, 1528, 1456, 1367, 1305, 1276, 1220, 1131, 1070, 1048 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35-7.27 (m, 15H, ArH), 5.41 (ddd, *J* = 9.6, 5.4, 3.0 Hz, 1H, H-8''), 5.31 (dd, *J* = 9.6, 2.4 Hz, 1H, H-7''), 5.14 (d, *J* = 10.2 Hz, 1H, NH), 4.92-4.75 (m, 7H, H-4'', CH_2Ph), 4.40 (d, *J* = 7.8 Hz, 1H, H-1'), 4.21 (dd, *J* = 13.2, 2.4 Hz, 1H, H-9a''), 4.17 (dd, *J* = 11.4, 4.8 Hz, 1H, H-6a'), 4.13 (ddd, *J* = 9.6, 5.4, 3.0 Hz, 1H, H-4), 4.09 (dd, *J* = 10.8, 1.8 Hz, 1H, H-6''), 4.07-4.02 (m, 2H, H-1a, H-5''), 3.98 (dd, *J* = 12.6, 5.4 Hz, 1H, H-9b"), 3.90 (dd, *J* = 10.8, 3.0 Hz, 1H, H-1b), 3.79 (dd, *J* = 9.6, 6.0 Hz, 1H, H-3), 3.77 (s, 3H, CH_3), 3.68 (t, *J* = 9.0 Hz, 1H, H-4'), 3.63-3.57 (m, 3H, H-2, H-3', H-

6b'), 3.46 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2'), 3.41 (ddd, *J* = 5.4, 4.2, 1.8 Hz, 1H, H-5'), 2.68 (dd, *J* = 12.6, 4.8 Hz, 1H, H-3a''), 2.13 (s, 3H, CH_3), 2.029 (s, 3H, CH_3), 2.026 (s, 3H, CH_3), 1.99-1.94 (m, 4H, H-3b'', CH_3), 1.87 (s, 3H, CH_3), 1.59-1.51 (m, 2H, CH_2), 1.42 (s, 3H, CH_3), 1.38-1.26 (m, 27H, CH_2, CH_3), 0.88 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (C), 170.6 (C), 170.3 (C), 170.0 (C), 169.8 (C), 167.9 (C), 138.6 (C), 138.5 (C), 138.4 (C), 128.4 (CH × 4), 128.3 (CH × 3), 128.1 (CH × 2), 127.9 (CH × 2), 127.8 (CH × 2), 127.6 (CH × 2), 108.4 (C), 103.7 (CH), 98.7 (C), 84.4 (CH), 82.3 (CH), 77.8 (CH), 77.2 (CH), 75.8 (CH), 75.7 (CH_2), 74.9 (CH_2), 74.0 (CH), 72.2 (CH), 70.7 (CH_2), 69.1 (CH), 67.9 (CH), 66.9 (CH), 63.5 (CH_2), 62.1 (CH_2), 60.5 (CH), 52.6 (CH_3), 49.4 (CH), 38.1 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 4), 29.6 (CH_2 × 4), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.2 (CH_3), 26.5 (CH_2), 25.6 (CH_3), 23.2 (CH_3), 22.7 (CH_2), 21.1(CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{68}H_{96}O_{20}N_4Na$ 1311.6510, found 1311.6552.

(Methyl 5-*tert*-butyl carbonate acetamido-7,8,9-tri-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-2,3,4-tri-*O*-benzyl-β-glucopyranosyl-(1→1)-(2S,3S,4R)-2-azido-3,4-isopropylidene-octadecane-1,3,4-triol (18b). A solution of donor **5d** (63 mg, 0.10 mmol) and primary alcohol **17** (71 mg, 0.09 mmol) in DCM/ACN (1/2 ratio, 1.2 mL) was stirred for 1 h at room temperature with activated 3 Å molecular sieves (200 mg). After cooling to -30 °C, NIS (59 mg, 0.26 mmol) and TfOH (8 μL, 0.04 mmol) were added and reaction mixture was stirred for 3 h. When the reaction was completed, molecular sieves was removed by filtration through celite. The filtrate was extracted with aqueous $Na_2S_2O_3$ (10 mL) and brine (10 mL), and the organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to *vacuo*. The residue was purified by column chromatography on silica gel to give the desired product **18b** (93 mg, 77%, αβ/ββ=2/1) as white solid. R_f 0.15 (EtOAc/Hex = 1/3); $[\alpha]^{25}_D$ +13.57 (*c* 2.1, CH_2Cl_2); IR (CH_2Cl_2) *v* 3032, 2982, 2926, 2855, 2112, 1748, 1706, 1456, 1369, 1230, 1076, 1038 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.27 (m, 15H, ArH), 5.39-5.35 (m, 2H, H-4'', H-8''), 5.16 (dd, *J* = 8.4, 1.2 Hz, 1H, H-5''), 4.92-4.74 (m, 7H, H-7'', CH_2Ph), 4.70 (dd, *J* = 10.2, 1.8 Hz, 1H, H-6''), 4.40 (d, *J* = 7.8 Hz, 1H, H-1'), 4.26 (dd, *J* = 12.6, 2.4 Hz, 1H, H-9a''), 4.18-4.11 (m, 2H, H-6a', H-4), 4.05 (dd, *J* = 10.8, 9.0 Hz, 1H, H-1a), 3.94-3.88 (m, 2H, H-9b'', H-1b), 3.80 (dd, *J* = 7.5 Hz, 1H, H-3), 3.77 (s, 3H, CH_3), 71-3.56 (m, 4H, H-6b, H-4', H-3', H-2), 3.48-3.44 (dd, *J* = 13.8, 6.0 Hz, 1H, H-2'), 3.41-3.38 (ddd, *J* = 9.6, 3.6, 1.2 Hz, 1H, H-5'), 2.82 (dd, *J* = 12.6, 4.8 Hz, 1H, H-3a''), 2.35 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.97-1.93 (m, 4H, H-3b'', CH_3), 1.86 (s, 3H, CH_3), 1.57-1.52 (m, 11H, NHBoc, CH_2), 1.42 (s, 3H, CH_3), 1.37-1.25 (m, 27H, CH_2, CH_3), 0.88 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9 (C), 170.6 (C), 170.1 (C), 169.9 (C), 169.8 (C), 167.7 (C), 151.8 (C), 138.6 (C), 138.5 (C), 138.4 (C), 128.33 (CH × 4), 128.30 (CH × 3), 128.1 (CH × 2), 127.84 (CH × 2), 127.75 (CH × 2), 127.6 (CH × 2), 127.5 (CH), 108.3 (C), 103.6 (CH), 98.7 (C), 84.6 (CH), 84.5 (CH), 82.3 (CH), 77.8 (CH), 77.1 (CH), 75.8 (CH), 75.6 (CH_2), 74.9 (CH_2), 73.9 (CH), 71.0 (CH_2), 68.1 (CH), 66.7 (CH), 66.5 (CH), 60.5 (CH), 52.6 (CH_3), 52.4 (CH), 31.9 (CH_2), 29.7 (CH_2 × 4), 29.64 (CH_2 × 4), 29.60 (CH_2), 29.57 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.2 (CH_3), 27.9 (CH_3), 27.8 (CH_3 × 4), 26.7 (CH_3), 26.4 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 21.2 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{73}H_{104}O_{22}N_4Na$ 1411.7034, found 1411.7064.

(Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→1)-(2S,3S,4R)-3,4-isopropylidene-2-octadecanoylaminooctadecane-1,3,4-triol (19). To a solution of azide **18a** (70 mg, 0.05 mmol) in THF (3.5 mL) was added triphenylphosphine (26 mg, 0.10 mmol) at 0 °C and then the reaction mixture was stirred at 0 °C for 5 min. After addition of water (4 μL, 0.23 mmol) at 0 °C, the reaction mixture was heated at 50 °C for 12 h and then concentrated under reduced pressure. The residue was used in the next step without further purification. A solution of amine in DCM (3.40 mL) was added stearic acid (20 mg, 0.07 mmol), HOBt (19 mg, 0.10 mmol) and EDC (13 mg, 0.10 mmol). The reaction mixture was stirred for 4 days at room temperature and then concentrated under reduced pressure to form a residue which was purified by column chromatography on silica gel to give the product **19** (42 mg, 51%). R_f 0.54 (EtOAc/Hex = 3/1); $[\alpha]^{24}_D$ +12.0 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v* 3420, 3064, 3031, 2915, 2871, 1740, 1640, 1496, 1453, 1362, 1236, 1146, 1070, 1029 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.28 (m, 15H, ArH), 5.84 (d, *J* = 9.6 Hz, 1H, NH), 5.38 (ddd, *J* = 9.0, 4.8, 2.4 Hz, 1H, H-8''), 5.30 (dd, *J* = 9.0, 1.8 Hz, 1H, H-7''), 5.13 (d, *J* = 9.6 Hz, 1H, NHAc), 4.94 (d, *J* = 10.8 Hz, 1H, CH_2Ph), 4.89-4.83 (m, 4H, H-4'', CH_2Ph), 4.76 (d, *J* = 10.2 Hz, 1H, CH_2Ph), 4.75 (d, *J* = 10.8 Hz, 1H, CH_2Ph), 4.24 (d, *J* = 7.8 Hz, 1H, H-1'), 4.20-4.15 (m, 3H, H-1a, H-6a', H-9a''), 4.10-4.02 (m, 3H, H-2, H-5'', H-6''), 3.96-3.87 (m, 3H, H-3, H-4, H-9b''), 3.76 (s, 3H, CH_3), 3.67-3.60 (m, 2H, H-3', H-4'), 3.55-3.53 (m, 2H, H-1b, H-6b'), 3.45 (t, *J* = 8.4 Hz, 1H, H-2'), 3.38 (dd, *J* = 9.6, 3.0 Hz, 1H, H-5'), 2.66 (dd, *J* = 12.6, 4.2 Hz, 1H, H-3a''), 2.13 (s, 3H, CH_3), 2.034 (s, 3H, CH_3), 2.029 (s, 3H, CH_3), 1.96 (t, *J* = 12.6 Hz, 1H, H-3b''), 1.90 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.80-1.76 (m, 4H, CH_2), 1.48-1.42 (m, 4H, CH_2), 1.40 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.31-1.18 (m, 50H, CH_2), 0.88 (t, *J* = 7.2, 6.0 Hz, 6H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5 (C), 171.0 (C), 170.6 (C), 170.2 (C), 169.9 (C), 169.8 (C), 167.9 (C), 128.6 (CH × 2), 128.4 (CH × 4), 128.1 (CH), 128.0 (CH × 4), 127.8 (CH × 3), 127.7 (CH), 107.9 (C), 104.6 (CH), 98.7 (C), 84.9 (CH), 82.2 (CH), 77.6 (CH × 2), 75.7 (CH), 75.4 (CH_2), 74.9 (CH_2), 74.0 (CH), 72.3 (CH), 70.6 (CH_2), 69.0 (CH), 67.8 (CH), 66.9 (CH), 63.4 (CH_2), 62.1 (CH_2), 52.7 (CH_3), 49.4 (CH), 48.4 (CH), 38.1 (CH_2), 36.5 (CH_2), 31.9 (CH_2 × 2), 29.7 (CH_2 × 14), 29.5 (CH_2 × 2), 29.4 (CH_2), 29.3 (CH_2 × 2), 28.1 (CH_3), 26.4 (CH_2), 25.9 (CH_3), 25.7 (CH_2), 23.2 (CH_3), 22.7 (CH_2 × 2), 21.1 (CH_3), 20.8 (CH_3 × 2), 20.5 (CH_3), 14.1 (CH_3 × 2); HRMS (ESI, M+H^+) calcd for $C_{86}H_{133}O_{21}N_2$ 1529.9395, found 1529.9425.

(5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosyloic-acid)-(2→6)-β-D-glucopyranosyl-(1→1)-(2S,3S,4R)-2-octadecanoylaminoheotadecan-1,3,4-triol (1). To a solution of trisaccharide derivative **19** (74 mg, 0.05 mmol) in methanol (2 mL) was added NaOH (1 mL, 1 N). The reaction mixture was stirred at 50 °C. After 1 h, the reaction mixture was concentrated

under reduced pressure without further purification to get the residue. The residue (45 mg) was dissolved in a mixed solvent of MeOH/$CHCl_3$ (3/1 ratio, 0.60 mL) at room temperature. The $Pd(OH)_2$/C (45 mg, Degussa type) was added to the solution and followed by addition 3 drops of acetic acid, the reaction vessel was purged with hydrogen gas, and the mixture was stirred under 60 psi pressure at room temperature for 5 h. The resulting solution was filtered through celite and the filtrate was concentrated in vacuo. Since, several attempts to purify the target compound **1** using column chromatography with various solvent systems were unsuccessful. However, we have developed simple technique to purify the target compound **1**. Vertical glass column was packed using 29.26 g of silica gel 60 (230-400 mesh, E. Merck) in the $CHCl_3$ mobile phase. The crude compound of **1** (45 mg) in 3 mL mixture solution of MeOH and $CHCl_3$ = 1/3 is placed inside the top of the vertical glass column. The 200 mL eluent (MeOH/$CHCl_3$, 50 mL/150 mL) were used as eluting solvent flowing down through the column. Subsequently, eluent phase was changed to (MeOH/$CHCl_3$/H_2O, 50 mL/150 mL/5 mL) so that the impurity could remove easily. Final eluent solvent (MeOH/$CHCl_3$/H_2O, 50 mL/150 mL/10 mL) was loaded in the vertical column solvent reservoir and solvent phase in the column becomes heterogeneous mixture (lower MeOH/$CHCl_3$ layer and higher H_2O layer). The higher H_2O layer were removed by pipette and remaining homogenous layer was used as eluting solvent flowing down through the column to get highly pure target compound **1** (15 mg, 85%). R_f 0.54 (MeOH/$CHCl_3$/H_2O = 1/2.4/0.2); $[\alpha]^{25}_D$ -2.4 (*c* 0.25, MeOH); IR (KBr) *v* 3316, 2926, 2850, 1632, 1552, 1466, 1383, 1135, 1036 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 4.24 (d, *J* = 7.8 Hz, 1H, H-1'), 4.13-4.07 (m, 2H, H-8'', H-9a''), 4.01 (dd, *J* = 10.8, 4.8 Hz, 1H, H-6a'), 3.86 (ddd, *J* = 9.0, 6.0, 3.0 Hz, 1H, H-5''), 3.81 (dd, *J* = 11.4, 2.4 Hz, 1H, H-1a), 3.74 (dd, *J* = 10.8, 2.4 Hz, 1H, H-6b'), 3.71-3.64 (m, 4H, H-3, H-4'', H-7'', H-9b''), 3.61 (dd, *J* = 11.4, 5.4 Hz, 1H, H-1b), 3.56-3.49 (m, 3H, H-2, H-4, H-6''), 3.42 (t, *J* = 9.0 Hz, 1H, H-4'), 3.36-3.32 (m, 2H, H-3', H-5'), 3.20 (t, *J* = 8.4 Hz, 1H), 2.84 (dd, *J* = 12.0, 3.6 Hz, 1H, H-3a''), 2.22-2.20 (m, 2H, CH_2), 2.01 (s, 3H, CH_3), 1.63-1.52 (m, 5H, H-3b'', CH_2), 1.45-1.42 (m, 2H, CH_2), 1.30 (bs, 50H, CH_2), 0.89 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.0 (C), 175.6 (C), 174.2 (C), 104.7 (CH), 101.5 (C), 77.6 (CH), 76.4 (CH), 75.1 (CH), 74.7 (CH), 74.3 (CH), 72.9 (CH), 72.8 (CH), 71.3 (CH), 70.2 (CH × 1, CH_2 × 1), 69.4 (CH), 64.4 (CH_2), 64.1 (CH_2), 54.2 (CH), 52.0 (CH), 42.5 (CH_2), 37.3 (CH_2), 33.1 (CH_2 × 2), 31.9 (CH_2), 31.0 (CH_2 × 2), 30.9 (CH_2 × 7), 30.8 (CH_2 × 5), 30.7 (CH_2 × 2), 30.53 (CH_2 × 2), 30.50 (CH_2 × 2), 30.45 (CH_2 × 2), 27.2 (CH_2), 23.8 (CH_2 × 1, CH_3 × 1), 22.6 (CH_2), 14.5 (CH_3 × 2); HRMS (ESI, $M+Na^+$) calcd for $C_{53}H_{100}O_{17}N_2Na$ 1059.6914, found 1059.6900.

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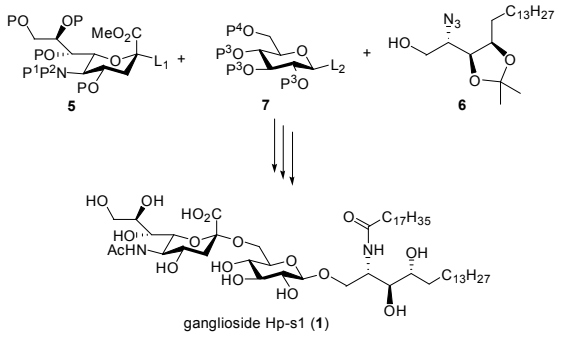
Graphical Abstract



Total synthesis of the ganglioside Hp-s1 (**1**) in ten steps is described.