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Synthesis of Hydroxylated Analogues of α-Galactosyl Ceramide (KRN7000) with Varying Stereochemistry

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The synthesis of analogues of α-galactosyl ceramide (KRN7000) with an additional hydroxy group in the phytosphingosine chains and with varying stereochemistry is described. Careful selection of glucose, galactose, mannose, and talose hexopyranoses allowed us to control the stereochemistry of some of the hydroxy groups in the sphingosine chain to give some interesting hydroxylated KRN7000 analogues.

Introduction

Glycolipids are important components of the cell membrane, and play central roles in numerous biological processes. The immune system recognizes glycolipids, and recruits them as tumor-associated antigens; this is exploited to provide immunotherapy for some types of cancer.[1] The effects of α-linked glycolipids on in vitro and in vivo NKT cell (natural killer T cell) activity have been reported.[2] α-Galactosyl ceramide (α-GalCer, **1**), also known as KRN7000, is the most well-characterized antigen for CD1d-reactive T-cells in both mice and humans.[3] The search for potent and selective modulators of the sphingolipid/CD1/NKT-cell-mediated response is an important one, but only modest progress has been made, particularly for human cell lines. Literature reports reveal that modifications to the ceramide and sugar parts, and of the anomeric configuration have seemingly unpredictable outcomes.[4] Historically, KRN7000 has been used to investigate the structure–activity relationship of related synthetic glycolipids.[4] The hydroxy groups in the sugar moiety play significant roles, for example, in hydrogen bonding between the N–H hydrogen on the phytosphingosine and the oxygen of the hydroxy group of the adjacent threonine-156 residue of mouse CD1d (mCD1d) (or threonine-154 residue of human CD1d), as can be seen from X-ray crystallographic analysis.[5,6] We chose to study the hydroxylated KRN7000 analogues described in this paper because of the importance of the solved structures of NKT TCR/glycolipid/CD1d complexes.[6]

The inversion of one of the OH groups of the sphingosine moiety has been documented in the literature.[7] The D-galactose, D-glucose, D-mannose, and D-talose derived structural units in KRN7000 analogues D-*galacto*-phytosphingosine **2a**, D-*gluco*-phytosphingosine **2b**, D-*manno*-phytosphingosine **2c**, and D-*talo*-phytosphingosine **2d** (Figure 1) have chiral centres at the necessary positions, and

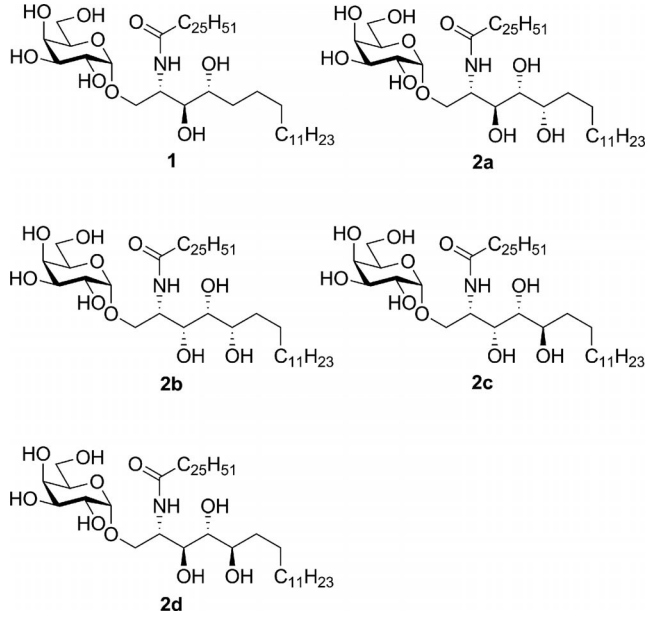

Figure 1. Structure of α-galactosyl ceramide **1** and analogues **2a**–**2d**.

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have additional hydroxy groups in the phytosphingosine chain. We used various hexopyranose derivatives to obtain target compounds **2a**–**2d**.

Results and Discussion

We have previously reported a concise synthesis of KRN7000 (Figure 2). This synthetic route could be used to vary the hydrophobic regions of the sphingoid long-chain base and lipid, and so control selective cytokine release.[8] Based on the route described in that paper, we planned a five-step synthesis of KRN7000 derivatives with an extra hydroxy group in the phytosphingosine chain.[8]

We prepared α-GalCer analogues **2a**–**2d** containing an additional hydroxy group in the phytosphingolipid chain. D-Glucose, D-galactose, D-mannose, and D-talose contain the requisite chiral centres in suitable positions for use as precursors for phytosphingolipid isomers. They also contain a further hydroxy substituent that would result in an additional hydroxy group at C-5 in the sphingosine chain. During the preparation of this manuscript, Siozali and coworkers reported the synthesis of hydroxylated KRN7000 analogue D-*galacto*-phytosphingosine **2a**, which was derived from D-galactose (Figure 1), but no report of the synthesis of the other analogues (i.e., **2b**, **2c**, and **2d**) exist.[9]

The synthesis began with the stereo- and regioselective preparation of disaccharides **10a**–**10c** from a solution of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl iodide **4**. Compound **4** was prepared by treatment of 1,2,3,4,6-penta-*O*-benzyl-D-galactose with iodotrimethylsilane (TMSI), *N*,*N*-diisopropylethylamine (DIPEA, 1 equiv.), and tetra-*n*-butylammonium iodide (TBAI, 3 equiv.) in toluene for 1 h at 65 °C, followed by azeotropic distillation.[10]

This process gave a good overall yield of α-linked disaccharides **10a** (75%), **10b** (72%), and **10c** (69%), starting from protected D-galactose **9a**, D-glucose **9b**, and D-mannose **9c**[11] (Scheme 1). Thus, the reactions between glycosyl iodide **4** and 1,6-diols **9a**–**9c** were stereoselective, but also the reactions were regioselective, as the primary hydroxy groups reacted leaving the hemiacetal hydroxy group at the 1-position free for further derivatization. Wittig reaction[12] of **10a**–**10c** gave the desired olefins (i.e., **11a**–**11c**), containing an extra hydroxy group in the phytosphingosine chain, in good to excellent yields (**11a**: 90%, **11b**: 72%, **11c**: 70%).

To achieve the total synthesis of the KRN7000 analogues, we used Mitsunobu conditions[13] to conduct an azide displacement reaction, and obtained azido compounds **12a**–**12c** in very good to excellent yields (**12a**: 94%, **12b**: 95%, **12c**: 88%). The Staudinger reaction of the azide groups of compounds **12a**–**12c** and subsequent amide-bond formation resulted in the formation of the expected products (i.e., **13a**–**13c**) in good overall yields (**13a**: 75%, **13b**: 62%, **13c**: 60%).[4b] Finally, global deprotection[8] of **13a**–**13c** gave crude **2a**–**2c**. The TLC plates of these target compounds showed a major spot corresponding to the product, lower isolated yields were obtained because the compounds were very difficult to purify using Sephadex G10 and C18 gels. With a Sephadex G10 column, the target compounds were eluted directly in the first five test tubes. Purification of the target compounds by flash column chromatography on gave solubility problems and resulted in lower yields (**2a**: 40%, **2b**: 42%, **2c**: 51%).

Because D-talose is an expensive and rare sugar, we developed a simple route to access D-talose from D-galactose (Scheme 2). The synthesis began with the protection of the primary alcohol in **14** with a TBDPS (*tert*-butyldiphenyl-

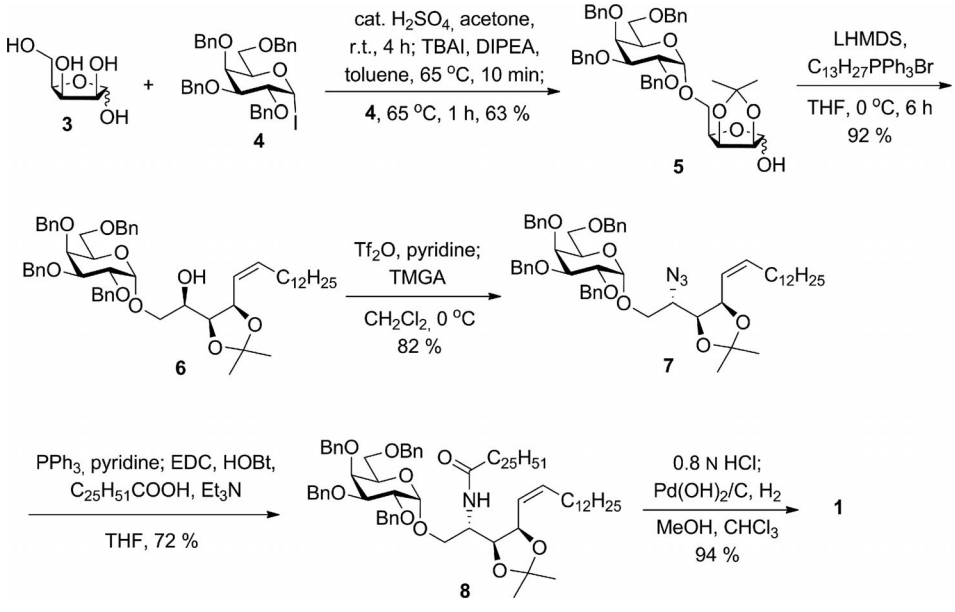
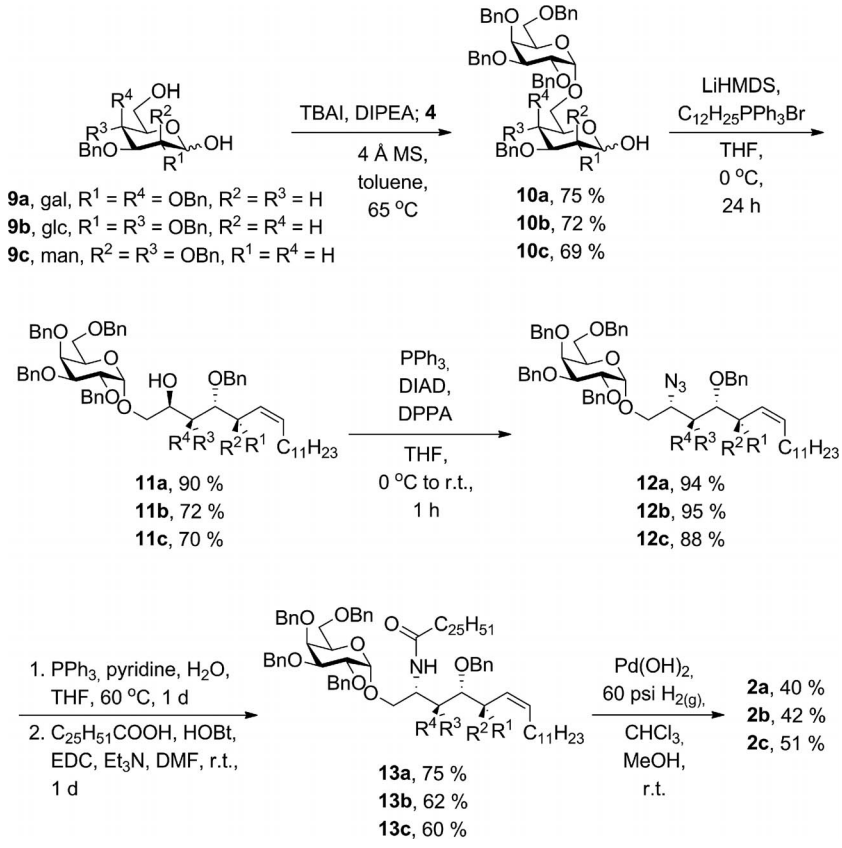


Figure 2. Previous report of the synthesis of KRN7000 in five steps.[8] TMGA = tetramethylguanidinium azide. EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

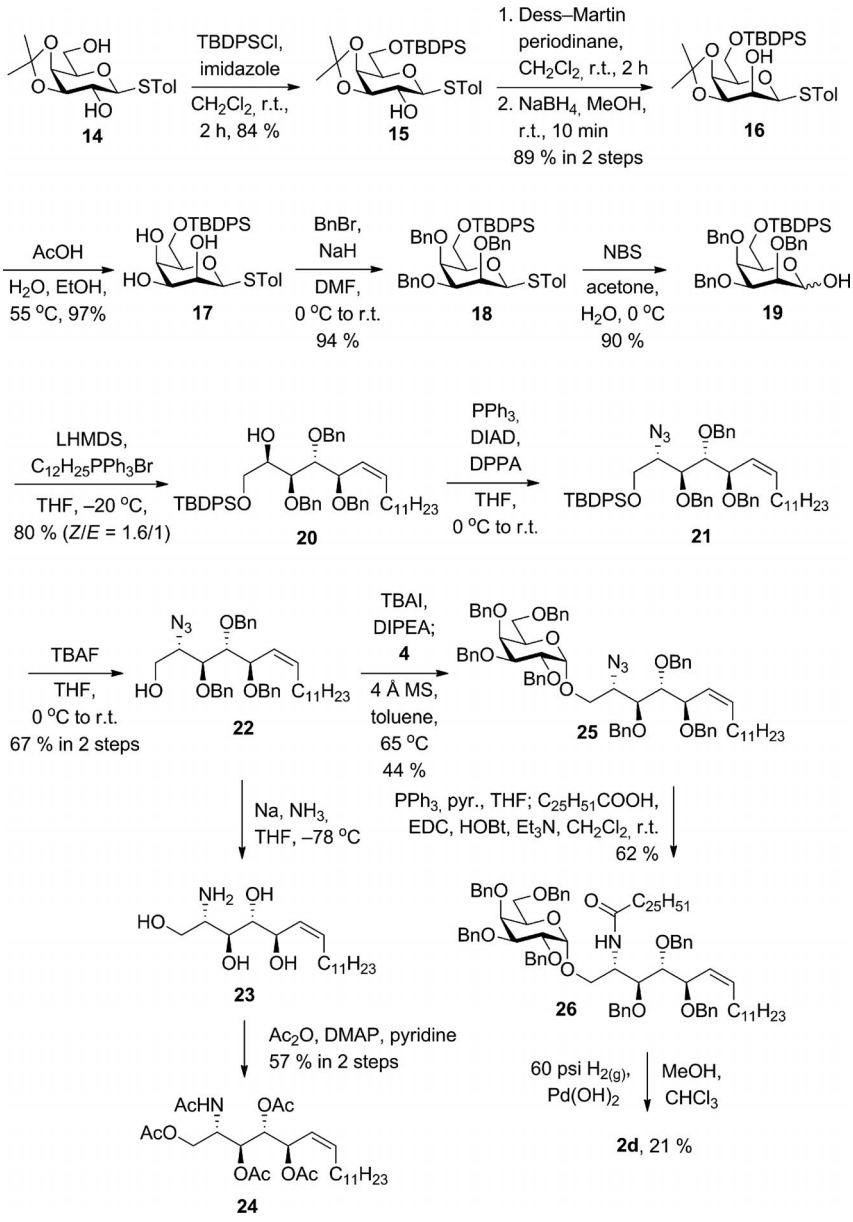


Scheme 1. Preparation of KRN7000 analogues **2a**–**2c**. DIAD = diisopropyl azodicarboxylate; DPPA = diphenylphosphoryl azide.

silyl) group to give an 84% yield of compound **15**.[14] The epimerization of D-galactose derivative **15** to give D-talose derivative **16** was achieved by Dess–Martin periodinane oxidation followed by $NaBH_4$ reduction.[15] The acetonide group was then hydrolysed under acidic conditions to give triol **17** in excellent yield (97%). After several attempts at the benzylation of **17**, we achieved excellent results using sodium hydride and benzyl bromide in DMF to give fully protected D-talose compound **18** in 94% yield.

Hydrolysis of the thiocresol group at the anomeric position using *N*-bromosuccinimide in acetone and water at 0 °C resulted in a very good yield of hemiacetal **19** (90%). Olefin **20** was prepared by Wittig reaction[12] of hemiacetal **19** using Wittig reagent $C_{12}H_{25}PPh_3Br$ in the presence of lithium hexamethyldisilazide (LHMDS) in THF at 0 °C. However, the product was obtained in 75% yield with a *Z*/*E* ratio of 1.4:1. When the reaction was carried out at lower temperatures (–78 to –30 °C), reduced yields were observed, because the starting material (i.e., **19**) was not completely consumed. However, when the reaction was carried out at –30 to 0 °C, the product was formed in 75% yield, and the *Z*/*E* ratio increased to 1.58:1. Finally, the highest yield of compound **20** of 80% and a *Z*/*E* ratio of 1.6:1 were obtained when the reaction was carried out at –20 °C. The isomers were separated using column chromatography to obtain the major *Z* isomer of **20**. This *Z* isomer of **20** was used to continue the synthesis; the desired LCB (long-chain base) derivative **24** should have the *Z* configuration.[16d] The introduction of azide into compound **20** with inversion of configuration was achieved under Mitsunobu conditions to give azido compound **21**. We found that compound **21** was unstable and that its azide and olefin moieties underwent an intramolecular cycloaddition reaction. Thus, compound **21** was deprotected by treatment with tetra-*n*-butylammonium fluoride (TBAF) to remove the TBDPS group, and primary alcohol **22** was obtained in 67% yield over two steps.

Compound **22** is a crucial intermediate, because it gives access to the talose derivative of KRN7000 and also to tetrahydroxy-LCB (**23**). Tetrahydroxy-LCB is a component of some natural cerebrosides that have significant biological activity, and few reports are available in the literature for the synthesis of these molecules.[16] Birch reduction of azido primary alcohol derivative **22** gave tetrahydroxy-LCB (**23**). Compound **23** was characterized after acetylation to give its peracetylated derivative (i.e., **24**), and the identity of the material was confirmed by comparison with literature data.[16d] We subsequently attempted the glycosylation reaction of compound **22** with galactosyl iodide **4**. The glycosylation reaction of galactosyl iodide **4** with alcohol **22** in toluene gave only a low yield of azide **25** (23%) when donor, base, and TBAI were used in a 1.1:3:3 molar ratio. When 3 equiv. donor, 3 equiv. base, and 9 equiv. TBAI were used in dichloromethane, azide **25** was formed in a similar 23% yield. When the reaction was carried out in toluene with similar molar ratios of these reagents, azide **25** was formed



Scheme 2. Preparation of α-GalCer analogue **2d**. NBS = *N*-bromosuccinimide; DMAP = 4-(dimethylamino)pyridine.

in a maximum 44% yield. Azide **25** was used to form an amine using the Staudinger reaction, which was then converted into amide **26** in 62% yield. Finally, global deprotection gave crude compound **2d**. We faced the same problem of purification as we had seen with compounds **2a**–**2c**, and the target compound could not be purified by using Sephadex G10 or C18. Flash column chromatography on silica gel gave target compound **2d** in a lower yield (21%).

To evaluate the NKT-cell-stimulated activities of the synthetic analogues, A20-mCD1d cells (B lymphoma cells overexpressing mouse CD1d) were used to present these compounds to stimulate the Vα14-expressing mNK1.2 cells, and IL-2 (interleukin 2) secretion was determined by ELISA (enzyme-linked immunosorbent assay). As shown in Figure 3, all of the compounds induced IL-2 production in a dose-dependent manner. Their IL-2 production was comparable to that of α-GalCer with no statistically significant difference at 5 μM (α-GalCer: 304.9 ± 7.3, **2a**: 227.6 ± 19.2, **2b**: 280.9 ± 39.3, **2c**: 248 ± 3.9, **2d**: 235.8 ± 27.8) or 25 μM (α-GalCer: 404 ± 9.7, **2a**: 405.6 ± 47.9, **2b**: 388.9 ± 8.8, **2c**: 330.4 ± 28.2, **2d**: 422.2 ± 56.2), as judged by one-way ANOVA (analysis of variance) with Tukey's multiple comparison test. These results indicate that the addition of hydroxy groups at the C-5 position and the configuration of the chiral centres at C-2, C-3, C-4, and C-5 in the sphingosine chain of the α-GalCer analogues might not affect their presentation by the CD1d molecule to T-cell receptor of NKT cells. The question as to whether these analogues could drive Th1/Th2 polarization (Th cells = T helper cells) requires further investigation.

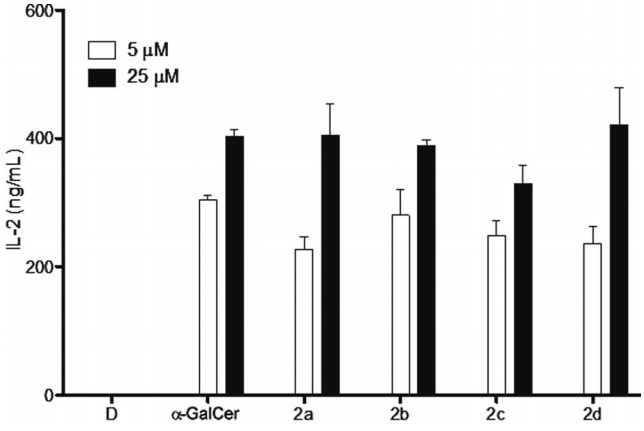


Figure 3. Activities of α-GalCer analogues. A20-mCD1d cells were loaded with the indicated α-GalCer (5 μM and 25 μM) and co-cultured with mNK1.2 cells. Three days after incubation, the supernatants were collected to determine the production of IL-2 by ELISA. Data are presented as mean ± standard deviation. D: DMSO only.

Conclusions

We have prepared four interesting analogues **2a**–**2d** of KRN7000 following a simple synthetic strategy. Careful selection of hexopyranose hemiacetals provided several unique stereoisomers. During the synthesis of the talose derivative of KRN7000, we also developed a new route for the synthesis of tetrahydroxy-LCB. A biological assay of these newly synthesized isomers with varying stereochemistries using CD1d-reactive T-cells helped to decipher the effects on their biological activities of an additional hydroxy group in the sphingosine chain.

Experimental Section

General Remarks: Some reactions were conducted in flame-dried glassware, under a nitrogen atmosphere. Dichloromethane, tetrahydrofuran, toluene, methanol, and *N*,*N*-dimethylformamide were purified and dried using a safe purification system containing activated Al_2O_3. All reagents obtained from commercial suppliers were used without purification unless otherwise stated. Flash column chromatography was carried out on silica gel 60 (230–400 mesh). TLC was carried out on pre-coated glass plates of silica gel 60 F254 (0.25 mm). Plates were visualized 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 then heating on a hot plate. Optical rotations were measured at 589 nm (Na) at ca. 27 °C. ^1H and ^{13}C NMR spectra, and DEPT, ^1H–^1H COSY, ^1H–^{13}C COSY, and ^1H–^1H NOESY spectra were recorded with 400 and 600 MHz instruments. Chemical shifts are given in ppm relative to Me_4Si, and spectra were calibrated using the $CDCl_3$ lock signal at δ = 7.24 ppm. IR spectra were recorded with a FTIR spectrometer using KBr plates. Mass spectra were recorded with an Orbitrap instrument with an ESI source.

2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranose (10a): Iodotrimethylsilane (232 μL, 1.63 mmol) was added to a stirred solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (760 mg, 1.31 mmol) in anhydrous dichloromethane (8 mL) at 0 °C under nitrogen. After 30 min, the mixture was concentrated in vacuo. Toluene (7 mL) was added to the residue, then it was evaporated in vacuo, and this was repeated three times in all. In a another flask, a mixture of acceptor **9a** (600 mg, 1.33 mmol), diisopropylethylamine (227 μL, 1.31 mmol), tetrabutylammonium iodide (1.44 g, 3.92 mmol), and 4 Å molecular sieves in anhydrous toluene (7 mL) was stirred for 10 min at 65 °C under nitrogen. A solution of crude iodide **4** in toluene (7 mL) was transferred into the reaction flask containing the acceptor. The mixture was stirred for 1 h, and then ethyl acetate (20 mL) was added. The white precipitate and the molecular sieves were removed by filtration through Celite. The filtrate was washed with aqueous $Na_2S_2O_3$ (3× 15 mL) and brine (15 mL), and the organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound **10a** (960 mg, 75%). R_f = 0.5 (EtOAc/Hex, 1:2). $[\alpha]_D^{29}$ = +38.9 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3445, 3030, 1454, 1098 cm^{-1}. Data for α anomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 35 H, ArH), 5.18 (d, *J* = 2.4 Hz, 1 H, 1-H), 4.91 (d, *J* = 10.4 Hz, 1 H, CH_2Ph), 4.90 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.89 (d, *J* = 10.4 Hz, 1 H, CH_2Ph), 4.88 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.78 (d, *J* = 11.6 Hz, 2 H, CH_2Ph), 4.75 (d, *J* = 3.2 Hz, 1 H, 1′-H), 4.60 (d, *J* = 10.4 Hz, 2 H, CH_2Ph), 4.53 (d, *J* = 11.6 Hz, 2 H, CH_2Ph), 4.46 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.42 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.35 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.30 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.13 (m, 1 H, 3′-H), 4.03–3.89 (m, 7 H, 2-H, 2′-H, 3-H, 4-H, 4′-H, 5-H, 5′-H), 3.62–3.48 (m, 4 H, 6a-H, 6b-H, 6′a-H, 6′b-H), 3.41 (s, 1 H, OH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.62 (C), 138.58 (C), 138.5 (C), 138.4 (2 C), 138.2 (C), 137.5 (C), 128.4 (2 CH), 128.3 (4 CH), 128.23 (2 CH), 128.19 (2 CH), 128.15 (4 CH), 128.1 (2 CH), 128.04 (2 CH), 128.01 (2 CH), 127.96 (2 CH), 127.9 (2 CH), 127.8 (CH), 127.61 (CH), 127.57 (CH), 127.5 (2 CH), 127.4 (2 CH), 127.34 (2 CH), 127.30 (2 CH), 98.4 (CH), 91.5 (CH), 78.9 (CH), 78.6 (CH), 76.4 (CH), 76.3 (CH), 75.2 (CH), 74.6 (CH), 74.4 (CH_2), 73.5 (CH_2), 73.43 (CH_2), 73.39 (CH_2), 73.3 (CH_2), 73.0 (CH_2), 72.9 (CH_2), 72.8 (CH_2), 69.7 (CH), 69.3 (CH), 68.9 (CH_2) ppm. Data for β anomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 35 H, ArH), 4.82–4.63 (m, 15 H, 1′-H, CH_2Ph), 4.56 (d, *J* = 8.4 Hz, 1 H, 1-H), 4.03–3.89 (m, 4 H, 2′-H, 3-H, 3′-H, 4′-H), 3.82–3.68 (m, 4 H, 2-H, 5-H, 6a-H, 6′a-H), 3.64–3.48 (m, 4 H, 4-H, 5′-H, 6b-H, 6′b-H), 3.41 (s, 1 H, OH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.62 (C), 138.58 (C), 138.5 (C), 138.4 (2 C), 138.2 (C), 137.5 (C), 128.4 (2 CH), 128.3 (4 CH), 128.23 (2 CH), 128.19 (2 CH), 128.15 (4 CH), 128.1 (2 CH), 128.04 (2 CH), 128.01 (2 CH), 127.96 (2 CH), 127.9 (2 CH), 127.8 (CH), 127.61 (CH), 127.57 (CH), 127.5 (2 CH), 127.4 (2 CH), 127.34 (2 CH), 127.30 (2 CH), 98.2 (CH), 97.6 (CH), 81.9 (CH), 80.6 (CH), 79.0 (CH), 76.2 (CH), 74.8 (CH_2), 74.3 (CH), 74.3 (CH), 74.0 (CH), 73.5 (CH_2), 73.43 (CH_2), 73.39 (CH_2), 73.3 (CH_2), 73.0 (CH_2), 72.9 (CH_2), 72.8 (CH_2), 69.4 (CH), 68.4 (CH_2) ppm. HRMS (ESI): calcd. for $C_{61}H_{64}O_{11}Na$ [M + Na]$^+$ 995.4341; found 995.4380.

2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranose (10b): Iodotrimethylsilane (578 μL, 4.08 mmol) was added to a stirred solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (1.90 g, 3.26 mmol) in anhydrous dichloromethane (20 mL) at 0 °C under nitrogen. After 30 min, the mixture was concentrated in vacuo. Toluene (17 mL) was added to the residue, then it was evaporated in vacuo, and this was repeated three times in all. In a another flask, a mixture of acceptor **9b** (1.50 g, 3.33 mmol), diisopropylethylamine (567 μL, 3.26 mmol), tetrabutylammonium iodide (3.60 g, 9.78 mmol), and 4 Å molecular sieves in anhydrous toluene (17 mL) was stirred for 10 min at 65 °C under nitrogen. A solution of crude iodide **4** in

toluene (17 mL) was transferred into the reaction flask containing the acceptor. The mixture was stirred for 1 h, then ethyl acetate (30 mL) was added. The white precipitate and the molecular sieves were removed by filtration through Celite. The filtrate was washed with aqueous $Na_2S_2O_3$ (3× 20 mL) and brine (20 mL), and the organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound **10b** (2.33 g, 72%). R_f = 0.5 (EtOAc/Hex, 1:2). $[\alpha]_D^{29}$ = +39.0 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 3030, 1454, 1096 cm^{-1}. Data for α anomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 35 H, ArH), 5.09 (d, *J* = 2.8 Hz, 1 H, 1-H), 4.97 (d, *J* = 3.2 Hz, 1 H, 1′-H), 4.95–4.53 (m, 12 H, CH_2Ph), 4.42 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.35 (d, *J* = 12.4 Hz, 1 H, CH_2Ph), 4.07–4.00 (m, 2 H, 2′-H, 5-H), 3.97–3.83 (m, 4 H, 3-H, 3′-H, 4′-H, 6′a-H), 3.75–3.68 (m, 1 H, 6′b-H), 3.54 (m, 4 H, 4-H, 5′-H, 6a-H, 6b-H), 3.40 (dd, *J* = 9.2, 3.6 Hz, 1 H, 2-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.64 (C), 138.59 (C), 138.5 (C), 138.4 (C), 138.1 (C), 137.9 (C), 137.7 (C), 128.3 (2 CH), 128.24 (2 CH), 128.18 (2 CH), 128.11 (2 CH), 128.09 (2 CH), 128.07 (2 CH), 128.0 (CH), 127.82 (2 CH), 127.78 (2 CH), 127.74 (2 CH), 127.72 (2 CH), 127.71 (2 CH), 127.69 (2 CH), 127.67 (2 CH), 127.65 (2 CH), 127.6 (CH), 127.54 (CH), 127.49 (CH), 127.42 (CH), 127.37 (CH), 127.31 (CH), 98.2 (CH), 90.7 (CH), 81.6 (CH), 80.1 (CH), 78.2 (CH), 77.9 (CH), 76.5 (CH), 75.5 (CH_2), 74.84 (CH_2), 74.83 (CH), 74.58 (CH_2), 74.56 (CH_2), 73.2 (CH_2), 72.8 (CH_2), 72.7 (CH_2), 70.3 (CH), 69.3 (CH), 68.9 (CH_2), 67.3 (CH_2) ppm. Data for β anomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 35 H, ArH), 5.00 (d, *J* = 3.6 Hz, 1 H, 1′-H), 4.97–4.53 (m, 13 H, CH_2Ph, 1-H), 4.44 (d, *J* = 11.2 Hz, 1 H, CH_2Ph), 4.30 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.07–3.39 (m, 11 H, 2′-H, 3-H, 3′-H, 4-H, 4′-H, 5-H, 5′-H, 6a-H, 6b-H, 6′a-H, 6′b-H), 3.27 (dd, *J* = 8.4, 8.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.64 (C), 138.59 (C), 138.5 (C), 138.4 (C), 138.2 (C), 138.1 (C), 137.5 (C), 128.3 (2 CH), 128.24 (2 CH), 128.18 (2 CH), 128.11 (2 CH), 128.09 (2 CH), 128.07 (2 CH), 128.0 (CH), 127.82 (2 CH), 127.78 (2 CH), 127.74 (2 CH), 127.72 (2 CH), 127.71 (2 CH), 127.69 (2 CH), 127.67 (2 CH), 127.65 (2 CH), 127.6 (CH), 127.54 (CH), 127.49 (CH), 127.42 (CH), 127.37 (CH), 127.31 (CH), 98.1 (CH), 97.1 (CH), 84.3 (CH), 83.2 (CH), 78.4 (CH), 77.6 (CH), 75.3 (CH_2), 75.2 (CH), 74.8 (CH), 74.7 (CH_2), 74.5 (CH), 74.3 (CH_2), 73.3 (CH_2), 73.0 (CH_2), 72.7 (CH_2), 71.9 (CH_2), 71.6 (CH), 69 (CH_2), 67.9 (CH_2) ppm. HRMS (ESI): calcd. for $C_{61}H_{64}O_{11}Na$ [M + Na]$^+$ 995.4341; found 995.4343.

2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-D-mannopyranoside (10c): Iodotrimethylsilane (62 μL, 0.43 mmol) was added to a stirred solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside (200 mg, 0.34 mmol) in anhydrous dichloromethane (2 mL) at 0 °C under nitrogen. After 30 min, the mixture was concentrated in vacuo. Toluene (2 mL) was added to the residue, then it was evaporated in vacuo, and this was repeated three times in all. A mixture of acceptor **9c** (170 mg, 0.38 mmol), diisopropylethylamine (60 μL, 0.34 mmol), tetrabutylammonium iodide (380 mg, 1.02 mmol), and 4 Å molecular sieves in anhydrous toluene (2 mL) was stirred for 10 min at 65 °C under nitrogen. A solution of crude iodide **4** in toluene (2 mL) was transferred into the reaction flask containing the acceptor. The mixture was stirred for 1 h, then ethyl acetate (10 mL) was added. The white precipitate and the molecular sieves were removed by filtration through Celite. The filtrate was washed with aqueous $Na_2S_2O_3$ (3× 5 mL) and brine (5 mL), and the organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound **10c** (229 mg, 69%). R_f = 0.5 (EtOAc/Hex, 1:2). $[\alpha]_D^{29}$ = +36.7 (*c* = 0.9, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3422, 3030, 1454, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 35 H, ArH), 5.13 (s, 1 H, 1-H), 5.01 (d, *J* = 3.2 Hz, 1 H, 1′-H), 4.92 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.86 (d, *J* = 10.8 Hz, 1 H, CH_2Ph), 4.79 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.74–4.59 (m, 7 H, CH_2Ph), 4.55 (d, *J* = 10.8 Hz, 1 H, CH_2Ph), 4.53 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.42 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.35 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.07–4.00 (m, 3 H, 2′-H, 4-H, 5′-H), 3.96–3.93 (m, 2 H, 3-H, 6a-H), 3.87 (m, 2 H, 3′-H, 4′-H), 3.78–3.71 (m, 3 H, 2-H, 5-H, 6b-H), 3.53 (dd, *J* = 9.6, 6.4 Hz, 1 H, 6′a-H), 3.42 (dd, *J* = 9.6, 6.4 Hz, 1 H, 6′b-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8 (C), 138.6 (C), 138.51 (C), 137.46 (C), 138.4 (C), 138.3 (C), 137.6 (C), 128.5 (2 CH), 128.43 (2 CH), 128.36 (5 CH), 128.3 (4 CH), 128.2 (2 CH), 128.1 (2 CH), 128.02 (2 CH), 128.01 (2 CH), 127.94 (2 CH), 127.88 (2 CH), 127.8 (CH), 127.7 (2 CH), 127.61 (2 CH), 127.56 (2 CH), 127.50 (2 CH), 127.47 (CH), 98.1 (CH), 92.6 (CH), 79.9 (CH), 78.7 (CH), 76.7 (CH), 75.4 (CH), 75.1 (CH), 75.02 (CH), 74.96 (CH_2), 74.7 (CH_2), 73.4 (CH_2), 73.2 (CH_2), 73.0 (CH_2), 72.8 (CH_2), 72.2 (CH_2), 72.0 (CH), 69.4 (CH), 69.3 (CH_2), 68.50 (CH_2) ppm. HRMS (ESI): calcd. for $C_{61}H_{64}O_{11}Na$ [M + Na]$^+$ 995.4341; found 995.4331.

(2*R*,3*S*,4*R*,5*S*)-3,4,5-Tri-*O*-benzyl-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-octadec-6-en-1,2,3,4,5-pentaol (11a): A mixture of disaccharide **10a** (1.00 g, 1.03 mmol) and tridecanyltriphenylphosphonium bromide (3.15 g, 6.17 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to 0 °C under nitrogen. Lithium hexamethyldisilazide (1.0 M solution in THF; 6.2 mL, 6.17 mmol) was added, and the reaction mixture was stirred for 24 h at 0 °C. Water (20 mL) was added to quench the reaction, and the mixture was extracted with EtOAc (3× 30 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography to give olefin **11a** (1.05 g, 90%, *cis*/*trans* = 1.2:1.6) as a colourless oil. R_f = 0.3 (EtOAc/Hex, 1:4). $[\alpha]_D^{28}$ = +46.8 (*c* = 1.6, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3483, 2925, 2360, 1497, 1061 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.15 (m, 70 H), 5.72 (dt, *J* = 15.6, 6.8 Hz, 1 H), 5.58 (dt, *J* = 11.6, 7.2 Hz, 1 H), 5.50–5.44 (m, 2 H), 4.91 (d, *J* = 11.2 Hz, 2 H), 4.83 (d, *J* = 4.8 Hz, 2 H), 4.18–4.64 (m, 11 H), 4.60 (d, *J* = 12.0 Hz, 3 H), 4.54 (d, *J* = 11.2 Hz, 2 H), 4.47–4.44 (m, 3 H), 4.41 (d, *J* = 11.2 Hz, 3 H), 4.35 (d, *J* = 11.6 Hz, 2 H), 4.27 (d, *J* = 11.6 Hz, 3 H), 4.14–4.07 (m, 2 H), 4.05 (m, 5 H), 3.93–3.89 (m, 4 H), 3.81–3.71 (m, 6 H), 3.57 (dd, *J* = 10. 4, 5.6 Hz, 2 H), 3.48 (d, *J* = 6.4 Hz, 4 H), 3.26–3.21 (m, 2 H), 2.09–1.95 (m, 4 H), 1.38–1.95 (m, 36 H), 0.88 (t, *J* = 6.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8 (2 C), 138.6 (2 C), 138.51 (2 C), 138.48 (2 C), 138.33 (C), 137.32 (C), 138.26 (C), 138.2 (C), 137.92 (C), 137.90 (C), 136.0 (CH), 135.0 (CH), 128.36 (5 CH), 128.35 (5 CH), 128.3 (7 CH), 128.24 (5 CH), 128.21 (3 CH), 128.19 (3 CH), 128.15 (3 CH), 128.07 (3 CH), 127.06 (3 CH), 127.9 (3 CH), 127.8 (3 CH), 127.7 (3 CH), 127.60 (3 CH), 127.57 (3 CH), 127.52 (3 CH), 127.48 (3 CH), 127.45 (3 CH), 127.42 (3 CH), 127.35 (3 CH), 127.3 (3 CH), 98.12 (CH), 98.06 (CH), 82.06 (CH), 82.04 (CH), 79.9 (CH), 79.2 (CH), 79.1 (CH), 77.40 (CH), 76.3 (CH), 75.3 (CH_2), 75.2 (CH_2), 74.9 (3 CH), 74.78 (CH_2), 74.76 (CH_2), 73.9 (CH), 73.5 (CH_2), 73.44 (2 CH_2), 73.40 (CH_2), 73.34 (CH_2), 73.32 (CH_2), 73.0 (CH_2), 72.9 (CH_2), 70.4 (CH_2), 70.3 (CH_2), 69.80 (CH_2), 69.78 (CH_2), 69.5 (CH), 69.42 (2 CH), 69.37 (CH), 68.9 (CH_2), 68.8 (CH_2), 32.4 (CH_2), 32.0 (3 CH_2), 29.7 (5 CH_2), 29.59 (CH_2), 29.55 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.39 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.1 (CH_2), 22.7 (3 CH_2), 14.2 (2 CH_3) ppm. HRMS (ESI): calcd. for $C_{73}H_{88}O_{10}Na$ [M + Na]$^+$ 1147.6270; found 1147.6261.

(2*R*,3*R*,4*R*,5*S*,6*Z*)-3,4,5-Tri-*O*-benzyl-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-octadec-6-en-1,2,3,4,5-pentaol (11b): A mix-

ture of disaccharide **10b** (730 mg, 0.75 mmol) and tridecanyltriphenyl phosphonium bromide (2.30 g, 4.50 mmol) in anhydrous tetrahydrofuran (7 mL) was cooled to 0 °C under nitrogen. Lithium hexamethyldisilazide (1.0 M solution in THF; 4.50 mL, 4.50 mmol) was added, and the reaction mixture was stirred for 24 h at 0 °C. Water (10 mL) was added to quench the reaction, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography to give olefin **11b** (610 mg, 72%) as a colourless oil. R_f = 0.3 (EtOAc/Hex, 1:4). $[\alpha]_D^{27}$ = +51.2 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3463, 3030, 2925, 1497, 1061 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 35 H, ArH), 5.68–5.58 (m, 1 H, 7-H), 5.40 (t, *J* = 10.8 Hz, 1 H, 6-H), 4.92 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.86 (d, *J* = 3.6 Hz, 1 H, 1′-H), 4.82–4.51 (m, 11 H, CH_2Ph, 5-H), 4.42 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.37 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.34 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.04 (dd, *J* = 9.6, 3.6 Hz, 1 H, 2′-H), 4.01–3.97 (m, 2 H, 2-H, 5′-H), 3.95–3.90 (m, 2 H, 3-H, 4-H), 3.81–3.68 (m, 4 H, 1a-H, 1b-H, 3′-H, 4-H), 3.55–3.44 (m, 2 H, 6′a-H, 6′b-H), 2.08–1.85 (m, 2 H, 8a-H, 8b-H), 1.31–1.17 (m, 18 H, CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7 (C), 138.63 (C), 138.60 (C), 138.57 (2 C), 138.3 (C), 137.8 (C), 135.8 (CH), 128.4 (CH), 128.3 (5 CH), 128.21 (CH), 128.19 (2 CH), 128.16 (4 CH), 128.1 (5 CH), 128.00 (CH), 127.98 (2 CH), 127.9 (CH), 127.79 (CH), 127.76 (2 CH), 127.68 (CH), 127.66 (CH), 127.53 (CH), 127.49 (CH), 127.44 (CH), 127.38 (3 CH), 127.33 (CH), 127.30 (CH), 126.7 (CH), 98.7 (CH), 81.8 (CH), 79.01 (CH), 78.84 (CH), 76.4 (CH), 75.5 (CH), 74.9 (CH_2), 74.8 (CH), 74.7 (CH_2), 73.5 (CH_2), 73.4 (CH_2), 73.0 (CH_2), 72.9 (CH_2), 70.7 (CH_2), 70.2 (CH_2), 70.1 (CH), 70.0 (CH), 68.8 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.64 (CH_2), 29.63 (CH_2), 29.61 (CH_2), 29.5 (CH_2), 29.43 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{73}H_{88}O_{10}Na$ $[M + Na]^+$ 1147.6270; found 1147.6296.

(2*R*,3*R*,4*R*,5*R*,6*Z*)-3,4,5-Tri-*O*-benzyl-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-octadec-6-en-1,2,3,4,5-pentaol (11c): A mixture of disaccharide **10c** (903 mg, 0.92 mmol) and tridecanyltriphenyl phosphonium bromide (2.84 g, 5.57 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to 0 °C under nitrogen. Lithium hexamethyldisilazide (1.0 M solution in THF; 5.6 mL, 5.6 mmol) was added, and the reaction mixture was stirred for 24 h at 0 °C. Water (10 mL) was added to quench the reaction, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography to give olefin **11c** (726 mg, 70%) as a colourless oil. R_f = 0.3 (EtOAc/Hex, 1:4). $[\alpha]_D^{27}$ = +42.6 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 3089, 2924, 1455, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 35 H, ArH), 5.81–5.75 (m, 1 H, 7-H), 5.45 (dd, *J* = 11.2, 9.6 Hz, 1 H, 6-H), 4.91 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.87 (d, *J* = 3.6 Hz, 1 H, 1′-H), 4.82 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.73 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.67 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.66 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.63–4.53 (m, 6 H, CH_2Ph), 4.50 (t, *J* = 9.2 Hz, 1 H, 5-H), 4.42 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.34 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.13 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.06–4.00 (m, 4 H, 2′-H, 3′-H, 4′-H, 5′-H), 3.95–3.82 (m, 2 H, 2-H, 3-H), 3.81–3.75 (m, 3 H, 1a-H, 1b-H, 4-H), 3.51–3.44 (m, 2 H, 6′a-H, 6′b-H), 2.20–2.01 (m, 2 H, 8a-H, 8b-H), 1.40–1.25 (m, 18 H, CH_2), 0.88 (t, *J* = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.67 (C), 138.66 (2 C), 138.54 (C), 138.52 (C), 138.1 (C), 137.8 (C), 136.7 (CH), 128.37 (3 CH), 128.3 (3 CH), 128.19 (6 CH), 128.18 (4 CH), 128.1 (CH), 128.0 (4 CH), 127.8 (CH), 127.70 (3 CH), 127.65 (CH), 127.60 (3 CH), 127.54 (CH), 127.48 (CH), 127.41 (2 CH), 127.38 (CH), 127.33 (CH), 127.26 (CH), 99.1 (CH), 80.6 (CH), 79.3 (CH), 78.8 (CH), 76.4 (CH), 74.7 (CH_2, CH), 74.5 (CH_2), 73.9 (CH_2), 73.7 (CH_2), 73.6 (CH), 73.4 (CH_2), 72.9 (CH_2), 71.4 (CH_2), 69.73 (CH), 69.69 (CH), 69.4 (CH_2), 68.8 (CH_2), 31.9 (CH_2), 29.66 (CH_2), 29.64 (CH_2), 29.63 (CH_2), 29.61 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{73}H_{88}O_{10}Na$ $[M + Na]^+$ 1147.6270; found 1147.6305.

(2*S*,3*S*,4*R*,5*S*)-3,4,5-Tri-*O*-benzyl-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-hexacosanoylamino-octadec-6-en-1,3,4,5-tetraol (13a): Diisopropyl azodicarboxylate (208 μL, 1.08 mmol) was added to a solution of alcohol **11a** (400 mg, 0.36 mmol) and triphenylphosphane (280 mg, 1.08 mmol) in anhydrous THF (4 mL) at 0 °C, and then diphenylphosphoryl azide (252 μL, 1.16 mmol) was added dropwise. After the addition was complete, the reaction mixture was brought to room temperature and stirred for 1 h. When the reaction was complete, the mixture was diluted with EtOAc (40 mL), and the mixture was washed with water (20 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give compound **12a** (388 mg, 94%). Because the olefin in **12a** reacted with the azido group in an intramolecular cycloaddition reaction, we used compound **12a** in the next step directly without characterization.

Azide **12a** (276 mg, 0.24 mmol), triphenylphosphane (126 mg, 0.48 mmol), pyridine (1 mL), water (300 μL), and tetrahydrofuran (3 mL) were added to a round-bottomed flask, and the mixolvent was evaporated in vacuo. The crude amine was dissolved in CH_2Cl_2 (3 mL) at room temperature, 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimidehydrochloride (EDC; 83 mg, 0.43 mmol), hexaeicosanoic acid (123 mg, 0.31 mmol), and HOBt (58 mg, 0.43 mmol) were sequentially added to the solution, and the mixture was stirred for 12 h. The reaction mixture was diluted with EtOAc, and the resulting mixture was washed with water. The organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give amide **13a** (271 mg, 75%). R_f = 0.4 (EtOAc/Hex, 1:5). $[\alpha]_D^{28}$ = +27.2 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3355, 2924, 2360, 1674, 1455, 1098 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 70 H), 5.97–5.94 (m, 2 H), 5.73 (dt, *J* = 15.6 Hz, 1 H), 5.64 (dt, *J* = 11.2 Hz, 1 H), 5.50 (t, *J* = 12.0 Hz, 2 H), 4.90 (d, *J* = 11.6 Hz, 2 H), 4.85 (t, *J* = 3.6 Hz, 2 H), 4.78–4.67 (m, 10 H), 4.62 (d, *J* = 11.6 Hz, 1 H), 4.61 (d, *J* = 12.4 Hz, 1 H), 4.58–4.51 (m, 6 H), 4.48–4.39 (m, 8 H), 4.35 (d, *J* = 11.6 Hz, 2 H), 4.30 (m, *J* = 11.6 Hz, 1 H), 4.29 (d, *J* = 11.6 Hz, 1 H), 4.04–3.98 (m, 4 H), 3.94–3.86 (m, 6 H), 3.84–3.73 (m, 4 H), 3.69–3.63 (m, 2 H), 3.50–3.43 (m, 4 H), 2.05–1.85 (m, 8 H), 1.83–1.71 (m, 12 H), 1.45–1.07 (m, 124 H), 0.88 (t, *J* = 6.8 Hz, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8 (C), 172.2 (C), 138.8 (C), 138.7 (C), 138.68 (C), 138.66 (C), 138.62 (C), 138.60 (2 C), 138.56 (2 C), 138.53 (C), 138.45 (C), 138.4 (C), 137.9 (C), 137.8 (C), 136.2 (CH), 135.4 (CH), 128.31 (6 CH), 128.25 (6 CH), 128.21 (6 CH), 128.18 (7 CH), 127.94 (4 CH), 127.89 (4 CH), 127.84 (5 CH), 127.82 (7 CH), 127.78 (3 CH), 127.7 (CH), 127.6 (CH), 127.54 (3 CH), 127.51 (3 CH), 127.44 (2 CH), 127.42 (2 CH), 127.37 (2 CH), 127.35 (2 CH), 127.30 (3 CH), 127.28 (3 CH), 127.2 (CH), 126.9 (CH), 98.8 (CH), 98.7 (CH), 82.8 (CH), 82.4 (CH), 81.2 (CH), 79.20 (CH), 79.18 (CH), 79.08 (CH), 79.05 (CH), 76.6 (2 CH), 75.1 (CH), 74.8 (2 CH), 74.7 (2 CH_2), 74.4 (CH_2), 74.0 (CH_2), 73.5 (CH_2), 73.4 (CH_2), 73.32 (CH_2), 73.31 (CH_2), 73.28 (CH_2), 72.9 (CH_2), 72.8 (CH_2), 72.7 (CH_2), 70.1 (CH_2), 69.9 (CH_2), 69.51 (CH), 69.46 (CH), 68.9 (CH_2), 68.8 (CH_2), 68.1 (CH_2), 67.8 (CH_2), 50.3 (CH), 50.0 (CH),

36.59 (CH_2), 36.55 (CH_2), 32.4 (CH_2), 31.9 (5 CH_2), 29.71 (13 CH_2), 29.68 (13 CH_2), 29.64 (5 CH_2), 29.59 (5 CH_2), 29.43 (5 CH_2), 29.36 (5 CH_2), 29.3 (5 CH_2), 29.1 (CH_2), 28.0 (CH_2), 25.64 (CH_2), 26.61 (CH_2), 22.7 (5 CH_2) 14.1 (4 CH_3) ppm. HRMS (ESI): calcd. for $C_{99}H_{139}O_{10}NNa$ $[M + Na]^+$ 1525.0291; found 1525.0275.

(2*S*,3*R*,4*R*,5*S*,6*Z*)-3,4,5-Tri-*O*-benzyl-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-hexacosanoylamino-octadec-6-en-1,3,4,5-tetraol (13b): Diisopropyl azodicarboxylate (364 μL, 1.85 mmol) was added to a solution of alcohol **11b** (520 mg, 0.46 mmol) and triphenylphosphane (485 mg, 1.85 mmol) in anhydrous THF (5 mL) at 0 °C, and then diphenylphosphoryl azide (431 μL, 1.94 mmol) was added dropwise. After the addition was complete, the reaction mixture was brought to room temperature and stirred for 1 h. When the reaction was complete, the mixture was diluted with EtOAc (20 mL), and the mixture was washed with water (10 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give compound **12b** (506 mg, 95%).

Azido compound **12b** (405 mg, 0.35 mmol), triphenylphosphane (185 mg, 0.74 mmol), pyridine (1.3 mL), water (400 μL), and tetrahydrofuran (4 mL) were added to a round-bottomed flask, and the mixture was warmed to 60 °C. The mixture was stirred for 12 h, then the solvent was evaporated in vacuo. The crude amine was dissolved in CH_2Cl_2 (4 mL) at room temperature, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 121 mg, 0.63 mmol), hexaeicosanoic acid (181 mg, 0.46 mmol), and HOBt (86 mg, 0.63 mmol) were sequentially added, and the resulting mixture was stirred for 12 h. The reaction mixture was diluted with EtOAc, and the resulting mixture was washed with water. The organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give amide **13b** (327 mg, 62%). R_f = 0.4 (EtOAc/Hex, 1:5). $[\alpha]_D^{25}$ = +30.8 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 2924, 2360, 1717, 1455, 1230 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.14 (m, 35 H, ArH), 5.89 (d, *J* = 9.6 Hz, 1 H, NH), 5.62–5.60 (m, 2 H, 6-H, 7-H), 4.88 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.80 (d, *J* = 3.6 Hz, 1 H, 1′-H), 4.78 (d, *J* = 11.2 Hz, 1 H, CH_2Ph), 4.72–4.48 (m, 11 H, CH_2Ph, 2-H, 5-H), 4.40 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.35 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.29 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.15 (dd, *J* = 8.0, 2.0 Hz, 1 H, 3-H), 3.93–3.90 (m, 2 H, 2′-H, 5′-H), 3.80–3.75 (m, 2 H, 3′-H, 4′-H), 3.66–3.54 (m, 2 H, 1a-H, 1b-H), 3.51 (dd, *J* = 8.0, 3.2 Hz, 1 H, 4-H), 3.47–3.38 (m, 2 H, 6′a-H, 6′b-H), 2.12–1.91 (m, 4 H, 8a-H, 8b-H, CH_2), 1.58–1.50 (m, 2 H, CH_2), 1.30–1.17 (m, 62 H, CH_2), 0.88 (t, *J* = 4.8 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (C), 138.9 (C), 138.8 (C), 138.67 (C), 138.66 (C), 137.53 (C), 137.48 (C), 137.9 (C), 135.0 (CH), 128.3 (4 CH), 128.24 (4 CH), 128.22 (4 CH), 128.18 (4 CH), 128.1 (4 CH), 128.0 (4 CH), 127.7 (4 CH), 127.6 (CH), 127.5 (CH), 127.42 (4 CH), 127.40 (CH), 127.3 (CH), 98.4 (CH), 84.0 (CH), 78.7 (CH), 78.6 (CH), 76.63 (CH), 75.56 (CH_2), 75.0 (CH), 74.9 (CH_2), 74.7 (CH_2), 74.2 (CH), 73.4 (CH_2), 73.2 (CH_2), 72.9 (CH_2), 70.4 (CH_2), 69.7 (CH), 69.0 (CH_2), 68.7 (CH_2), 48.6 (CH), 36.7 (CH_2), 31.9 (3 CH_2), 29.8 (CH_2), 29.70 (9 CH_2), 29.68 (9 CH_2), 29.64 (CH_2), 29.60 (CH_2), 29.5 (CH_2), 29.41 (CH_2), 29.36 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 25.7 (CH_2), 22.7 (3 CH_2), 14.1 (2 CH_3) ppm. HRMS (ESI): calcd. for $C_{99}H_{140}O_{10}N$ $[M + H]^+$ 1503.0512; found 1503.0472.

(2*S*,3*R*,4*R*,5*R*,6*Z*)-3,4,5-Tri-*O*-benzyl-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-hexacosanoylamino-octadec-6-en-1,3,4,5-tetraol (13c): Diisopropyl azodicarboxylate (530 μL, 2.71 mmol) was added to a solution of alcohol **11c** (760 mg, 0.70 mmol) and triphenylphosphane (710 mg, 2.71 mmol) in anhydrous THF (10 mL) at 0 °C, and then diphenylphosphoryl azide (610 μL, 2.80 mmol) was added dropwise. After the addition was complete, the reaction mixture was brought to room temperature and stirred for 1 h. When the reaction was complete, the mixture was diluted with EtOAc (100 mL), and the mixture was washed with water (50 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give compound **12c** (680 mg, 88%).

Azido compound **12c** (260 mg, 0.23 mmol), triphenylphosphane (120 mg, 0.46 mmol), pyridine (825 μL), water (270 μL), and tetrahydrofuran (2.5 mL) were added to a round-bottomed flask, and the mixture was warmed to 60 °C. The mixture was stirred for 12 h, then the solvent was evaporated in vacuo. The crude amine was dissolved in CH_2Cl_2 (2.5 mL) at room temperature, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 79 mg, 0.412 mmol), hexaeicosanoic acid (117 mg, 0.30 mmol), and HOBt (56 mg, 0.41 mmol) were sequentially added, and the mixture was stirred for 12 h. The reaction mixture was diluted with EtOAc, and the resulting mixture was washed with water. The organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give amide **13c** (205 mg, 60%). R_f = 0.4 (EtOAc/Hex, 1:5). $[\alpha]_D^{24}$ = +17.6 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2923, 1677, 1455, 1060 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.15 (m, 35 H, ArH), 6.00 (d, *J* = 9.0 Hz, 1 H, NH), 5.74–5.70 (m, 1 H, 7-H), 5.60 (t, *J* = 10.2 Hz, 1 H, 6-H), 4.88 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.86 (d, *J* = 12.6 Hz, 1 H, CH_2Ph), 4.798 (d, *J* = 10.8 Hz, 1 H, CH_2Ph), 4.795 (d, *J* = 3.6 Hz, 1 H, 1′-H) 4.73 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.71 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.63–4.58 (m, 4 H, CH_2Ph), 4.55 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.51 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.47 (dd, *J* = 10.2, 4.8 Hz, 1 H, 5-H), 4.38–4.34 (m, 2 H, 2-H, CH_2Ph), 4.263 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.260 (d, *J* = 12.0 Hz, 1 H, CH_2Ph) 4.00 (dd, *J* = 9.0, 3.0 Hz, 1 H, 2′-H), 3.92 (dd, *J* = 6.6, 2.4 Hz, 1 H, 4′-H), 3.88 (t, *J* = 6.6 Hz, 1 H, 5′-H), 3.80–3.76 (m, 3 H, 3-H, 3′-H, 4-H), 3.65 (t, *J* = 10.2 Hz, 1 H, 1a-H), 3.52 (dd, *J* = 9.6, 4.8 Hz, 1 H, 1b-H), 3.43–3.37 (m, 2 H, 6′a-H, 6′b-H), 2.26–2.19 (m, 1 H, 8a-H), 2.19–2.11 (m, 1 H, 8b-H), 2.06–1.97 (m, 2 H, CH_2), 1.52 (t, *J* = 7.2 Hz, 2 H, CH_2), 1.31–1.21 (m, 62 H, CH_2), 0.88 (t, *J* = 7.2 Hz, 6 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.8 (C), 139.0 (C), 138.94 (C), 138.86 (C), 138.8 (C), 137.62 (C), 138.55 (C), 137.8 (C), 136.9 (CH), 128.29 (5 CH), 128.26 (5 CH), 128.2 (4 CH), 128.13 (3 CH), 127.79 (3 CH), 127.76 (CH), 127.6 (3 CH), 127.5 (3 CH), 127.4 (3 CH), 127.34 (2 CH), 127.29 (2 CH), 127.18 (CH), 125.8 (CH), 98.5 (CH), 83.4 (CH), 78.8 (CH), 77.6 (CH), 76.6 (CH), 75.1 (CH_2), 74.88 (CH), 74.86 (CH), 74.8 (CH_2), 74.6 (CH_2), 73.4 (CH_2), 73.1 (2 CH_2), 69.8 (CH), 69.7 (CH_2), 69.0 (CH_2), 68.4 (CH_2), 49.7 (CH), 36.6 (CH_2), 31.9 (2 CH_2), 29.7 (23 CH_2), 29.5 (CH_2), 29.39 (CH_2), 29.35 (2 CH_2), 28.1 (CH_2), 25.7 (CH_2), 22.7 (2 CH_2), 14.1 (2 CH_3) ppm. HRMS (ESI): calcd. for $C_{99}H_{140}O_{10}N$ $[M + H]^+$ 1503.0515; found 1503.0472.

(2*S*,3*S*,4*R*,5*S*)-1-*O*-(α-D-Galactopyranosyl)-2-hexacosanoylamino-octadec-1,3,4,5-tetraol (2a): Compound **13a** (555 mg, 0.37 mmol) was dissolved in a mixed solvent of MeOH/$CHCl_3$ (3:1 v/v; 6 mL) at room temperature. $Pd(OH)_2$/C (Degussa type; 555 mg) was added to the solution, the reaction vessel was purged with hydrogen gas, and the mixture was stirred under 60 psi pressure at room temperature for 1 d. The resulting solution was filtered through Celite, the filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel to give compound **2a** (104.8 mg, 40%). R_f = 0.6 (MeOH/CH_2Cl_2, 1:7), m.p. 166–170 °C. $[\alpha]_D^{24}$ = +26.7 (*c* = 0.3, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 3294, 2825, 1466, 1071 cm^{-1}. ^1H NMR (400 MHz, C_5D_5N): δ = 8.54 (d, *J* = 8.4 Hz, 1 H, NH), 5.57 (d, *J* = 3.6 Hz, 1 H, 1′-H), 5.28–5.05

(m, 1 H, 2-H), 4.76 (dd, J = 8.4, 3.6 Hz, 1 H, 4-H), 4.70 (dd, J = 10.8, 6.0 Hz, 1 H, 1a-H), 4.64 (dd, J = 9.6, 3.6 Hz, 1 H, 2′-H), 4.59–4.49 (m, 3 H, 4′-H, 5-H, 5′-H), 4.44–4.34 (m, 4 H, 1b-H, 3′-H, 6′a-H, 6′b-H), 4.27 (d, J = 8.4 Hz, 1 H, 3-H), 2.41–2.37 (m, 2 H, CH_2), 2.12–1.86 (m, 4 H, CH_2), 1.78–1.70 (m, 4 H, CH_2), 1.64–1.13 (m, 62 H, CH_2), 0.84 (t, J = 6.8 Hz, 6 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9 (C), 100.7 (CH), 73.4 (CH), 73.2 (CH), 72.5 (CH), 71.1 (CH), 70.6 (CH), 70.4 (CH), 69.8 (CH), 67.6 (CH_2), 62.1 (CH_2), 51.2 (CH), 36.2 (CH_2), 34.5 (CH_2), 31.6 (5 CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (14 CH_2), 29.4 (2 CH_2), 29.33 (CH_2), 29.28 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 22.4 (5 CH_2), 13.8 (2 CH_3) ppm. HRMS (ESI): calcd. for $C_{50}H_{100}O_{10}N$ [M + H]$^+$ 874.7342; found 874.7336.

(2*S*,3*R*,4*R*,5*S*)-1-*O*-(α-D-Galactopyranosyl)-2-hexacosanoylamino-octadec-1,3,4,5-tetraol (2b): Compound **13b** (152 mg, 0.10 mmol) was dissolved in a mixed solvent of MeOH/$CHCl_3$ (3:1 v/v; 2 mL) at room temperature. $Pd(OH)_2$/C (Degussa type; 160 mg) was added to the solution, the reaction vessel was purged with hydrogen gas, and the mixture was stirred under 60 psi pressure at room temperature for 1 d. The resulting solution was filtered through Celite, the filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel to give compound **2b** (36.7 mg, 42%). R_f = 0.6 (MeOH/CH_2Cl_2, 1:7), m.p. 154–158 °C. $[\alpha]_D^{24}$ = –6.33 (c = 0.3, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 3079, 2850, 1162, 1042 cm^{-1}. ^{1}H NMR (400 MHz, C_5D_5N): δ = 8.84 (d, J = 8.4 Hz, 1 H, NH), 5.39 (d, J = 2.8 Hz, 1 H, 1′-H), 5.21–5.14 (m, 1 H, 2-H), 4.89–4.82 (m, 1 H, 4′-H), 4.69–4.31 (m, 8 H, 1a-H, 2′-H, 3-H, 4-H, 5-H, 5′-H, 6′a-H, 6′b-H), 4.23 (m, 1 H, 3′-H), 4.10–4.06 (m, 1 H, 1b-H), 2.56–2.49 (m, 2 H, CH_2), 2.04–1.08 (m, 70 H, CH_2), 0.85 (t, J = 4.8 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (C), 100.3 (CH), 74.2 (CH), 72.1 (CH), 71.6 (CH), 70.9 (CH), 70.1 (CH), 69.8 (2 CH), 68.4 (CH_2), 61.8 (CH_2), 50.6 (CH), 36.2 (CH_2), 34.5 (CH_2), 33.4 (CH_2), 31.59 (2 CH_2), 31.56 (3 CH_2), 29.8 (CH_2), 29.6 (2 CH_2), 29.5 (4 CH_2), 29.43 (4 CH_2), 29.42 (4 CH_2), 29.36 (3 CH_2), 29.3 (CH_2), 29.10 (2 CH_2), 29.05 (2 CH_2), 26.1 (CH_2), 26.0 (CH_2), 22.4 (3 CH_2), 14.3 (2 CH_3) ppm. HRMS (ESI): calcd. for $C_{50}H_{100}O_{10}N$ [M + H]$^+$ 874.7342; found 874.7336.

(2*S*,3*R*,4*R*,5*R*)-1-*O*-(α-D-Galactopyranosyl)-2-hexacosanoylamino-octadec-1,3,4,5-tetraol (2c): Compound **13c** (133 mg, 0.09 mmol) was dissolved in a mixed solvent of MeOH/$CHCl_3$ (3:1 v/v; 2 mL) at room temperature. $Pd(OH)_2$/C (Degussa type; 133 mg) was added to the solution, the reaction vessel was purged with hydrogen gas, and the mixture was stirred under 60 psi pressure at room temperature for 1 d. The resulting solution was filtered through Celite, the filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel to give compound **2c** (40.1 mg, 51%). R_f = 0.6 (MeOH/CH_2Cl_2, 1:7), m.p. 146–150 °C. $[\alpha]_D^{24}$ = +28.8 (c = 0.3, $CHCl_3$/MeOH). IR (KBr): $\tilde{\nu}$ = 3280, 2850, 1648, 1454 cm^{-1}. ^{1}H NMR (600 MHz, C_5D_5N): δ = 8.47 (d, J = 8.4 Hz, 1 H, NH), 5.48 (d, J = 3.6 Hz, 1 H, 1′-H), 5.15–5.11 (m, 1 H, 2-H), 5.00–4.97 (m, 1 H, 1a-H), 4.64 (dd, J = 9.6, 3.6 Hz, 1 H, 2′-H), 4.57–4.55 (m, 2 H, 4-H, 5′-H), 4.48–4.38 (m, 5 H, 3-H, 3′-H, 5-H, 6′a-H, 6′b-H), 4.33 (t, J = 6.6 Hz, 1 H, 4′-H), 4.24 (m, 1 H, 1b-H), 2.49–2.43 (m, 4 H, CH_2), 2.26–2.19 (m, 2 H, CH_2), 1.92–1.83 (m, 2 H, CH_2), 1.80–1.74 (m, 2 H, CH_2), 1.68–1.56 (m, 2 H, CH_2), 1.41–1.16 (m, 60 H, CH_2), 0.84 (t, J = 7.2 Hz, 6 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.1 (C), 101.1 (CH), 75.1 (CH), 72.9 (CH), 72.4 (CH), 71.6 (CH), 70.8 (CH), 70.6 (CH), 70.4 (CH), 69.1 (CH_2), 62.5 (CH_2), 53.1 (CH), 36.8 (CH_2), 34.6 (CH_2), 32.1 (4 CH_2), 30.3 (CH_2), 30.1 (CH_2), 30.0 (13 CH_2), 29.9 (2 CH_2), 29.82 (CH_2), 29.77 (CH_2), 29.7 (CH_2), 29.6 (4 CH_2), 26.5 (CH_2), 26.3 (CH_2), 22.9 (4 CH_2), 14.3 (2 CH_3) ppm. HRMS (ESI): calcd. for $C_{50}H_{100}O_{10}N$ [M + H]$^+$ 874.7342; found 874.7349.

4-Methylphenyl 3,4-*O*-Isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-galactopyranoside (15): Diol **14** (153 mg, 0.47 mmol) was dissolved in anhydrous dichloromethane (1.5 mL), and imidazole (96 mg, 1.41 mmol) was added. This was immediately followed by the addition of *tert*-butylchlorodiphenylsilane (126 μL, 0.49 mmol). The mixture was stirred at room temperature for 2 h, then the reaction was quenched by the addition of methanol (2 mL), and the mixture was concentrated to dryness under reduced pressure. H_2O (5 mL) was added to the residue, and the mixture was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel to give compound **15** (222 mg, 84%) as a white solid. R_f = 0.3 (EtOAc/Hex, 1:4). $[\alpha]_D^{28}$ = –9.7 (c = 1.1, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 3424, 3062, 2935, 2863, 1594, 1483, 1229, 1104 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.69 (m, 4 H, ArH), 7.45–7.34 (m, 8 H, ArH), 7.07 (d, J = 8.0 Hz, 2 H, ArH), 4.38 (d, J = 10.0 Hz, 1 H, 1-H), 4.27 (dd, J = 5.6, 2.0 Hz, 1 H, 4-H), 4.07 (dd, J = 7.0, 5.6 Hz, 1 H, 3-H), 3.99–3.91 (m, 2 H, 6a-H, 6b-H), 3.89–3.86 (m, 1 H, 5-H), 3.53 (ddd, J = 10.0, 7.0, 2.2 Hz, 1 H, 2-H), 2.52 (d, J = 2.2 Hz, 1 H, 2-OH), 2.31 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.06 (s, 9 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.1 (C), 135.59 (2 CH), 135.57 (2 CH), 133.3 (C), 132.9 (2 CH), 129.71 (2 CH), 129.67 (2 CH), 129.65 (C), 128.4 (C), 127.7 (2 CH), 127.6 (2 CH), 110.0 (C), 88.5 (CH), 78.9 (CH), 77.1 (CH), 73.2 (CH), 71.5 (CH), 62.8 (CH_2), 28.1 (CH_3), 16.7 (3 CH_3), 26.3 (CH_3), 21.1 (CH_3), 19.2 (C) ppm. HRMS (EI): calcd. for $C_{32}H_{40}O_5SSi$ [M]$^+$ 564.2366; found 564.2358.

4-Methylphenyl 3,4-*O*-Isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-talopyranoside (16): Alcohol **15** (2.6 g, 4.60 mmol) was dissolved in dichloromethane (520 mL). The round-bottomed flask containing the reaction mixture was wrapped in aluminum foil, and then Dess–Martin periodinane (3.9 g, 9.20 mmol) was added in the dark. The reaction mixture was stirred for 0.5 h, then further Dess–Martin periodinane (0.8 g, 1.92 mmol) was added, and the mixture was stirred for a further 1 h. After the reaction was complete, the reaction mixture was treated with satd. $NaHCO_3$/$Na_2S_2O_3$ solution (1:1 v/v; 200 mL), and the resulting mixture was stirred for 1 h. Then, the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, and the solvent was evaporated. The residue was dried under high vacuum for 1 h, then it was dissolved in anhydrous methanol (260 mL), and then sodium borohydride (345 mg, 9.20 mmol) was added. The mixture was stirred for 10 min, then the reaction was quenched with acetic acid, and the solvent was evaporated. The residue was diluted with water, and the mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give compound **16** (2.32 g, 89%) as a white solid. R_f = 0.3 (EtOAc/Hex, 1:5). $[\alpha]_D^{27}$ = –69.7 (c = 1.2, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 3680, 3067, 2936, 2862, 1590, 1380, 1213, 1106 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.69 (m, 4 H, ArH), 7.42–7.35 (m, 8 H, ArH), 7.05 (d, J = 8.0 Hz, 2 H, ArH), 4.68 (d, J = 0.8 Hz, 1 H, 1-H), 4.22–4.18 (m, 2 H, 3-H, 4-H), 4.02–3.94 (m, 3 H, 2-H, 6a-H, 6b-H), 3.87 (t, J = 6.4 Hz, 1 H, 5-H), 2.53 (d, J = 9.2 Hz, 1 H, 2-OH), 2.30 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.06 (s, 9 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 137.3 (C), 135.60 (C), 135.58 (4 CH), 133.2 (C), 131.6 (C), 131.4 (2 CH), 129.7 (4 CH), 127.7 (2 CH), 127.6 (2 CH), 109.9 (C), 88.2 (CH), 76.8 (CH), 73.9 (CH), 70.9 (CH), 68.0

(CH), 62.9 (CH_2), 26.7 (3 CH_3), 25.7 (CH_3), 25.4 (CH_3), 21.1 (CH_3), 19.2 (C) ppm. HRMS (EI): calcd. for $C_{32}H_{40}O_5SSi$ $[M]^+$ 564.2366; found 564.2354.

4-Methylphenyl 6-*O*-*tert*-Butyldiphenylsilyl-1-thio-β-D-talopyranoside (17): A solution of **16** (2.8 g, 4.96 mmol) in a mixture of ethanol (25 mL), acetic acid (50 mL), and water (10 mL) was stirred at 55 °C for 3 h. The reaction mixture was concentrated, and the residue was purified by column chromatography to give compound **17** (2.52 g, 97%) as a white solid. R_f = 0.2 (EtOAc/Hex, 1:4). $[\alpha]_D^{26}$ = –75.8 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3425, 2958, 1644, 1493, 1111 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.71–7.70 (m, 4 H, ArH), 7.44–7.35 (m, 8 H, ArH), 7.04 (d, *J* = 7.8 Hz, 2 H, ArH), 4.70 (d, *J* = 0.6 Hz, 1 H, 1-H), 4.08 (d, *J* = 4.8 Hz, 1 H, 3-H), 4.03 (s, 1 H, 2-H), 3.97 (d, *J* = 5.4 Hz, 2 H, 6a-H, 6b-H), 3.80 (s, 1 H, 3-OH), 3.71 (s, 1 H, 2-OH), 3.54 (s, 1 H, 4-H), 3.44 (t, *J* = 4.8 Hz, 1 H, 5-H), 1.87 (s, 1 H, 4-OH), 2.31 (s, 3 H, CH_3), 1.05 (s, 9 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 137.4 (C), 135.6 (2 CH), 135.5 (2 CH), 132.8 (C), 132.6 (C), 131.5 (2 CH), 131.0 (C), 129.9 (2 CH), 129.7 (2 CH), 127.8 (4 CH), 88.9 (CH), 78.63 (CH), 78.59 (CH), 73.0 (CH), 69.9 (CH), 64.2 (CH_2), 26.8 (3 CH_3), 21.1 (CH_3), 19.1 (C) ppm. HRMS (ESI): calcd. for $C_{29}H_{36}O_5NaSSi$ $[M]^+$ 547.1945; found 547.1944.

4-Methylphenyl 2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-talopyranoside (18): Triol **17** (180 mg, 0.34 mmol) and benzyl bromide (184 μL, 1.54 mmol) were dissolved in *N*,*N*-dimethylformamide (1.8 mL). The mixture was cooled to 0 °C, and sodium hydride (3× 15 mg, 3× 0.38 mmol) was added. The mixture was stirred at this temperature for 1.5 h, then it was stirred at room temperature for 1 h. Then the reaction mixture was cooled again in ice bath, water (2 mL) was added dropwise, and the mixture was concentrated in vacuo. The residue was diluted with water (5 mL), and the mixture was extracted with ethyl acetate (3× 15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **18** (253 mg, 94%) as a white solid. R_f = 0.46 (EtOAc/Hex, 1:5). $[\alpha]_D^{25}$ = –79.7 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 2930, 1636, 1492, 1109 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.55 (m, 4 H, ArH), 7.54–7.01 (m, 22 H, ArH), 6.90 (d, *J* = 8.0 Hz, 2 H, ArH), 4.96 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.89 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.86 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.62 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.57 (d, *J* = 1.4 Hz, 1 H, 1-H), 4.51 (s, 2 H, CH_2Ph), 4.03 (t, *J* = 1.4 Hz, 1 H, 2-H), 3.90 (dd, *J* = 10.4, 6.4 Hz, 1 H, 6a-H), 3.81–3.77 (m, 2 H, 4-H, 6b-H), 3.39–3.34 (m, 2 H, 3-H, 5-H), 2.19 (s, 3 H, CH_3), 0.97 (s, 9 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9 (C), 138.7 (C), 137.8 (C), 136.7 (C), 135.6 (2 CH), 135.5 (2 CH), 133.39 (C), 133.37 (C), 132.7 (C), 130.8 (2 CH), 129.6 (2 CH), 129.5 (2 CH), 128.5 (2 CH), 128.3 (2 CH), 128.1 (2 CH), 127.93 (2 CH), 127.91 (2 CH), 127.7 (CH), 127.64 (2 CH), 127.63 (2 CH), 127.24 (2 CH), 127.22 (CH), 127.1 (CH), 89.4 (CH), 81.1 (CH), 80.5 (CH), 76.3 (CH), 74.7 (CH_2), 74.0 (CH_2), 71.9 (CH), 70.9 (CH_2), 63.4 (CH_2), 26.9 (3 CH_3), 21.0 (CH_3), 19.2 (C) ppm. HRMS (ESI): calcd. for $C_{50}H_{54}O_5NaSSi$ $[M + Na]^+$ 817.3353; found 817.3348.

2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-D-talopyranose (19): NBS (173 mg, 0.97 mmol) was added to a solution of **18** (253 mg, 0.32 mmol) in acetone/H_2O (9:1 v/v; 3.3 mL), and the mixture was stirred at 0 °C for 1 h. Saturated $NaHCO_3$ was added to quench the reaction, and the mixture was concentrated under reduced pressure. The residue was diluted with water (2 mL), and the mixture was extracted with ethyl acetate (3× 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel to give **19** (201 mg, 90%) as a colourless oil. R_f = 0.2 (EtOAc/Hex, 1:4). $[\alpha]_D^{26}$ = –28.6 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3425, 2858, 1641, 1102 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.64–7.63 (m, 6 H, ArH), 7.61–7.60 (m, 2 H, ArH), 7.42–7.21 (m, 41 H, ArH), 5.24 (s, 1 H), 5.06 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.96 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.95 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.83–4.80 (m, 3 H, CH_2Ph), 4.73–4.69 (m, 2 H, CH_2Ph), 4.67 (d, *J* = 12.6 Hz, 1 H, CH_2Ph), 4.61 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.57 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.55 (s, 1 H), 4.54 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.10–4.00 (m, 5 H), 3.96 (s, 1 H), 3.87–3.85 (m, 2 H), 3.82 (s, 1 H), 3.80 (t, *J* = 3.0 Hz, 1 H), 3.69 (s, 1 H), 3.49 (t, *J* = 3.0 Hz, 1 H), 3.50–3.43 (m, 1 H), 2.58 (s, 1 H, 1-OH), 1.08 (s, 9 H, CH_3), 1.05 (s, 9 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.0 (C), 138.9 (C), 138.6 (C), 138.3 (C), 137.9 (C), 137.7 (C), 135.59 (4 CH), 135.58 (4 CH), 135.53 (4 CH), 135.50 (4 CH), 133.6 (C), 133.4 (C), 133.22 (C), 133.17 (C),129.7 (2 CH), 129.6 (2 CH), 128.6 (2 CH), 128.5 (2 CH), 128.4 (2 CH), 128.3 (2 CH), 128.14 (2 CH), 128.08 (3 CH), 128.01 (3 CH), 127.99 (3 CH), 127.9 (CH), 127.8 (CH), 127.7 (3 CH), 127.63 (2 CH), 127.60 (2 CH), 127.5 (CH), 127.4 (CH), 127.3 (2 CH), 127.2 (2 CH), 94.0 (CH), 93.7 (CH), 80.3 (CH), 76.6 (CH), 75.5 (CH), 74.8 (CH_2, CH), 74.5 (CH), 74.3 (CH_2), 73.7 (CH_2), 73.5 (CH), 73.0 (CH_2), 72.5 (CH), 71.7 (CH), 71.2 (2 CH_2), 62.6 (CH_2), 61.8 (CH_2), 26.94 (3 CH_3), 26.90 (3 CH_3), 19.2 (2 C) ppm. HRMS (ESI): calcd. for $C_{43}H_{48}O_6NaSi$ $[M + Na]^+$ 711.3112; found 711.3124.

(2*R*,3*S*,4*R*,5*R*,6*Z*)-3,4,5-Tri-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-octadec-6-ene-1,2,3,4,5-pentaol (20): A solution of hemiacetal **19** (971 mg, 1.41 mmol) and dodecyltriphenylphosphonium bromide (2.9 g, 5.65 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to –20 °C under nitrogen. Lithium hexamethyldisilazide (1.0 M solution in THF; 5.6 mL, 5.65 mmol) was slowly added, and the reaction mixture was stirred for a further 8 h at the same temperature. Ammonium chloride (saturated aq.; 10 mL) was added to quench the reaction, and the mixture was extracted with EtOAc (3× 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to give olefin **20** (956 mg, 80%; **20*Z*/20**E = 1.6:1) as a colourless oil.

Data for **20***Z*: R_f = 0.33 (EtOAc/Hex, 1:10). $[\alpha]_D^{26}$ = –21.5 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3423, 2926, 2855, 1642, 1493, 1109 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.54 (m, 4 H, ArH), 7.34–7.11 (m, 21 H, ArH), 5.68 (dt, *J* = 10.8, 7.6 Hz, 1 H, 7-H), 5.44 (dt, *J* = 10.8, 9.6 Hz, 1 H, 6-H), 4.66 (d, *J* = 11.2 Hz, 1 H, CH_2Ph), 4.58 (d, *J* = 11.2 Hz, 1 H, CH_2Ph), 4.55 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.53 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.45 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.39 (dd, *J* = 9.6, 5.2 Hz, 1 H, 5-H), 4.29 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.08 (m, 1 H, 2-H), 3.91 (dd, *J* = 5.0, 1.6 Hz, 1 H, 3-H), 3.83 (t, *J* = 5.0 Hz, 1 H, 4-H), 3.72–3.64 (m, 2 H, 1a-H, 1b-H), 3.24 (d, *J* = 4.8 Hz, 1 H, 2-OH), 1.97–1.81 (m, 2 H, 8-H), 1.24–1.13 (m, 18 H, CH_2), 0.97 (s, 9 H, CH_3), 0.81 (t, *J* = 6.8 Hz, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.3 (C), 138.2 (C), 138.2 (C), 136.4 (CH), 135.6 (4 CH), 133.4 (C), 133.3 (C), 129.6 (2 CH), 128.2 (5 CH), 128.0 (3 CH), 127.63 (8 CH), 127.57 (CH), 127.5 (CH), 127.4 (CH), 126.6 (CH), 81.9 (CH), 76.9 (CH), 74.3 (CH_2), 74.2 (CH), 73.2 (CH_2), 71.7 (CH), 69.9 (CH_2), 64.2 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.63 (CH_2), 29.61 (2 CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 26.9 (3 CH_3), 22.7 (CH_2), 19.2 (C), 14.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{55}H_{72}O_5NaSi$ $[M + Na]^+$ 863.5041; found 863.5054.

Data for **20**E: R_f = 0.3 (EtOAc/Hex, 1:10). $[\alpha]_D^{26}$ = –15.7 (*c* = 1.1, CH_2Cl_3). IR ($CHCl_3$): $\tilde{\nu}$ = 3419, 3066, 2926, 1639, 1109 cm^{-1}. ^1H

NMR (600 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 4 H, ArH), 7.41–7.15 (m, 21 H, ArH), 5.66–5.45 (m, 2 H, 6-H, 7-H), 5.55 (dd, *J* = 15.0, 8.4 Hz, 1 H, 6-H), 4.80 (d, *J* = 11.1 Hz, 1 H, CH_2Ph), 4.67 (d, *J* = 11.1 Hz, 1 H, CH_2Ph), 4.62 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.59 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.51 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.35 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.03 (dt, *J* = 9.6, 9.0 Hz, 1 H, 2-H), 4.04 (dd, *J* = 8.4, 4.2 Hz, 1 H, 5-H), 3.93–3.89 (m, 2 H, 3-H, 4-H), 3.75–3.70 (m, 2 H, 1a-H, 1b-H), 3.02 (d, *J* = 4.8 Hz, 1 H, 2-OH), 2.09 (dt, *J* = 7.2, 6.6 Hz, 2 H, 8-H), 1.40–1.36 (m, 2 H, CH_2), 1.30–1.25 (m, 16 H, CH_2), 1.04 (s, 9 H, CH_3), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.5 (C), 138.4 (C), 138.1 (C), 137.5 (CH), 135.6 (5 CH), 133.4 (C), 133.3 (C), 129.6 (2 CH), 128.29 (2 CH), 128.27 (2 CH), 128.2 (2 CH), 128.0 (2 CH), 127.8 (2 CH), 127.66 (2 CH), 127.65 (2 CH), 127.6 (2 CH), 127.5 (CH), 127.3 (CH), 126.6 (CH), 81.6 (CH), 80.7 (CH), 76.8 (CH), 74.3 (CH_2), 73.4 (CH_2), 71.2 (CH), 69.7 (CH_2), 64.3 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (2 CH_2), 29.5 (CH_2), 29.3 (2 CH_2), 29.2 (CH_2), 26.9 (3 CH_3), 22.7 (CH_2), 19.2 (C), 14.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{55}H_{72}O_5NaSi$ $[M + Na]^+$ 863.5041; found 863.5059.

(2*R*,3*R*,4*R*,5*R*,6*Z*)-2-Azido-3,4,5-tri-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-octadec-6-ene-1,3,4,5-tetraol (21): A solution of olefin **20** (106 mg, 0.12 mmol) and triphenylphosphane (99 mg, 0.38 mmol) in anhydrous THF (1 mL) was stirred at 0 °C. Diisopropyl azodicarboxylate (72 μL, 0.38 mmol) and diphenylphosphoryl azide (87 μL, 0.40 mmol) were slowly added to the reaction mixture at 0 °C. Then the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was purified by column chromatography to give azide **21** (79 mg, 72%) as a colourless oil. R_f = 0.54 (EtOAc/Hex, 1:15). $[\alpha]_D^{25}$ = –13.1 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2926, 2855, 2098, 1458, 1109, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.55 (m, 5 H, ArH), 7.35–7.14 (m, 18 H, ArH), 7.02–7.00 (m, 2 H, ArH), 5.66 (dt, *J* = 10.8, 7.6 Hz, 1 H, 7-H), 5.38 (t, *J* = 9.6 Hz, 1 H, 6-H), 4.63 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.63 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.46–4.38 (m, 4 H, CH_2Ph, 5-H), 4.24 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 3.94–3.87 (m, 2 H, 1a-H, 2-H), 3.74 (dd, *J* = 10.4, 8.0 Hz, 1 H, 1b-H), 3.68 (t, *J* = 5.0 Hz, 1 H, 4-H), 3.57 (t, *J* = 5.0 Hz, 1 H, 3-H), 1.98–1.83 (m, 2 H, 8-H), 1.22–1.12 (m, 18 H, CH_2), 0.98 (s, 9 H, CH_3), 0.80 (t, *J* = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5 (C), 138.4 (C), 138.0 (C), 136.3 (CH), 135.61 (3 CH), 134.8 (2 CH), 133.2 (C), 133.1 (C), 129.6 (2 CH), 128.23 (2 CH), 128.19 (2 CH), 128.1 (2 CH), 127.8 (2 CH), 127.69 (CH), 127.66 (3 CH), 127.6 (CH), 127.5 (2 CH), 127.4 (CH), 127.4 (2 CH), 126.7 (CH), 80.8 (CH), 78.7 (CH), 74.4 (CH), 73.9 (CH_2), 72.9 (CH_2), 69.9 (CH_2), 64.8 (CH), 64.7 (CH_2), 31.9 (CH_2), 29.68 (CH_2), 29.65 (2 CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.40 (CH_2), 29.35 (CH_2), 28.1 (CH_2), 26.7 (2 CH_3), 26.5 (CH_3), 22.7 (CH_2), 19.1 (C), 14.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{55}H_{71}O_4N_3NaSi$ $[M + Na]^+$ 888.5106; found 888.5105.

(2*R*,3*R*,4*R*,5*R*,6*Z*)-2-Azido-3,4,5-tribenzyloxy-6-octadecene-1-ol (22)

Method A: Compound **21** (90 mg, 0.1 mmol) was dissolved in THF (1 mL), and TBAF (1 M solution in THF; 155 μL) was added. The brown reaction mixture was stirred at room temperature until TLC indicated that all of the starting material had been consumed. The solvent was evaporated, and the residue was purified by column chromatography to give compound **22** (36.6 mg, 56%) as a colourless oil.

Method B: A solution of alcohol **21** (2.32 g, 2.76 mmol) and triphenylphosphane (2.2 g, 8.27 mmol) in THF (23 mL) was stirred at 0 °C, and diisopropyl azodicarboxylate (1.6 mL, 8.27 mmol) and diphenylphosphoryl azide (1.9 mL, 8.8 mmol) were slowly added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated, the residue was dissolved in THF (23 mL), and TBAF (1 M solution in THF; 11.5 mL) was added. The brown reaction mixture was stirred at room temperature until TLC indicated that the starting material had been completely consumed. The solvent was evaporated, and the residue was purified by column chromatography to give compound **22** (1.15 g, 67% over two steps) as a colourless oil. R_f = 0.6 (EtOAc/Hex, 1:10). $[\alpha]_D^{26}$ = –68.53 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3030, 2925, 2098, 1496, 1068, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 15 H, ArH), 5.79 (dt, *J* = 10.8, 7.6 Hz, 1 H, 7-H), 5.44 (dd, *J* = 12.4, 10.8 Hz, 1 H, 6-H), 4.73 (d, *J* = 11.2 Hz, 1 H, CH_2Ph), 4.65 (d, *J* = 11.2 Hz, 2 H, CH_2Ph), 4.60 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.57 (d, *J* = 11.2 Hz, 1 H, CH_2Ph), 4.45 (dd, *J* = 9.2, 6.0 Hz, 1 H, 5-H), 4.32 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 3.89–3.70 (m, 5 H, 1a-H, 1b-H, 2-H, 3-H, 4-H), 2.55 (t, *J* = 5.6 Hz, 1 H, 1-OH), 2.07–1.92 (m, 2 H, 8-H), 1.33–1.21 (m, 18 H, CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (C), 137.8 (C), 137.7 (C), 136.8 (CH), 128.4 (2 CH), 128.31 (2 CH), 128.27 (2 CH), 128.1 (2 CH), 127.80 (2 CH), 127.76 (2 CH), 127.7 (2 CH), 127.6 (CH), 126.6 (CH), 80.5 (CH), 79.8 (CH), 74.4 (CH_2), 74.0 (CH), 73.1 (CH_2), 69.9 (CH_2), 63.3 (CH), 62.1 (CH_2), 31.9 (CH_2), 29.64 (CH_2), 29.62 (2 CH_2), 29.59 (CH_2), 29.50 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{39}H_{53}O_4N_3Na$ $[M + Na]^+$ 650.3928; found 650.3938.

Tetrahydroxy-LCB Pentaacetate (24): Sodium (273 mg, 11.8 mmol) and THF (4 mL) were added into a two-necked flask equipped with a dry-ice condenser. The mixture was cooled to –78 °C, ammonia gas was condensed in the reaction vessel, and a solution of **22** (128 mg, 0.20 mmol) in THF (2 mL) was added to the flask. After 20 min, anhydrous ethanol (7 mL) was added to the reaction mixture. The reaction flask was allowed to warm up slowly to room temperature, and the mixture was concentrated in vacuo. A mixture of the crude tetrahydroxy-LCB **23**, pyridine (7 mL), DMAP (0.3 mg, 10 μmol), and acetic anhydride (3.5 mL) was stirred at room temperature overnight. Methanol (3.5 mL) was added to the reaction mixture to destroy the excess acetic anhydride, the mixture was stirred for 30 min, then it was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/Hex, 1:1) to give tetrahydroxy-LCB pentaacetate **24** (62.8 mg, 57% over two steps). The ^1H and ^{13}C NMR spectroscopic data of **24** was corroborated well with the literature report. R_f = 0.15 (EtOAc/Hex, 1:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3288, 2925, 2856, 1743, 1236 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 6.24 (d, *J* = 9.0 Hz, 1 H), 5.79 (dd, *J* = 9.0, 5.4 Hz, 1 H), 5.70 (dt, *J* = 10.8, 7.8 Hz, 1 H), 5.37 (dd, *J* = 10.8, 9.0 Hz, 1 H), 5.24 (t, *J* = 5.4 Hz, 1 H), 5.02 (t, *J* = 5.4 Hz, 1 H), 4.61–4.59 (m, 1 H), 4.16 (dd, *J* = 11.4, 5.4 Hz, 1 H), 4.07 (dd, *J* = 10.8, 4.2 Hz, 1 H), 2.11 (s, 3 H), 2.08 (s, 3 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 1.69 (s, 2 H), 1.34–1.24 (m, 18 H), 0.87 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.8 (C), 170.3 (C), 170.2 (2 C), 169.7 (C), 137.9 (CH), 122.3 (CH), 72.0 (CH), 71.6 (CH), 68.0 (CH), 62.4 (CH_2), 48.0 (CH), 31.9 (CH_2), 30.0 (2 CH_2), 29.63 (CH_2), 29.58 (CH_2), 29.5 (CH_2), 29.32 (CH_2), 29.28 (CH_2), 28.0 (CH_2), 23.3 (CH_3), 22.7 (CH_2), 21.1 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 14.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{28}H_{47}O_9NNa$ $[M + Na]^+$ 564.3143; found 564.3141.

(2*R*,3*R*,4*R*,5*R*,6*Z*)-2-Azido-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-3,4,5-tri-*O*-benzyl-octadec-6-ene-1,3,4,5-tetraol (25): Iodotrimethylsilane (58 μL, 0.39 mmol) was added to a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside

(181 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred for 20 min, then anhydrous toluene (2 mL) was added, and the mixture was azeotroped with toluene (3× 2 mL). The slightly yellow residue was dissolved in toluene (2 mL) and kept under nitrogen. In a separate flask, molecular sieves (4 Å; 100 mg), TBAI (344 mg, 0.93 mmol), acceptor **22** (65 mg, 0.10 mmol), and DIPEA (54 μL, 0.31 mmol) were added to toluene (1 mL). The mixture was stirred under nitrogen at 65 °C for 10 min. After the TBAI had dissolved, glycosyl iodide **4** was added to the reaction mixture by cannula, and the resulting mixture was stirred at 65 °C for 2.5 h. EtOAc (5 mL) was added, the mixture was cooled to 0 °C, and the white precipitate and molecular sieves were removed by filtration through Celite. The filtrate was washed with $Na_2S_2O_3$ (satd. aq.; 5 mL) and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography to give **25** (52 mg, 44%) as a colourless oil. R_f = 0.3 (EtOAc/Hex, 1:6). $[\alpha]_D^{24}$ = +16.9 (c = 1.8, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3030, 2922, 2098, 1492, 1455, 1099, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 35 H, ArH), 5.74 (dt, J = 10.6, 7.2 Hz, 1 H, 7-H), 5.48 (dd, J = 10.6, 6.8 Hz, 1 H, 6-H), 4.90 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.87 (d, J = 3.6 Hz, 1 H, 1′-H), 4.79 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.77 (d, J = 11.2 Hz, 1 H, CH_2Ph), 4.76 (d, J = 12.4 Hz, 1 H, CH_2Ph), 4.69 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.67 (d, J = 11.6 Hz, 2 H, CH_2Ph), 4.62 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.59–4.53 (m, 3 H, CH_2Ph, 5-H), 4.48 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.40 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.34 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.31 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.10–4.01 (m, 2 H, 2-H, 4′-H), 3.97–3.88 (m, 4 H, 1a-H, 2′-H, 3′-H, 5′-H), 3.84 (t, J = 4.4 Hz, 1 H, 4-H), 3.73 (t, J = 4.8 Hz, 1 H, 3-H), 3.65 (dd, J = 10.8, 8.0 Hz, 1 H, 1b-H), 3.48–3.37 (m, 2 H, 6′a-H, 6′b-H), 2.06–1.90 (m, 2 H, 8-H), 1.29–1.22 (m, 18 H, CH_2), 0.88 (t, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8 (C), 138.7 (C), 138.64 (C), 138.60 (C), 138.4 (C), 138.05 (C), 137.9 (C), 136.5 (CH), 128.31 (2 CH), 128.27 (2 CH), 128.26 (2 CH), 128.24 (3 CH), 128.19 (2 CH), 128.17 (2 CH), 128.15 (2 CH), 127.9 (CH), 127.82 (2 CH), 127.78 (2 CH), 127.7 (2 CH), 127.61 (CH), 127.55 (2 CH), 127.51 (CH), 127.46 (CH), 127.43 (2 CH), 127.38 (2 CH), 127.36 (2 CH), 127.3 (2 CH), 126.2 (CH), 98.5 (CH), 80.8 (CH), 79.0 (CH), 78.8 (CH), 76.4 (CH), 75.0 (CH), 74.7 (CH_2), 74.5 (CH), 73.9 (CH_2), 73.4 (CH_2), 73.1 (2 CH_2), 73.0 (CH_2), 69.9 (CH_2), 69.5 (CH), 68.8 (CH_2), 68.4 (CH_2), 62.5 (CH), 31.9 (CH_2), 30.1 (CH_2), 29.70 (CH_2), 29.65 (2 CH_2), 29.5 (CH_2), 29.40 (2 CH_2), 29.36 (CH_2), 22.7 (CH_2), 14.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{73}H_{87}O_9N_3Na$ $[M + Na]^+$ 1172.6335; found 1172.6331.

(2*S*,3*R*,4*R*,5*R*,6*Z*)-2-Hexacosanoylamino-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-3,4,5-tri-*O*-benzyl-octadec-6-en-1,3,4,5-tetraol (26): Pyridine (413 μL) and water (104 μL) were sequentially added to a solution of compound **25** (135 mg, 117 μmol) in tetrahydrofuran (1.3 mL) at room temperature. The reaction flask was warmed up to 60 °C, triphenylphosphane (62 mg, 235 μmol) was added, and the mixture was stirred for 12 h. The reaction mixture was allowed to cool down slowly to room temperature, and the mixture was concentrated in vacuo for 3 h. This crude amine was dissolved in dichloromethane (1.3 mL) at room temperature, hexaeicosanoic acid (60 mg, 152 μmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 40 mg, 210 μmol), and HOBt (28 mg, 210 μmol) were sequentially added to the solution, and the mixture was stirred for 12 h. The reaction mixture was diluted with EtOAc (5 mL), and the resulting mixture was washed with water (2× 3 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give compound **26** (108 mg, 62%). R_f = 0.2 (EtOAc/Hex, 1:6). $[\alpha]_D^{24}$ = +3.1 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3352, 3030, 2923, 1457, 1098, 698 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 35 H, ArH), 5.90 (d, J = 8.4 Hz, 1 H, NH), 5.71 (dt, J = 11.1, 7.2 Hz, 1 H, 7-H), 5.51 (dd, J = 11.1, 9.6 Hz, 1 H, 6-H), 4.91 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.86 (d, J = 3.6 Hz, 1 H, 1′-H), 4.75 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.73 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.68 (d, J = 11.4 Hz, 1 H, CH_2Ph), 4.67 (s, 2 H, CH_2Ph), 4.63 (d, J = 12.0 Hz, 1 H, CH_2Ph), 3.57 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.56–4.53 (m, 3 H, CH_2Ph, 5-H), 4.49 (dd, J = 10.2, 4.8 Hz, 1 H, 2-H), 4.46 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.44 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.34 (d, J = 11.4 Hz, 2 H, CH_2Ph), 4.02 (dd, J = 9.6, 3.6 Hz, 1 H, 2′-H), 3.97–3.93 (m, 2 H, 3′-H, 5′-H), 3.89 (dd, J = 9.0, 3.0 Hz, 2 H, 3-H, 4′-H), 3.83 (dd, J = 10.2, 4.8 Hz, 1 H, 1a-H), 3.77 (t, J = 4.8 Hz, 1 H, 4-H), 3.73 (dd, J = 10.2, 6.6 Hz, 1 H, 1b-H), 3.50–3.45 (m, 2 H, 6′a-H, 6′b-H), 2.03–1.86 (m, 2 H, 8-H), 1.72–1.68 (m, 2 H, CH_2), 1.42–1.40 (m, 2 H, CH_2), 1.30–1.12 (m, 62 H, CH_2), 0.88 (t, J = 7.2 Hz, 6 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9 (C), 138.8 (C), 138.7 (2 C), 138.6 (C), 138.5 (C), 138.4 (C), 137.9 (C), 136.2 (CH), 128.32 (2 CH), 128.29 (3 CH), 128.28 (3 CH), 128.25 (6 CH), 128.18 (3 CH), 128.15 (2 CH), 127.9 (2 CH), 127.8 (2 CH), 127.70 (2 CH), 127.68 (2 CH), 127.5 (3 CH), 127.41 (2 CH), 127.36 (CH), 127.3 (2 CH), 126.4 (CH), 98.5 (CH), 80.7 (CH), 79.1 (CH), 78.5 (CH), 76.6 (CH), 74.9 (CH), 74.8 (CH_2), 74.7 (CH), 73.5 (CH_2), 73.2 (CH_2), 72.9 (2 CH_2), 72.6 (CH_2), 69.9 (CH_2), 69.5 (CH), 68.9 (CH_2), 68.2 (CH_2), 50.0 (CH), 36.5 (CH_2), 31.9 (3 CH_2), 29.72 (4 CH_2), 29.70 (9 CH_2), 29.67 (3 CH_2), 29.65 (3 CH_2), 29.60 (CH_2), 29.58 (CH_2), 29.47 (CH_2), 29.43 (CH_2), 29.36 (3 CH_2), 28.1 (CH_2), 25.7 (CH_2), 22.7 (2 CH_2), 14.13 (2 CH_3) ppm. HRMS (ESI): calcd. for $C_{99}H_{140}NO_{10}$ $[M + Na]^+$ 1503.0472; found 1503.0462.

(2*S*,3*R*,4*R*,5*R*,6*Z*)-1-*O*-(α-D-Galactopyranosyl)-2-hexacosanoylamino-octadec-1,3,4,5-tetraol (2d): Compound **26** (67.6 mg, 0.046 mmol) was dissolved in a mixed solvent of $CHCl_3$/MeOH (4:1 v/v; 1.0 mL) at room temperature. $Pd(OH)_2$/C (Degussa type; 67.6 mg) was added to the solution, the reaction vessel was purged with hydrogen, and the mixture was stirred under 60 psi pressure at the same temperature for 16 h. The resulting solution was filtered through Celite, the filtrate was concentrated in vacuo, and the crude residue was purified by flash column chromatography on silica gel to give target molecule **2d** (8.3 mg, 21%). A lot of compound **2d** was trapped on the silica gel. R_f = 0.6 ($CHCl_3$/MeOH, 1:4), m.p. 162–165 °C. $[\alpha]_D^{21}$ = +30.3 (c = 0.3, MeOH/$CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3362, 2918, 2850, 1627, 1550, 1467, 1151 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.60 (d, J = 7.8 Hz, 1 H, NH), 5.58 (d, J = 3.6 Hz, 1 H, 1′-H), 5.40–5.36 (m, 1 H, 2-H), 4.74 (dd, J = 10.8, 6.0 Hz, 1 H, 1a-H), 4.65 (dd, J = 9.6, 3.6 Hz, 1 H, 2′-H), 4.61 (d, J = 8.4 Hz, 1 H, 3-H), 4.54 (d, J = 3.6 Hz, 1 H, 4-H), 4.49 (t, J = 6.0 Hz, 1 H, 4′-H), 4.44–4.34 (m, 6 H, 1b-H, 5-H, 3′-H, 5′-H, 6′a-H, 6′b-H), 2.42 (t, J = 7.2 Hz, 2 H, CH_2), 2.22–2.14 (m, 1 H, CH_2), 1.97–1.87 (m, 4 H, CH_2), 1.80–1.75 (m, 2 H, CH_2), 1.63–1.58 (m, 1 H, CH_2), 1.29–1.19 (m, 62 H, CH_2), 0.84 (t, J = 6.6 Hz, 6 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.0 (C), 101.7 (CH), 76.7 (CH), 75.5 (CH), 75.4 (CH), 73.5 (CH), 72.1 (CH), 71.5 (CH), 70.7 (CH), 68.3 (CH_2), 63.1 (CH_2), 51.9 (CH), 37.2 (CH_2), 34.2 (CH_2), 32.6 (3 CH_2), 30.8 (2 CH_2), 30.6 (2 CH_2), 30.5 (9 CH_2), 30.41 (4 CH_2), 30.35 (2 CH_2), 30.3 (2 CH_2), 30.2 (2 CH_2), 30.1 (3 CH_2), 26.9 (CH_2), 26.8 (CH_2), 23.4 (3 CH_2), 14.8 (2 CH_3) ppm. HRMS (CI): calcd. for $C_{50}H_{100}O_{10}N$ $[M + H]^+$ 874.7342; found 874.7341.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all key intermediates and final products.

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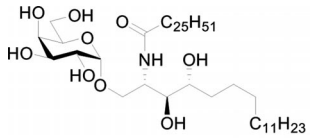
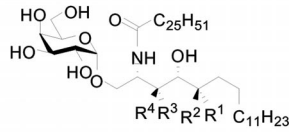


1, KRN7000



2a, $R^1 = R^4 = OH$, $R^2 = R^3 = H$
2b, $R^1 = R^3 = OH$, $R^2 = R^4 = H$
2c, $R^2 = R^3 = OH$, $R^1 = R^4 = H$
2d, $R^2 = R^4 = OH$, $R^1 = R^3 = H$

A short, efficient method for the synthesis of hydroxylated analogues of α-galactosyl ceramide (KRN7000) with an extra hydroxy group at the 5-position and altered stereochemistry at the 3-position of the sphingosine moiety is presented.

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Synthesis of Hydroxylated Analogues of α-Galactosyl Ceramide (KRN7000) with Varying Stereochemistry

Keywords: Carbohydrates / Glycolipids / Sphingolipids / Cerebrosides / Structure–activity relationships

