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Synthesis of β-C-Galactosyl Ceramide and Its New Aza Variant via the Horner−Wadsworth−Emmons Reaction

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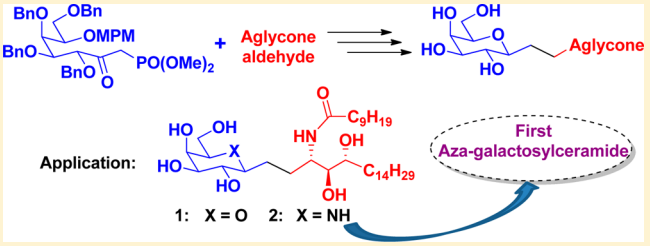
Supporting Information

ABSTRACT: A simple strategy for the synthesis of β-C-galactosyl ceramide and its new aza-variant analogue is described using the Horner−Wadsworth−Emmons reaction as the key step in combining the sugar and aglycone portions.



INTRODUCTION

Mammalian glycosphingolipids (GSLs) are essential components of cellular membranes which play a critical role in a variety of biochemical functions.[1] A simple GSL comprises a β-glycosidic linkage of a carbohydrate attached to the primary hydroxyl group of ceramide. The carbohydrate portion is present in the outer leaflet of the plasma membrane, serving as a receptor for various pathogens.[2] An important initial event behind HIV infection is interaction of cell surface expressed GSL galactosylceramide (GalCer) with the V3 loop region of HIV gp120.[3] This and other findings enabled the exploration of GalCer analogues, with β-anomeric configuration, as potential inhibitors for HIV infection.[4] In a different design for β-GalCer mimetics, a derivative with a simplified aliphatic chain in place of ceramide and replacement of galactose with 1-deoxynojirimycin has displayed a potent and specific affinity (28.5 mN/m) in an assay based on the change in surface pressure of the glycolipid monolayers on exposure to a solution of gp120.[5] The C-glycoside analogues of β-GalCer were also synthesized, using olefin cross metathesis and Wittig reaction as key steps, as these methylene isosteres render chemical and enzymatic stability to the analogues.[6]

In a related family of GSLs, KRN 7000, a synthetic glycolipid that was designed following structure−activity studies on the naturally occurring agelasphin which was discovered from the marine sponge *Agelas mauritianus*, has been well studied due to its potent immunomodulatory properties.[7] KRN 7000, also referred to as α-GalCer, contains the phytosphingosine base which upon complexation with an antigen presenting glycoprotein CD1d and subsequent complexation with an iNKT cell receptor results in the release of cytokines offering protection against several pathologies.[8] The C-glycoside analogue of α-GalCer was 100 times more effective in comparison to the O-glycoside at a 10 ng dosage level in a melanoma challenge assay on C57BL/6 mice.[9] Chaulagain et al. reported the first synthesis of a β-C-GalCer analogue, via the ring-closing metathesis approach, which exhibited antisolid tumor activity.[10]

A careful scrutiny of the reported β-GalCer analogues (vide supra) led us to design a piperidine aza-sugar coupled to phytosphingosine-derived ceramide. As aza-sugar C-glycosides offer promising biological and therapeutic properties,[11] we set our goal toward development of a methodology for the synthesis of aza-β-C-GalCer (**2**; Figure 1). In this pursuit, we

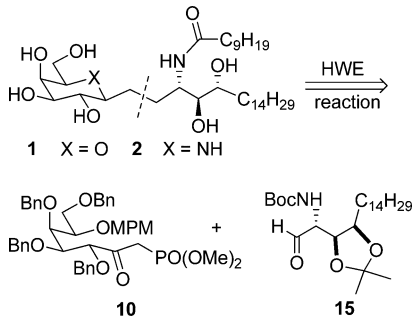


Figure 1. Retrosynthetic analysis for β-C-glycosides.

report a simple strategy for synthesis of β-C-glycosides in a convergent manner using the Horner−Wadsworth−Emmons (HWE) reaction of β-keto phosphonate **10** (Scheme 1) derived from D-galactose and the aglycone aldehyde **15** (Figure 1). Reports on the synthesis of β-C-GalCer for the most part relied on the stereoselective synthesis of the sphingosine backbone starting from a functionalized carbohydrate at the anomeric position.[10,12] Attempts concerning the application of the HWE

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methodology for *C*-glycoside synthesis have involved the presence of *β*-keto phosphonate in the aglycone portion.[13] In the present work, the HWE strategy was applied toward the total synthesis of *β*-C-GalCer **1** and its new variant aza-*β*-C-GalCer **2** from the common intermediate **17** (Scheme 3), derived from the HWE reaction using phytosphingosine-1-al **15** as the aglycone component. The present work offers a new entry to the repertoire of GSLs with a piperidine aza-sugar which could serve as a potential inhibitor for HIV infection and which may also have potential immunogenic properties.

RESULTS AND DISCUSSION

In our initial attempt, we sought a direct synthesis of aza-O-GalCer by extending the *O*-glycosidation of phytosphingosine by a galactose donor to the N-Boc azagalactose analogue **5** (Figure 2). The sugar portion with the N-Boc-protected

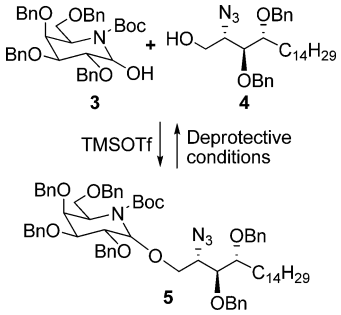
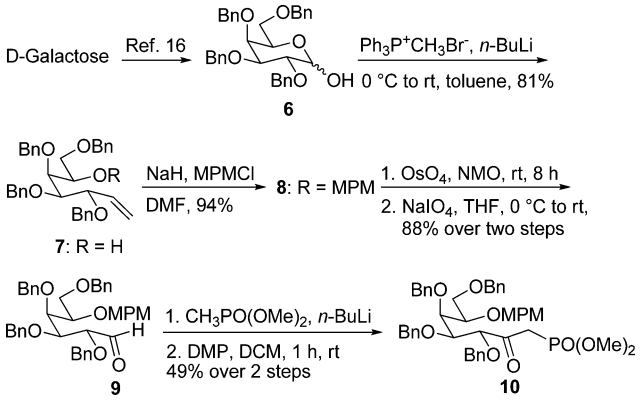


Figure 2. Attempt to synthesize aza-O-GalCer.

piperidin-2-ol **3** was synthesized from D-galactose in nine steps,[14] and phytosphingosin-1-ol **4** was prepared from phytosphingosine in four steps.[15] The glycosylation reaction was performed using TMSOTf as the promoter in THF at −10 °C, which afforded the desired glycosylated product **5**. Unfortunately, under deprotective conditions the glycosylated product cleaved to individual starting materials, as evidenced by TLC as well as mass spectral data of the crude reaction mixture (see the Supporting Information). This result demonstrated the labile nature of aza-O-GalCer **5**; therefore, we focused our attempts on *C*-glycoside using the HWE strategy.

Synthesis of HWE precursor *β*-keto phosphonate **10** (Scheme 1) commenced from lactol **6**, which was prepared in three steps from D-galactose.[16] The Wittig reaction of lactol **6** in dry THF led to formation of the diene product with

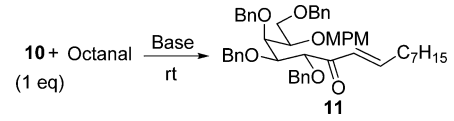
Scheme 1. Synthesis of *β*-Keto Phosphonate 10 from D-Galactose



elimination of the C-3 benzyl group; however, changing the solvent to dry toluene produced the desired alkene **7** in 81% yield. Protection of the 2° alcohol as an MPM afforded alkene **8** in 94% yield. Osmylation in the presence of stoichiometric oxidant NMO, followed by oxidative cleavage of the diol product using aqueous $NaIO_4$ in THF, produced aldehyde **9** in 88% yield over two steps. Nucleophilic addition of the anion generated from dimethyl methylphosphonate and *n*-BuLi to aldehyde **9** afforded the 2° alcohol, which was subsequently oxidized using Dess−Martin periodinane, giving rise to the galactosyl *β*-keto phosphonate **10** in 49% yield over two steps.

In an attempt to develop a simple HWE methodology for *β*-C-glycosides, *β*-keto phosphonate **10** was subjected to HWE conditions with octanal by variation of base and solvent. In all of the trials (Table 1) compound **10** was pretreated with base

Table 1. Horner−Wadsworth−Emmons Reaction Optimization Conditions



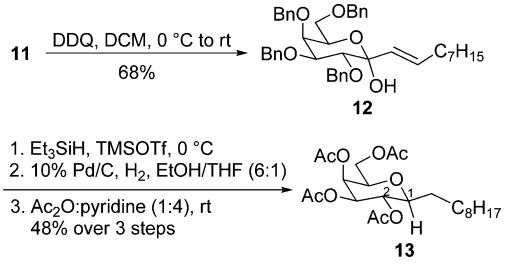
entry	base (amt, equiv)	amt of octanal, equiv	solvent	time, h	yield, %[a]
1	NaH (2)	2	THF	overnight	15
2	DIPEA (2)	3	CH_3CN	overnight	trace
3	K_2CO_3 (1.8)	3	EtOH	3	28
4	Cs_2CO_3 (2.1)	3	IPA	6	41
5	$Ba(OH)_2 \cdot 8H_2O$ (1.25)	2	THF	overnight	65
6	*t*-BuOK (4)	4	THF	overnight	47

[a]Isolated yields.

for 30 min before addition of octanal. The initial attempt with NaH in THF afforded the HWE product **11** in 15% yield (entry 1). Use of an organic base, DIPEA, gave rise to a trace amount of product (entry 2). However, with K_2CO_3 in EtOH the reaction was complete within 3 h, affording the product in 28% yield (entry 3). There was a slight improvement in the yield with Cs_2CO_3 to 41% (entry 4). Interestingly, using $Ba(OH)_2 \cdot 8H_2O$ (1.25 equiv) the reaction was complete overnight with an improved yield of 65%. Finally, with *t*-BuOK (4 equiv) the HWE product was formed in 47% yield.

α,β-unsaturated ketone **11** was subjected to deprotective conditions, DDQ in DCM, to produce the hemiketal **12** (Scheme 2). The 3° hydroxy group was removed by reduction using Et_3SiH and TMSOTf, followed by alkene reduction and debenzylation using 10% Pd/C under H_2, and finally the resulting product was subjected to global acetylation, affording

Scheme 2. Synthesis of *β*-*C*-Glycoside 13



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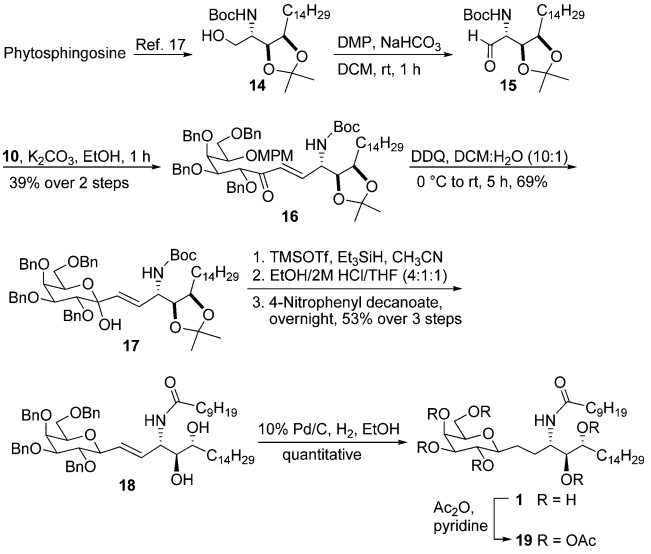
peracetylated galactosyl-β-*C*-glycoside **13** in 48% yield over three steps. The presence of COSY correlation between H-1 at δ_H 3.36 (m, 1H) and H-2 at δ_H 5.08 (app t, J = 9.5 Hz, 1H) and trans coupling constant helped to determine the β configuration of C-glycoside **13** (see the Supporting Information).

Successful synthesis of the β-C-glycoside **13** from ketophosphonate **10** and octanal via the HWE reaction encouraged us to apply this methodology toward the synthesis of biologically relevant structures β-C-GalCer **1** and its new variant aza-β-C-GalCer **2** from a common intermediate. In a convergent approach, first, the HWE aldehyde precursor of ceramide was synthesized from commercially available phytosphingosine following a known procedure to afford the protected phytosphingosin-1-ol **14** (Scheme 3).[17] Alcohol **14**

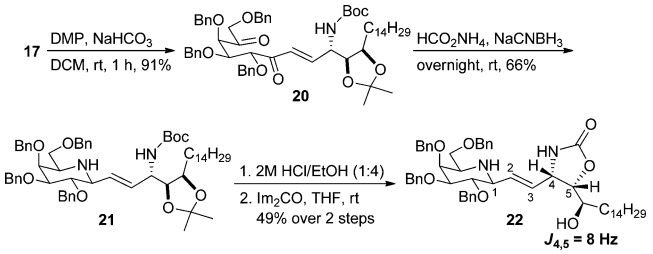
Scheme 3. Synthesis of β-C-GalCer 1



was oxidized using Dess−Martin periodinane in the presence of excess $NaHCO_3$, which resulted in phytosphingosin-1-al **15**. The initial HWE reaction between aldehyde **15** and β-keto phosphonate **10** using $Ba(OH)_2{\cdot}8H_2O$ afforded the HWE adduct **16** in a poor yield. However, a change of base to K_2CO_3 afforded the desired product **16** in 39% yield over two steps. MPM deprotection using DDQ in DCM/H_2O (10/1) formed the hemiketal product **17** in 69% yield. Removal of the 3° hydroxyl group under reductive conditions and deprotection of Boc and isopropylidene groups under acidic conditions resulted in free amine, which was subjected to amidation using *p*-nitrophenyl decanoate to afford the advanced intermediate **18** in 53% yield over three steps. Finally, debenzylation using 10% Pd/C under H_2 afforded β-C-GalCer **1** in a quantitative yield, which was subjected to global acetylation, affording the peracetylated β-C-GalCer **19**. In this context, the present work offers an alternative route to β-C-GalCer **1** prepared by Chaulagain et al.[10]

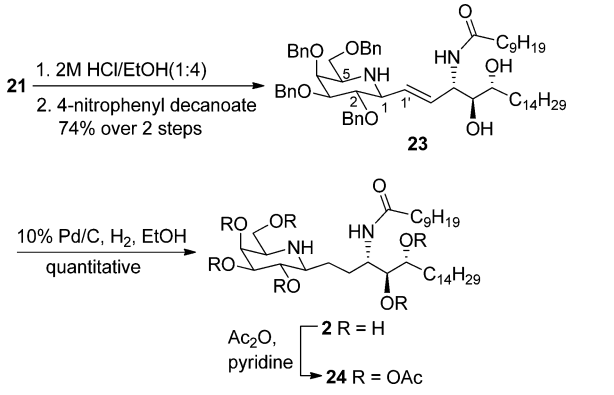
Synthesis of aza-β-C-GalCer **2** was envisaged by utilizing the standard double reductive amination conditions usually employed for piperidine aza-D-sugar synthesis.[18] Initially, the hemiketal product **17** was oxidized with Dess−Martin periodinane, which afforded diketone **20** (Scheme 4) in 91% yield. A double reductive amination reaction facilitated facile cyclization to form the piperidine aza-D-sugar **21** in 66% yield. To address the concern of stereochemical integrity of C-2 stereocenter of

Scheme 4. Confirmation of Stereochemistry



the phytosphingosine aldehyde **15** under HWE reaction conditions, compound **21** was converted into the oxazolidinone **22**. Comparison of the H-4 and H-5 coupling constant value ($J_{4,5}$ = 8 Hz) with that in the literature confirms that under HWE conditions the C-2 stereocenter did not undergo epimerization.[6a,12] Dondoni et al. reported epimerization of Garner aldehyde under Wittig reaction conditions using *n*-BuLi,[19] whereas Compostella et al. reported no such epimerization under HWE reaction conditions using a milder base such as K_2CO_3 even with stirring for 18 h.[12] Nevertheless, the present HWE reaction using K_2CO_3 facilitated consumption of phytosphingosin-1-al **15** within 1 h. Deprotection of Boc and isopropylidene groups of compound **21** in EtOH/2 M HCl (4/1) at 70 °C produced the free amine, which was subjected to amidation using *p*-nitrophenyl decanoate to afford ceramide **23** (Scheme 5) in 74% yield over two steps.

Scheme 5. Synthesis of aza-β-C-GalCer 2



Surprisingly, during the latter amidation conditions only the sphingosine amine was affected, leaving the piperidine aza-sugar unaltered, perhaps due to steric hindrance. The indifference of the 2° amine of the piperidine aza-sugar toward amide bond formation was further substantiated by a previous report for N-benzoylation utilizing Grignard reagent for deprotonation.[20] Finally, global debenzylation with 10% Pd/C under H_2 afforded aza-β-C-GalCer **2** in quantitative yield, which was treated with Ac_2O/pyridine to produce the peracetylated aza-β-C-GalCer **24**. The presence of a COSY correlation in compound **23** between H-1 at δ_H 3.14 (dd, J = 9, 7 Hz) with H-1′ at δ_H 5.72 (dd, J = 16, 7 Hz) and H-2 at δ_H 3.63 (app t, J = 9 Hz) helped to confirm the β configuration by trans-coupling constant (see Supporting Information). Furthermore, the presence of H-5 δ_H 2.85, which is upfield from H-1, indicates that H-1 and H-5 are neighbors to NH of the sugar. The presence of three COSY correlations for H-5 with δ_H 3.33, 3.48, and 3.95 further confirms the identity of H-5 in the sugar. This COSY analysis

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confirms amidation of the sphingosine backbone, leaving the aza portion of the sugar unaffected.

CONCLUSION

In summary, we have successfully demonstrated the Horner−Wadsworth−Emmons reaction in β-*C*-glycoside synthesis using a β-keto phosphonate generated from a sugar and an aglycone aldehyde. This methodology was successfully employed in the total synthesis of biologically relevant glycosphingolipids: β-*C*-galactosylceramide (GalCer) and its new variant aza-β-C-GalCer. In light of the importance of β-GalCer derivatives as potential inhibitors for HIV infection as well as possession of immunogenic properties by activation of iNKT cells leading to release of Th1/Th2 immune response which are involved in protection against several diseases, aza-β-C-GalCer marks a new entry in glycolipid-related therapeutic approaches. To the best of our knowledge, this is the first report of a glycosphingolipid with a piperidine aza-sugar. Aza substitution of a sugar also opens a new diversity element which can be further functionalized to prepare a library of therapeutically relevant molecules.

EXPERIMENTAL SECTION

The solvents were dried as follows: THF was heated at reflux over sodium, CH_3CN and CH_2Cl_2 were distilled over calcium hydride, toluene was dried over molecular sieves, and EtOH was dried over magnesium turnings. All reactions were carried out under an argon atmosphere using oven-dried glassware. Silica gel 60 F_{254} aluminum TLC plates were used to monitor the reactions with short-wavelength ultraviolet light to visualize the spots, charring the TLC plate after spraying with 15% sulfuric acid. Flash column chromatography was performed on silica gel 120−200 and 230−400 mesh. ^{1}H NMR spectra were recorded at 500 MHz, chemical shifts are given in parts per million and coupling constant in hertz. ^{13}C NMR spectra were recorded at 125 MHz. HRMS analysis was performed using electrospray ionization technique with ions given in *m*/*z*.

2,3,4,6-Tetra-*O*-benzyl-5-[*N*-(*tert*-butoxycarbonyl)amino]-5-deoxy-α-D-galactopyranosyl-(2*S*,3*S*,4*R*)-2-azido-3,4-di-*O*-benzyloctadecane-1,3,4-triol (5). To a solution of N-Boc-protected piperidin-2-ol **3** (60 mg, 0.093 mmol, 1 equiv) and phytosphingosin-1-ol **4** (97 mg, 0.102 mmol, 2 equiv) in dry THF (4 mL) was added TMSOTf (9 μL, 0.046 mmol, 0.5 equiv) at −10 °C, and the resulting mixture was stirred for 2 h at 0 °C under an argon atmosphere. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, washed with water (2 × 50 mL), and extracted with EtOAc (2 × 50 mL), and the extracts were dried over anhydrous $MgSO_4$ and concentrated. Purification by flash chromatography using hexane/EtOAc 90/10 to 80/20 afforded glycosylated product **5** (50 mg, 47%) as a colorless viscous solid: R_f 0.5 (hexane/EtOAc 9/1); HR-ESI-MS $[M + Na]^+$ $C_{71}H_{92}N_4O_9Na$ calcd for *m*/*z* 1167.6762, found 1167.6771.

3,4,5,7-Tetra-*O*-benzyl-D-galactohept-1-enitol (7). A solution of methyltriphenylphosphonium bromide (37.7 g, 105.5 mmol, 3 equiv) in dry toluene (200 mL) was stirred for 10 min at room temperature, and then a 1.6 M solution of *n*-BuLi in hexane (65.9 mL, 105.5 mmol, 3 equiv) was slowly added at 0 °C under an argon atmosphere. The resulting yellow solution was stirred for 2 h at 0 °C to room temperature, and then a solution of 2,3,4,6-tetra-*O*-benzyl-D-galactose **6** (19 g, 35.2 mmol, 1 equiv) in dry toluene (80 mL) was added at room temperature. After it was stirred overnight, the reaction mixture was brought to 0 °C, quenched with acetone (150 mL), and extracted with Et_2O (2 × 400 mL). The organic layer was washed with excess water, dried over anhydrous $MgSO_4$, concentrated, and purified by flash chromatography using hexane/EtOAc 95/5 to 90/10, which afforded compound **7** (15.3 g, 81%) as a pale brown viscous solid: R_f 0.4 (hexane/EtOAc 3/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.16 (m, 20H), 5.90−5.83 (m, 1H), 5.35−5.29 (m, 2H), 4.74 (s, 2H), 4.68−4.63 (m, 2H), 4.48 (d, *J* = 12 Hz, 1H), 4.49−4.33 (m, 4H), 4.12−4.06 (m, 2H), 3.82−3.78 (m, 1H), 3.53−3.46 (m, 2H), 3.03(d, *J* = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.3, 138.2, 138.1, 138.0, 135.7, 128.3, 128.1, 128.0, 127.74, 127.70, 127.6, 119.2, 80.7, 76.5, 75.2, 73.1, 71.2, 70.3, 69.6; HR-ESI-MS $[M + Na]^+$ $C_{35}H_{38}O_5Na$ calcd for *m*/*z* 561.2616, found 561.2625.

3,4,5,7-Tetra-*O*-benzyl-6-*O*-*p*-methoxybenzyloxy-D-galacto-hept-1-ene (8). To a solution of compound **7** (9.5 g, 17.6 mmol, 1 equiv) in DMF (70 mL) at 0 °C was added NaH 60% suspension in mineral oil (1.4 g, 35.3 mmol, 2 equiv), and the resulting mixture was stirred for 30 min. At the same temperature 4-methoxybenzyl chloride (3.6 mL, 26.4 mmol, 1.5 equiv) was added dropwise and the reaction mixture was warmed to room temperature slowly. After 3 h, the reaction mixture was quenched with ice−water (250 mL) at 0 °C and extracted with ethyl acetate (2 × 300 mL) and the extracts were dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography using hexane/EtOAc 95/5 to 90/10 afforded compound **8** (10.9 g, 94%) as a colorless viscous solid: R_f 0.38 (hexane/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.18 (m, 22H), 6.79 (d, *J* = 8.5 Hz, 2H), 5.98−5.90 (m, 1H), 5.34−5.25 (m., 2H), 4.68−4.61 (m, 3H), 4.56−4.50 (m, 4H), 4.42−4.30 (m, 3H), 4.16 (dd, *J* = 7.5, 4.5 Hz, 1H), 3.98−3.94 (m, 2H), 3.80−3.78 (m, 1H), 3.7 (s, 3H), 3.64 (dd, *J* = 10, 5.5 Hz, 1H), 3.59 (dd, *J* = 9.5, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0, 138.8, 138.7, 138.6, 138.2, 136.5, 131.1, 129.4, 128.3, 128.2, 127.8, 127.6, 127.5, 127.3, 118.5, 81.8, 78.5, 73.1, 72.2, 70.7, 70.5, 70.3, 55.2; HR-ESI-MS $[M + Na]^+$ $C_{43}H_{46}O_6Na$ calcd for *m*/*z* 681.3192, found 681.3195.

2,3,4,6-Tetra-*O*-benzyl-5-*O*-*p*-methoxybenzyloxy-D-galacto-1-hexanal (9). To a solution of compound **8** (10.9 g, 16.5 mmol, 1 equiv) in acetone/water (4/1, 150 mL) were added NMO (2.9 g, 24.8 mmol, 1.5 equiv) and OsO_4 (189.5 mg, 0.74 mmol, 0.045 equiv), and then the reaction mixture was stirred for 8 h at room temperature under an argon atmosphere. The reaction mixture was quenched with saturated aqueous $NaHSO_3$, washed with water (2 × 400 mL), and extracted with ethyl acetate (2 × 300 mL), and the extracts were dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography using hexane/EtOAc 90/10 to 70/30 afforded the diol as a colorless viscous solid: R_f 0.3 (hexane/EtOAc 6/4); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.14 (m, 22H), 6.81 (d, *J* = 8.5 Hz, 2H), 4.76−4.71 (m, 2H), 4.67−4.60 (m, 2H), 4.58−4.54 (m, 3H), 4.49−4.47 (m, 2H), 4.43−4.38 (m, 2H), 4.09 (app t, *J* = 5.5 Hz, 1H), 4.00−3.97 (m, 1H), 3.87−3.85 (m, 2H), 3.76 (s, 3H), 3.75 (s, 1H), 3,70−3.66 (m, 1H), 3.60−3.56 (m, 2H), 3.4 (d, *J* = 4 Hz, 1H), 1.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 138.2, 138.1, 137.9, 130.6, 129.9, 129.6, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 113.7, 79.6, 79.1, 78.2, 73.3, 73.0, 72.9, 71.8, 70.0, 63.8, 55.2; HR-ESI-MS $[M + Na]^+$ $C_{43}H_{48}O_8Na$ calcd for *m*/*z* 715.3246, found 715.3250.

To a solution of the diol (4.5 g, 6.5 mmol, 1 equiv) in THF (70 mL) was added a solution of aqueous $NaIO_4$ (2.79 g, 13.1 mmol, 2 equiv) at 0 °C, and the mixture was stirred overnight at room temperature under an argon atmosphere. The reaction mixture was quenched with brine (50 mL) and extracted with ethyl acetate (2 × 200 mL), and the extracts were washed with water (2 × 300 mL), dried over anhydrous $MgSO_4$, and concentrated. Purification by flash chromatography using hexane/EtOAc 90/5 to 90:10 afforded aldehyde **9** (3.98 g) as a colorless viscous solid (88% over 2 steps): R_f 0.4 (hexane/EtOAc 7/3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.68 (s, 1H), 7.32−7.17 (m, 22H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.63−4.56 (m, 3H), 4.51−4.47 (m, 2H), 4.45−4.40 (m, 4H), 4.11−4.09 (m, 2H), 4.01 (app t, *J* = 5 Hz, 1H), 3.95−3.94 (m, 1H), 3.77 (s, 3H), 3.61−3.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.6, 159.1, 138.3, 138.1, 137.8, 130.7, 130.4, 129.5, 128.5, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5, 113.6, 83.6, 79.2, 79.0, 76.8, 74.4, 73.3, 73.08, 73.0, 72.5, 69.9, 55.2; HR-ESI-MS $[M + Na]^+$ $C_{42}H_{44}O_7Na$ calcd for *m*/*z* 683.2984, found 683.2982 and $[M + MeOH + Na]^+$ 715.3239.

Dimethyl [(3,4,5,7-Tetra-*O*-benzyl-6-*O*-*p*-methoxybenzyloxy-D-galacto)-1-oxomethyl]phosphonate (10). To a solution of dimethyl methylphosphonate (1.28 mL, 11.9 mmol, 2.1 equiv) in THF (15 mL) at −78 °C was slowly added *n*-BuLi (7.13 mL, 11.4

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mmol, 2 equiv), and then the resulting yellow solution was stirred for 20 min at the same temperature under an argon atmosphere. A solution of compound **9** (3.7 g, 5.7 mmol, 1 equiv) in THF (30 mL) was added, and the resulting mixture was stirred for 1 h at −78 °C under an argon atmosphere. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (2 × 200 mL), and the extracts were washed with water (3 × 300 mL), dried over anhydrous $MgSO_4$, and concentrated. Purification by flash chromatography hexane/EtOAc 90/10 to 40/60 afforded the β-hydroxy phosphonate: R_f 0.2 (hexane/EtOAc 7/3); HR-ESI-MS $[M + Na]^+$ $C_{45}H_{53}O_{10}PNa$ calcd for m/z 807.3274, found 807.3281.

To a solution of the β-hydroxy phosphonate (3.15 g, 4.02 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was added Dess−Martin periodinane (3.4 g, 8.04 mmol, 2 equiv), and the mixture was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was then quenched with saturated aqueous $Na_2S_2O_3$ (75 mL) and saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 × 150 mL), and the extracts were washed with water (2 × 400 mL), dried over anhydrous $MgSO_4$, and concentrated. Purification by flash chromatography using hexane/EtOAc 95/5 to 80/20 to 60/40 afforded compound **10** (2.16 g, 49% over two steps) as a pale yellow viscous solid: R_f 0.3 (hexane/EtOAc 6/4); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.12 (m, 22H), 6.79 (d, J = 8.5 Hz, 2H), 4.68 (app t, J = 12 Hz, 2H), 4.61−4.58 (m, 1H), 4.55−4.51 (m, 3H), 4.49−4.44 (m, 2H), 4.39−4.36 (m, 2H), 4.29 (d, J = 11.5 Hz, 1H), 4.04−4.01 (m, 1H), 3.99−3.94 (m, 2H), 3.77 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H), 3.60−3.59 (m, 1H), 3.55−3.53 (m, 1H), 3.33 (dd, J_{HbHa} = 14.5 Hz, J_{HbP} = 22.0 Hz, CHaHbP, 1H), 2.91 (dd, J_{HaHb} = 14.5 Hz, J_{HaP} = 21.0 Hz, CHaHbP, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.9, 159.0, 138.4, 138.1, 137.8, 137.6, 130.8, 129.6, 129.4, 128.3, 127.9, 127.4, 113.6, 83.8, 79.6, 79.4, 74.9, 73.2, 72.7, 72.5, 69.8, 55.7, 52.7, 38.7, 37.6; HR-ESI-MS $[M + Na]^+$ $C_{45}H_{51}O_{10}PNa$ calcd for m/z 805.3117, found 805.3126.

2,3,4,6-Tetra-*O*-benzyl-5-(*p*-methoxybenzyloxy)-1-anhydro-D-galacto-1-*C*-nonene (11). To a solution of compound **10** (295 mg, 0.37 mmol, 1 equiv) in THF (6 mL) was added $Ba(OH)_2{\cdot}8H_2O$ (148.7 mg, 0.47 mmol, 1.25 equiv), and then the mixture was stirred for 30 min at room temperature under an argon atmosphere. Octanal (176.7 μL, 1.13 mmol, 3 equiv) was added directly to the reaction mixture, and this mixture was stirred at room temperature under an argon atmosphere. After the mixture was stirred overnight, the reaction was stopped and solvents were evaporated; the crude mixture was directly subjected to purification by flash chromatography using hexane/EtOAc 95/5, affording compound **11** (190 mg, 65%) as a colorless viscous solid: R_f 0.40 (hexane/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32−7.10 (m, 22H), 7.01−6.95 (m, 1H), 6.78 (d, J = 8.5 Hz, 2H), 6.58 (d, J = 15.5 Hz, 1H), 4.64−4.60 (m, 2H), 4.54−4.46 (m, 2H), 4.44−4.40 (m, 4H), 4.32−4.30 (m, 2H), 4.18 (dd, J = 8.5, 3 Hz, 1H), 3.99−3.97 (m, 1H), 3.75 (s, 3H), 3.68−3.66 (m, 1H), 3.63−3.61 (m, 1H), 2.11−2.07 (m, 2H), 1.33−1.26 (m, 10H), 0.86 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.9, 159.0, 138.5, 138.2, 138.1, 137.5, 130.8, 129.2, 128.3, 128.2, 127.7, 127.5, 126.2, 113.6, 84.1, 79.9, 78.0, 73.8, 73.6, 73.1, 72.6, 72.0, 55.2, 32.6, 31.7, 29.2, 29.0, 27.9, 22.6, 14.0; HR-ESI-MS $[M + Na]^+$ $C_{51}H_{60}O_7Na$ calcd for m/z 807.4236, found 807.4228.

2,3,4,6-Tetra-*O*-benzyl-1-*C*-nonenyl-β-D-galactopyranose (12). To a solution of compound **11** (170 mg, 0.21 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added DDQ (54.1 mg, 0.23 mmol, 1.1 equiv) at 0 °C, and the resulting brownish reaction mixture was stirred for 2.5 h at room temperature under an argon atmosphere. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (2 × 70 mL), and the extracts were washed with water (2 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated. Purification by flash chromatography using hexane/EtOAc 95/5 to 90/10 afforded compound **12** (97 mg, 68%) as a pale yellow viscous solid: R_f 0.37 (hexane/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.23 (m, 20H), 7.14−7.00 (m, 1H), 6.61 (d, J = 15.5 Hz, 1H), 4.71−4.57 (m, 3H), 4.53−4.43 (m, 3H), 4.38−4.30 (m, 3H), 4.22 (d, J = 3 Hz, 1H), 4.16−4.06 (m, 2H), 3.88−3.85 (m, 2H), 3.59−3.49 (m, 2H), 1.37−01.33 (m, 2H), 1.25−1.21 (m, 10H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.8, 149.2, 138.8, 137.9, 137.6, 137.2, 128.4, 128.3, 128.26, 128.21, 128.0, 127.9, 127.8, 127.74, 127.72, 127.6, 127.5, 126.0, 97.0, 84.1, 79.9, 74.7, 73.7, 73.4, 73.2, 72.5, 71.3, 69.0, 32.6, 31.8, 29.3, 29.1, 29.0, 28.8, 27.9, 22.6, 14.1; HR-ESI-MS $[M + Na]^+$ $C_{43}H_{52}O_6Na$ calcd for m/z 687.3661, found 687.3668.

2,3,4,6-Tetra-*O*-acetyl-1-*C*-nonyl-β-D-galactopyranose (13). To a solution of compound **12** (39 mg, 0.06 mmol, 1 equiv) in CH_3CN (3 mL) were added Et_3SiH (94 μL, 0.58 mmol, 10 equiv) and TMSOTf (32 μL, 0.17 mmol, 3 equiv), at 0 °C, and the mixture was stirred for 20 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 30 mL), and the extracts were washed with brine (25 mL), dried over anhydrous $MgSO_4$, and concentrated. The crude mixture was dissolved in 3 mL of EtOH/THF (6/1), and then 10% Pd/C (30 mg) and TFA (18 μL, 0.23 mmol, 4 equiv) were added. The resulting mixture was purged with H_2 gas for 5 min at room temperature, and then the reaction mixture was stirred overnight under an H_2 atmosphere (balloon). The reaction mixture was then diluted with EtOH (3 mL), filtered through a Celite pad, and washed with MeOH, and the filtrate was concentrated under vacuum, resulting in a white solid in a quantitative yield. The resulting product was dissolved in pyridine (2 mL) and Ac_2O (0.5 mL), and the reaction mixture stirred was overnight at room temperature under an argon atmosphere. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (2 × 25 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), dried over anhydrous $MgSO_4$, and concentrated. Purification by flash chromatography using hexane/EtOAc 90/10 to 85/15 afforded compound **13** (13 mg, 48% over three steps) as a white solid: R_f 0.46 (hexane/EtOAc 6/4); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.41 (d, J = 3 Hz, 1H), 5.08 (app t, J = 9.5 Hz, 1H), 5.02 (dd, J = 10.5, 3.5 Hz, 1H), 4.14 (dd, J = 9.5, 5 Hz, 1H), 4.06 (dd, J = 11, 6.5 Hz, 1H), 3.84 (app t, J = 6.5 Hz, 1H), 3.38−3.34 (m, 1H), 2.15 (s, 3H), 2.05 (s, 6H), 1.98 (s, 3H), 1.51−1.50 (m, 2H), 1.30−1.26 (m, 14H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 170.5, 170.4, 170.3, 169.9, 78.3, 74.0, 72.3, 69.5, 67.7, 31.9, 31.8, 31.4, 29.7, 29.5, 29.3, 25.1, 22.6, 20.8, 20.7, 20.6, 14.1; HR-ESI-MS $[M + Na]^+$ $C_{23}H_{38}O_9Na$ calcd for m/z 481.2413, found 481.2395.

(2*S*,3*S*,4*R*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-3,4-*O*-isopropylideneoctadecan-1-al (15). To a solution of protected phytosphingosin-1-ol **14** (100 mg, 0.22 mmol, 1 equiv) in CH_2Cl_2 (5 mL) were added $NaHCO_3$ (45.9 mg, 0.54 mmol, 2.5 equiv) and Dess−Martin periodinane (185.5 mg, 0.43 mmol, 2 equiv), and the reaction mixture was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL), and the extracts were dried over anhydrous Na_2SO_4, concentrated, and passed through a short silica pad by washing with ethyl acetate; the resulting filtrate was dried over anhydrous Na_2SO_4 and concentrated to afford phytosphingosin-1-al as a white solid, which was directly used for the next step without further purification: R_f 0.48 (hexane/EtOAc 7/3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 5.37 (d, J = 7 Hz), 4.45 (d, J = 5 Hz), 4.32−4.28 (m, 2H), 1.77−1.73 (m, 2H), 1.46 (s, 9H), 1.39 (s, 6H), 1.26 (m, 24H), 0.88 (t, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.7, 155.3, 108.7, 80.2, 78.9, 60.5, 31.9, 29.7, 29.65, 29.62, 29.55, 29.51, 29.4, 29.3, 28.2, 28.1, 26.9, 24.9, 22.6, 14.1; HR-ESI-MS $[M + MeOH + Na]^+$ $C_{27}H_{53}NO_6Na$ calcd for m/z 510.3770, found 510.3779.

(2*E*,3*S*,4*S*,5*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-4,5-*O*-isopropylidene-1-anhydro(2,3,4,6-tetra-*O*-benzyl-5-*O*-*p*-methoxybenzyloxy-D-galacto)-2-nonadecene (16). To a solution of compound **10** (341 mg, 0.44 mmol, 2 equiv) in EtOH (4 mL) were added a solution of phytosphingosin-1-al **15** (0.22 mmol) in EtOH (2.5 mL) and K_2CO_3 (90.6 mg, 0.65 mmol, 3 equiv), and the mixture was stirred at room temperature for 1 h under an argon atmosphere. The reaction mixture was quenched with aqueous citric acid (1 g in 5 mL of H_2O), washed with H_2O (30 mL), and extracted with EtOAc (2 × 50 mL), and the extracts were dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography using hexane/EtOAc 95/5 to 90/10 afforded compound **16** (95 mg, 39% over two

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steps) as a colorless viscous solid: R_f 0.45 (hexane/EtOAc 7/3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.19 (m, 22H), 7.10 (dd, J = 16, 8 Hz, 1H), 6.81 (d, J = 8 Hz, 2H), 6.75 (d, J = 15.5 Hz, 1H), 4.64−4.63 (m, 2H), 4.61−4.57 (m, 2H), 4.50−4.47 (m, 2H), 4.44−4.40 (m, 3H), 4.37−4.33 (m, 3H), 4.23 (d, J = 7.5 Hz, 1H), 4.14−4.11 (m, 1H), 4.01−3.98 (m, 2H), 3.93−3.91 (m, 1H), 3.78 (s, 3H), 3.69−3.60 (m, 2H), 1.44 (s, 9H), 1.34 (s, 6H), 1.31−1.27 (m, 26H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.3, 159.0, 154.7, 145.3, 138.5, 138.1, 138.0, 137.5, 130.8, 129.2, 128.4, 128.2, 127.7, 127.5, 127.4, 125.9, 113.6, 108.4, 84.3, 79.9, 79.5, 77.9, 73.5, 73.1, 72.8, 72.2, 70.2, 55.2, 52.0, 31.9, 31.5, 29.6, 29.3, 28.9, 28.3, 27.1, 26.9, 25.3, 22.7, 14.1; HR-ESI-MS [M + Na]$^+$ $C_{69}H_{93}NO_{11}Na$ calcd for m/z 1134.6646, found 1134.6648.

(2*E*,3*S*,4*S*,5*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-4,5-*O*-isopropylidene(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-2-nonadecene (17). To a solution of compound **16** (200 mg, 0.18 mmol, 1 equiv) in CH_2Cl_2/H_2O (10/1, 11 mL) was added DDQ (69 mg, 0.3 mmol, 1.7 equiv) at 0 °C, and the reaction mixture was warmed to room temperature under an argon atmosphere. After 5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 × 50 mL) and extracted with CH_2Cl_2 (2 × 75 mL), and the extracts were washed with water (2 × 100 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography using hexane/EtOAc 90/10 to 80/20 afforded compound **17** (123 mg, 69%) as a colorless viscous solid: R_f 0.23 (hexane/EtOAc 4/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.26 (m, 20H), 7.15 (dd, J = 8, 2 Hz, 1H), 6.19 (dd, J = 16, 4 Hz, 1H), 5.81 (d, J = 16 Hz, 1H), 4.95 (d, J = 12 Hz, 1H), 4.79−4.75 (m, 2H), 4.63−4.61 (m, 3H), 4.52−4.33 (m, 3H), 4.19−4.11 (m, 2H), 4.0 (d, J = 1.5 Hz, 1H), 3.95−3.91 (m, 1H), 3.85 (d, J = 10 Hz, 1H), 3.59−3.54 (m, 2H), 3.04 (s, 1H), 1.43 (s, 9H), 1.37 (s, 6H), 1.32−1.27 (m, 26H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.9, 138.8, 138.5, 138.1, 137.9, 128.5, 128.3, 128.1, 127.9, 127.7, 127.5, 108.2, 96.9, 80.5, 79.3, 75.7, 74.4, 73.4, 72.8, 70.3, 68.8, 31.9, 29.7, 29.6, 29.5, 29.3, 28.3, 22.7, 14.1; HR-ESI-MS [M + Na]$^+$ $C_{61}H_{85}NO_{10}Na$ calcd for m/z 1014.6071, found 1014.6066.

(2*E*,3*S*,4*S*,5*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-3-*N*-(decanoylamino)-4,5-dihydroxy-2-nonadecene (18). To a solution of compound **17** (40 mg, 0.04 mmol, 1 equiv) in CH_3CN (5 mL) were added Et_3SiH (64 μL, 0.40 mmol, 10 equiv) and TMSOTf (22 μL, 0.12 mmol, 3 equiv) at 0 °C, and the mixture was stirred for 10 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (2 × 50 mL), and the organic layer was washed with H_2O (30 mL), dried over anhydrous Na_2SO_4, and concentrated. Without further purification the resulting crude mixture was treated with 4 mL of EtOH/2 M HCl/THF (4/1/1) at 70 °C overnight. The reaction mixture was cooled to room temperature and then diluted with 20 mL of H_2O and extracted with $CHCl_3$/MeOH (7/1, 3 × 30 mL), and the extracts were dried over anhydrous Na_2SO_4 and concentrated. The resulting crude free 1° amine was dried under vacuum and then dissolved in 2 mL of DCM/DMF (5/2). 4-Nitrophenyldecanoate (17.1 mg, 0.06 mmol, 1.5 equiv) and K_2CO_3 (17 mg, 0.12 mmol, 3 equiv) were added, and the mixture was stirred vigorously overnight at room temperature under an argon atmosphere. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (2 × 30 mL), and the organic layer was thoroughly washed with water (3 × 30 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography using hexane/EtOAc 90/10 to 60/40 afforded compound **18** (21 mg, 53% over three steps) as a white solid: R_f 0.37 (hexane/EtOAc 7/3); [α] = −3.03° (0.33, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.26 (m, 20H), 6.04 (d, J = 8 Hz, 1H), 6.01 (d, J = 6 Hz, 1H), 5.78 (dd, J = 15.5, 6 Hz, 1H), 4.95 (d, J = 11.5 Hz, 1H), 4.81 (d, J = 12 Hz, 1H), 4.75−4.74 (m, 3H), 4.62 (dd, J = 10.5, 2.5 Hz, 2H), 4.48−4.40 (m, 2H), 3.95 (d, J = 2.5 Hz, 1H), 3.78−3.69 (m, 2H), 3.61−3.55 (m, 3H), 3.50−3.48 (m, 3H), 2.18−2.16 (m, 2H), 1.65−1.60 (m, 2H), 1.33−1.26 (m, 38H), 0.87−0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 138.5, 138.3, 138.2, 137.7, 130.2, 129.8, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 127.5, 84.1, 79.8, 78.7, 75.1, 74.6, 73.9, 73.5, 73.0, 72.6, 69.0, 53.5, 36.7, 33.7, 31.9, 31.8, 29.7, 29.6, 29.4, 29.3, 25.7, 22.7, 22.6, 14.1; HR-ESI-MS [M + Na]$^+$ $C_{63}H_{91}NO_8Na$ calcd for m/z 1012.6642, found 1012.6657.

(3*S*,4*S*,5*R*)-1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-3-*N*-(decanoylamino)-4,5-di-*O*-acetylnonadecane (19). To a solution of compound **18** (45 mg, 0.04 mmol, 1 equiv) in EtOH (4 mL) were added 35 mg of 10% Pd/C and TFA (14 μL, 0.18 mmol, 4 equiv). H_2 gas was purged into the reaction mixture for 2 min, and the mixture was stirred overnight under a H_2 atmosphere (balloon). The reaction mixture was diluted with MeOH (60 mL), filtered through a Celite pad, and concentrated to afford compound **1** in a quantitative yield. To 18 mg (0.03 mmol) of compound **1** in pyridine (2 mL) was added acetic anhydride (0.3 mL), and then the reaction mixture was stirred at room temperature overnight under an argon atmosphere. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 25 mL), and the extracts were dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography using hexane/EtOAc 80/20 to 50/50 afforded compound **19** (11 mg) as a white solid: R_f 0.60 (EtOAc 100%); [α] = +9.09° (0.11, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.71 (d, J = 10 Hz, 1H), 5.41 (s, 1H), 5.05−4.99 (m, 2H), 4.96−4.91 (m, 2H), 4.15−4.12 (m, 2H), 4.05 (dd, J = 11, 7.5 Hz, 1H), 3.86 (t, J = 6.5 Hz, 1H), 3.43−3.41 (m, 1H), 2.19−2.16 (m, 2H), 2.14 (s, 3H), 2.11 (s, 3H), 2.05 (s, 6H), 2.04 (s, 3H), 1.98 (s, 3H), 1.61−1.54 (m, 2H), 1.45−1.38 (m, 2H), 1.30−1.25 (m, 40H), 0.88 (t, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 171.0, 170.48, 170.46, 170.2, 170.1, 170.0, 75.6, 74.0, 72.8, 72.1, 67.8, 67.7, 61.5, 47.8, 36.7, 31.9, 31.8, 29.7, 29.6, 29.4, 29.3, 29.2, 28.7, 26.9, 25.7, 25.6, 22.6, 21.0, 20.9, 20.8, 20.7, 14.1; HR-ESI-MS [M + Na]$^+$ $C_{47}H_{81}NO_{14}Na$ calcd for m/z 906.5554, found 906.5528.

(2*E*,3*S*,4*S*,5*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-4,5-*O*-isopropylidene-(2,3,4,6-tetra-*O*-benzyl)-1,5-anhydro-D-galacto-2-nonadecene (20). To a solution of hemiketal **17** (160 mg, 0.16 mmol, 1 equiv) in DCM (15 mL) were added $NaHCO_3$ (67.7 mg, 0.8 mmol, 5 equiv) and Dess−Martin periodinane (205.4 mg, 0.48 mmol, 3 equiv), and then the reaction mixture was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (30 mL) and saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 × 80 mL), and the extracts were dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography using hexane/EtOAc 90/10 to 85/15 afforded diketone **20** (145 mg, 91%), as a colorless viscous solid: R_f 0.47 (hexane/EtOAc 7/3), [α] = −5.00° (c = 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32−7.16 (m, 20H), 7.08 (dd, J = 16, 4 Hz, 1H), 6.73 (d, J = 16 Hz, 1H), 4.64−4.61 (m, 2H), 4.56−4.47 (m, 2H), 4.43−4.36 (m, 4H), 4.32 (s, 2H), 4.26−4.23 (m, 2H), 4.20−4.17 (m, 2H), 4.10−4.06 (m, 1H), 3.98 (app t, J = 5.5 Hz, 1H), 1.44 (s, 9H), 1.38 (s, 6H), 1.30−1.27 (m, 26H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.0, 198.9, 154.7, 145.7, 137.3, 137.0, 136.8, 128.5, 128.39, 128.30, 128.1, 128.0, 127.9, 127.8, 127.6, 125.9, 108.4, 83.4, 81.0, 80.0, 74.6, 74.5, 73.3, 73.1, 72.4, 31.9, 29.7, 29.6, 29.5, 28.3, 26.9, 25.3, 22.7, 14.1; HR-ESI-MS [M + Na]$^+$ $C_{61}H_{83}NO_{10}Na$ calcd for m/z 1012.5914, found 1012.5922.

(2*E*,3*S*,4*S*,5*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-4,5-*O*-isopropylidene-(2,3,4,6-tetra-*O*-benzylaza-β-D-galactopyranosyl)-2-nonadecene (21). To a solution of diketone **20** (140 mg, 0.14 mmol, 1 equiv) in MeOH (8 mL) were added ammonium formate (35.5 mg, 0.56 mmol, 4 equiv) and $NaCNBH_3$ (35.6 mg, 0.56 mmol, 4 equiv), and then the reaction mixture was stirred overnight at room temperature under an argon atmosphere. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (2 × 80 mL), and the organic layer was washed with H_2O (2 × 70 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography using hexane/EtOAc 90/10 to 70/30 afforded compound **21** (90 mg, 66%) as a pale yellow viscous solid: R_f 0.40 (hexane/EtOAc 5/3); [α] = −7.89° (c = 0.38, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.27 (m, 20H), 5.93 (dd, J = 16, 3.5 Hz, 1H), 5.79 (dd, J = 15.5, 7 Hz, 1H), 4.95 (d, J = 11.5 Hz, 1H), 4.96−4.74 (m, 3H), 4.66−4.58 (m, 3H), 4.50−4.38 (m, 3H), 4.32 (m, 1H), 4.13−4.12 (m, 1H), 3.94−3.90 (m, 2H), 3.65 (app t, J = 9 Hz, 1H), 3.53−3.46 (m, 2H), 3.27 (app t, J = 7 Hz, 1H), 3.19 (app t, J = 8

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Hz, 1H), 2.85 (app t, J = 6.5 Hz, 1H), 1.43 (s, 9H), 1.29−1.31 (m, 32H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.8, 138.7, 138.6, 138.5, 137.9, 128.5, 128.4, 127.7, 127.5, 80.0, 80.8, 79.4, 75.3, 74.2, 73.9, 73.4, 72.8, 70.6, 57.5, 31.9, 29.7, 29.6, 29.5, 29.3, 28.8, 28.3, 25.4, 22.7, 14.1; HR-ESI-MS $[M + H]^+$ $C_{61}H_{87}N_2O_8$ calcd for m/z 975.6462, found 975.6483.

Oxazolidinone 22. A solution of compound **21** (28 mg, 0.03 mmol) in 3 mL of EtOH/2 M HCl (4/1) was heated at reflux for 3 h. After consumption of the starting material as indicated by TLC, the reaction mixture was diluted with MeOH (10 mL) and evaporated. The resulting crude mixture was lyophilized over benzene (3 mL). To 12 mg (0.014 mmol) of free amine in dry THF (1 mL) was added *N,N*-carbonyldiimidazole (21 mg, 0.126 mmol, 9 equiv) at 0 °C, and then the reaction mixture was stirred for 6 h at room temperature under an argon atmosphere. Evaporation of solvent and purification by flash chromatography using hexane/EtOAc 80/20 to 40/60 afforded compound **22** (6 mg, 49% over two steps) as a viscous solid: R_f 0.44 (hexane/EtOAc 2/8); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.27 (m, 20H), 5.80 (H-3, dd, J = 15.5, 7.5 Hz, 1H), 5.73 (H-2, dd, J = 15.5, 6 Hz, 1H), 4.96−4.92 (m, 2H), 4.79−4.69 (m, 3H), 4.64−4.56 (m, 2H), 4.48−4.36 (m, 2H), 4.30 (H-5, app t, J = 8.0 Hz, 1H), 4.20 (H-4, app t, J = 7.5 Hz, 1H), 3.98 (s, 1H), 3.63−3.56 (m, 3 H), 3.47 (app t, J = 9 Hz, 1H), 3.35 (app t, J = 8 Hz, 1H), 3.14 (H-1, dd, J = 9.5, 6 Hz, 1H), 2.87 (t, J = 7 Hz, 1H), 1.26 (m, 26H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.2, 138.4, 138.3, 138.1, 137.6, 133.9, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 85.6, 81.0, 79.6, 74.7, 74.5, 73.9, 73.5, 72.4, 70.1, 60.7, 57.5, 56.3, 33.9, 31.9, 29.7, 29.6, 29.3, 24.6, 22.7, 14.1; HR-ESI-MS $[M + H]^+$ $C_{54}H_{73}N_2O_7$ calcd for m/z 861.5417, found 861.5440.

(2*E*,3*S*,4*S*,5*R*)-1-(2,3,4,6-Tetra-*O*-benzylaza-β-D-galactopyranosyl)-3-*N*-(decanoylamino)-4,5-dihydroxy-2-nonadecene (23). Compound **21** (80 mg, 0.08 mmol) was dissolved in 8 mL of EtOH/2 M HCl (4/1), and then the mixture was heated at reflux for 3 h. After consumption of the starting material as indicated by TLC, the reaction mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$/MeOH (7/1, 4 × 50 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The resulting free amine was dried under vacuum and dissolved in 8 mL of DMF/DCM (2/5), and then 4-nitrophenyldecanoate (36.1 mg, 0.12 mmol, 1.5 equiv) and K_2CO_3 (34 mg, 0.24 mmol, 3 equiv) were added, and this mixture was stirred vigorously overnight at room temperature under an argon atmosphere. After completion of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 × 10 mL) and extracted with EtOAc (2 × 75 mL), the organic layer was thoroughly washed with water (3 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography (hexane/EtOAc 80/20 to 60/40 to 40/60) afforded compound **23** (60 mg, 74% over two steps) as a white solid: R_f 0.55 (EtOAc 100%), $[\alpha]$ = 10.7° (0.28, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.26 (m, 20H), 5.93 (dd, J = 15.5, 6 Hz, 1H), 5.91 (m, 1H), 5.72 (dd, J = 16, 7 Hz, 1H), 4.96 (d, J = 11.5 Hz, 1H), 4.84 (d, J = 10.5 Hz, 1H), 4.77−4.69 (m, 3H), 4.63−4.58 (m, 2H), 4.47−4.41 (m, 2H), 3.95 (s, 1H), 3.63 (app t, J = 9 Hz, 1H), 3.54−3.46 (m, 4H), 3.42 (dd, J = 6.5, 3 Hz, 1H), 3.33 (dd, J = 9, 7 Hz, 1H), 3.14 (dd, J = 9, 7 Hz, 1H), 2.85 (t, J = 7 Hz, 1H), 2.18−2.16 (m, 2H), 1.31−1.26 (m, 40H), 0.87−0.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.7, 138.6, 138.5, 137.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 85.2, 80.4, 76.8, 75.1, 74.4, 74.1, 73.0, 72.6, 70.1, 61.8, 57.6, 53.3, 36.7, 36.6, 31.9, 31.8, 29.7, 29.6, 29.4, 29.3, 25.7, 22.6, 14.1; HR-ESI-MS $[M + H]^+$ $C_{63}H_{93}N_2O_7$ calcd for m/z 989.6982, found 989.6996.

(3*S*,4*S*,5*R*)-1-(2,3,4,6-Tetra-*O*-acetylaza-β-D-galactopyranosyl)-3-*N*-(decanoylamino)-4,5-di-*O*-acetylnonadecane (24). To a solution of compound **23** (55 mg, 0.05 mmol, 1 equiv) in EtOH (5 mL) was added 40 mg of 10% Pd/C and 2 drops of concentrated HCl. H_2 gas was purged into the reaction mixture for 2 min, and the mixture was stirred overnight under an H_2 atmosphere (balloon). The reaction mixture was then diluted with MeOH (50 mL), filtered through a Celite pad, and concentrated to afford the desired compound **2** in quantitative yield. To 20 mg (0.03 mmol) of compound **2** were added pyridine (2 mL) and acetic anhydride (0.5 mL). The resulting mixture was stirred overnight under an argon atmosphere at room temperature. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 25 mL), and the extracts were dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography using hexane/EtOAc 80/20 to 40/60 afforded compound **24** (8 mg) as a white solid: R_f 0.45 (hexane/EtOAc 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.66 (d, J = 9.5 Hz, 1H), 5.40 (s, 1H), 4.95−4.89 (m, 4H), 4.17−4.16 (m, 1H), 4.05−3.95 (m, 2H), 3.16 (app t, J = 7 Hz, 1H), 2.71−2.68 (m, 1H), 2.18 (t, J = 7.5 Hz, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H), 1.30−1.26 (m, 44H), 0.89 (t, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 171.1, 170.6, 170.55, 170.53, 170.2, 170.0, 75.3, 73.2, 72.8, 70.9, 68.4, 62.3, 57.4, 54.9, 48.0, 36.8, 31.9, 31.8, 30.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.0, 25.9, 25.7, 25.4, 21.0, 20.9, 20.8, 20.7, 14.1; HR-ESI-MS $[M + H]^+$ $C_{47}H_{83}N_2O_{13}$ calcd for m/z 883.5895, found 883.5872.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving HRMS of aza-O-galactosylceramide **5**, ^{1}H and ^{13}C NMR spectra of **7**−**13**, **15**−**18**, **1**, and **19**−**24**, and COSY spectra of **13**, **22**, and **23** and a table giving a comparison of ^{1}H and ^{13}C NMR of compound **1** with reported data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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