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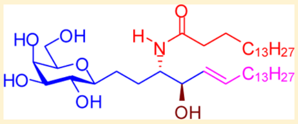
Synthesis of a *C*-Glycoside Analogue of *β*-Galactosyl Ceramide, a Potential HIV-1 Entry Inhibitor

V. Narasimharao Thota, Mula Brahmaiah, and Suvarn S. Kulkarni*

Department of Chemistry, Indian Institute of Technology Bombay, Mumbai 400076, India

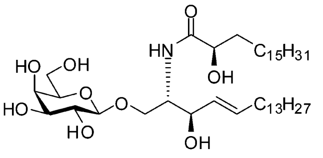
S *Supporting Information*

ABSTRACT: A *β*-*C*-galactosyl ceramide was synthesized in a stereoselective manner, employing a Sharpless AD reaction and olefin cross metathesis as key steps.

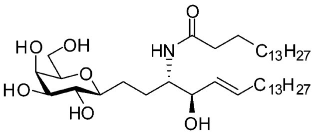


INTRODUCTION

It is well-established that human immunodeficieny virus (HIV-1 and HIV-2) gains entry into cells via binding of its envelope glycoprotein gp120 to CD4 molecules present on the host lymphoidal cells.[1] In cells lacking CD4, the infection takes place via an alternate pathway. In 1991, Harouse et al. showed that the antibodies specific for glycosphingolipid *β*-galactosyl ceramide (*β*-GalCer) **1** (Figure 1) inhibit infection of two neural CD4-negative cell lines and that the recombinant HIV surface glycoprotein gp120 specifically binds to **1**.[2] Further, Bhat and co-workers reported that *β*-GalCer and its derivatives including psychosine (*β*-GalCer devoid of fatty acid chain) and those containing various fatty acid chains (*N*-palmitoyl, *N*-steroyl, *N*-oleoyl, *N*-nervonyl) bind to recombinant gp120.[3] *β*-GalCer has also been shown to induce the requisite conformation change on the gp120 for binding with the chemokine coreceptor which ultimately leads to fusion with cell membrane and infection in CD4 presenting cells.[4] A number of soluble analogues of *β*-GalCer have been shown to inhibit HIV infection.[5] Thus, *β*-GalCer and its analogues have attracted considerable attention as potential inhibitors of the first step of HIV infection.[6] Structure−activity relationship studies followed, mainly focused on the variations in the sugar and fatty acid chain. Although the results vary as per the type of assay system used, it is generally observed that the D-galactose sugar is specifically needed for the binding, whereas the presence or absence of a fatty acid residue or change in its length or level of hydroxylation can be tolerated.[3,7,8] Still, anomalies with these results were reported.[9]



1. *β*-GalCer



2. *β*-*C*-GalCer analogue

Figure 1. Structures of *β*-*O* and *C*-GalCer analogues.

Over the years, *C*-glycosides, wherein an acetal linkage is replaced by a methylene group, have been introduced as chemically and enzymatically stable analogues of *O*-glycosides.[10] Immediately after the biological importance of *β*-GalCer **1** in HIV virulence was recognized, Bertozzi et al. synthesized the first nonisosteric water-soluble *C*-glycoside synthetic analogue of **1** that binds specifically to recombinant gp120 and blocks the interaction of gp120 with *β*-GalCer.[11] This nonisosteric analogue lacks a fatty acid residue and has a simplified ceramide chain with an alkyl amide substituent in place of the allyl alcohol. The first methylene isosteric analogue of *β*-GalCer, **2**, was synthesized by Dondoni and co-workers in 1999.[12] Compostella and co-workers synthesized a structurally related *C*-glycoside analogue of sulfatide.[13] Recently, a highly simplified *β*-*C*-glycoside analogue with a linear alkyl chain replacing the ceramide was shown to inhibit HIV binding.[14] However, simple, short-chain analogues have been shown to be inactive in previous studies and the presence of a rigidifying element such as an allylic alcohol or alkyl amide in the lipid chain was deemed necessary for the biological activity.[11] Thus, there is a paucity of data regarding structure and function studies on *β*-*C*-GalCer and gp120 and a systematic study is missing. For this purpose a divergent synthetic approach for the synthesis of stable *β*-*C*-glycoside analogues is desired. Herein we present a straightforward synthesis of a fully functionalized *C*-glycoside analogue of *β*-GalCer **2** that would allow divergent synthesis of various structurally related analogues.

RESULTS AND DISCUSSION

The key structural elements present in the *C*-glycoside **2** are a *β*-*C*-glycosidic linkage and a long lipid chain containing a *trans* double bond and an amide functionality. Previously, Dondoni and co-workers employed a Wittig olefination of a phosphorane derived from *β*-D-galactopyranosyl aldehyde with D-serine-derived aldehyde, whereas Compostella and co-workers utilized a [2,3]-sigmatropic rearrangement as key steps, for the construction of **2** and its sulfatide analogue, respectively.

Our synthesis of **2** (Scheme 1) began with the known lactone **3**,[15] which was first converted to the *β*-*C*-glycoside **4** following the procedure reported by Kielberg and co-workers.[16] The *C*-

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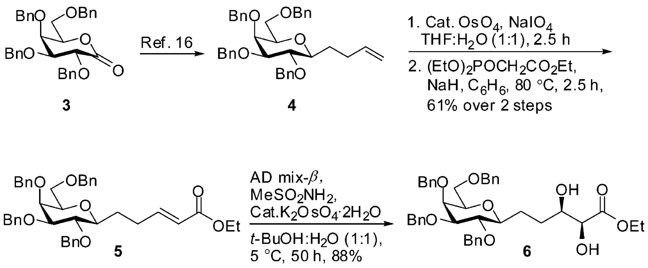
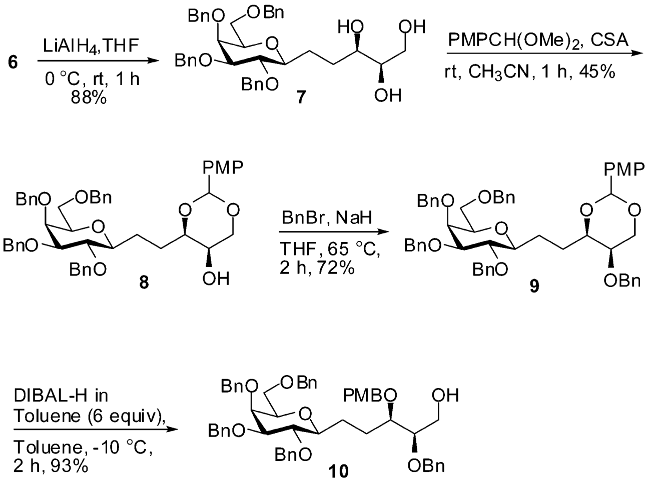
Scheme 1. Synthesis of Key Intermediate Diol 6 via Sharpless AD Reaction



homoallyl galactoside **4** was then subjected to oxidative cleavage of the double bond using catalytic OsO_4 and $NaIO_4$[17] to obtain an aldehyde, which upon Horner−Wadsworth−Emmons (HWE) olefination using triethylphosphono ester in benzene afforded the (*E*)-olefin ester **5** (61% over two steps). It should be noted that our initial attempts to effect this coupling in the presence of the mild base K_2CO_3[17] offered a poor *E*:*Z* ratio (2.5:1) of **5**. Employment of strongly basic conditions using sodium hydride and acetonitrile as a solvent improved the ratio (*E*:*Z* ratio 5:1). Since the *E*/*Z* isomers were not separable, it was essential to find out conditions that gave only the *E* isomer. Gratifyingly, compound **5** was obtained with exclusive *E* selectivity when the coupling was carried out using sodium hydride in the nonpolar solvent benzene. Sharpless dihydroxylation[18] of **5** using ADmix-*β* in the presence of methanesulfonamide and catalytic $K_2OsO_4{\cdot}2H_2O$[19] at 5 °C afforded the desired *syn*-diol ester **6** in 88% yield, exclusively. The stereochemistry of diol **6** was assigned as 2*S*,3*R* using the Sharpless mnemonic device.[18−20]

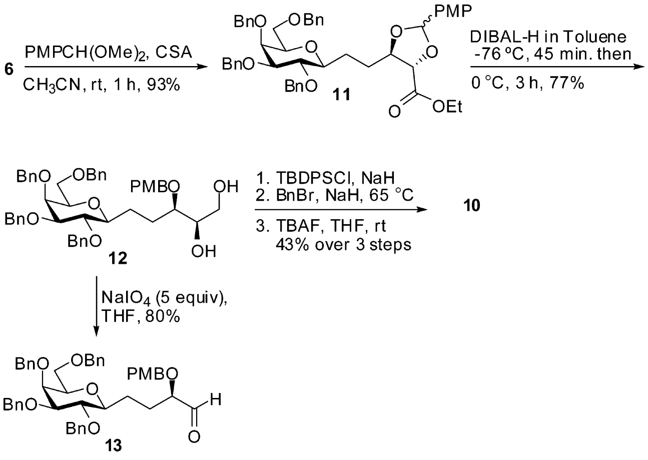
Scheme 2. Synthesis of Regioselectively Protected 1° Alcohol 10



Synthesis of the key intermediate primary alcohol **10** from **6** is shown in Scheme 2. LAH reduction of the ester diol **6** delivered the triol **7** (88%). Treatment of **7** with anisaldehyde dimethyl acetal and 10-camphorsulfonic acid (CSA) furnished a mixture of regioisomers, from which the desired 1,3-protected acetal **8** could be isolated after careful column chromatography in 45% yield. A fraction containing a mixture of **8** and the other regioisomer was also obtained to the extent of 32%. This mixture was recycled back by treatment with 80% AcOH at 80 °C to recover the triol **7** (90%). The identity of **8** was confirmed by carrying out chemical transformations. Accordingly, compound **8** was first benzylated (NaH, BnBr, 72%) to give **9**. A highly regioselective DIBAL reductive ring opening of *p*-methoxybenzylidene acetal **9** (−10 °C, toluene)[21] afforded the primary alcohol **10** (93%) as the sole product. Compound **10** upon Dess−Martin periodinane (DMP) oxidation[22] in the presence of sodium bicarbonate generated the corresponding aldehyde, confirming the presence of a primary alcohol.

In order to ascertain the regioselectivity and improve the yield of the overall transformation, compound **10** was synthesized by another route starting from ester diol **6**, as shown in Scheme 3. The *syn*-diol **6** upon treatment with anisaldehyde dimethyl acetal and catalytic CSA afforded the corresponding *p*-methoxybenzylidene acetal **11** (93%, 5:2 endo:exo), which upon a regioselective, ester-assisted reductive ring opening[23] of the benzylidene acetal furnished diol **12** (77%). That the diol **12** was indeed a 1,2-diol was further confirmed by carrying out its $NaIO_4$ cleavage, which afforded aldehyde **13**. Compound **12** was converted into **10** via a three-step sequence. The primary hydroxyl group of diol **12** was selectively protected as a TBDPS ether. The remaining hydroxyl was benzylated, and the TBDPS group was removed to give an alcohol, which was found to be **10** by TLC and NMR analysis. Thus, the regioselectivity and the structure of alcohol **10** was unambiguously confirmed by chemical transformations and spectroscopic means (see the Supporting Information).

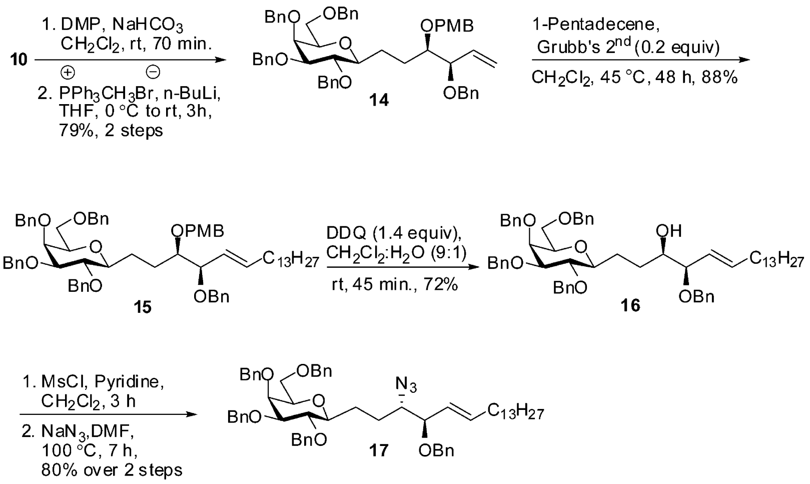
Scheme 3. Alternate Route for the Synthesis of 1° Alcohol 10



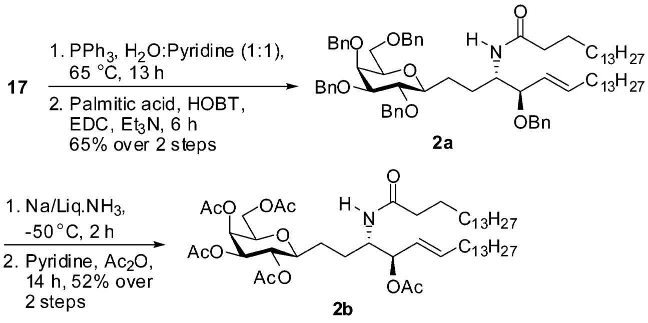
Transformation of the key intermediate **10** into the *C*-galactosyl azido sphingosine **17** is outlined in Scheme 4. Earlier, olefin cross metathesis was effectively used in the synthesis of *β*-*O*-GalCer,[24] *β*-*C*-GalCer,[25] and *α*-*C*-GalCer[26] analogues. DMP oxidation of the primary alcohol **10** followed by one-carbon homologation using Wittig olefination provided the terminal olefin **14** (79%), which was subsequently subjected to a cross metathesis reaction[24,26,27] with 1-pentadecene using Grubbs' second-generation catalyst to afford the (*E*)-olefin **15** (88%). The PMB group in **15** was removed using DDQ to give alcohol **16** (72%), which was converted into its mesylate and subsequently displaced by sodium azide[28] to form the *C*-galactosyl azido sphingosine derivative **17** (80%, two steps).

Reduction of the azido group in **17** followed by EDC coupling with palmitic acid[29] fashioned the perbenzylated *C*-GalCer derivative **2a** (Scheme 5). Selective removal of benzyl groups in the presence of the double bond was achieved under Birch reduction conditions to afford *C*-GalCer **2**, which was

Scheme 4. Synthesis of Galactosyl Sphingosine 17 via Wittig Olefination and Cross Metathesis



Scheme 5. Synthesis of Galactosyl Ceramide 2b



characterized as its known peracetate derivative **2b**. Our ^1H and ^{13}C NMR data of **2b** corroborated well with its reported data[12] (see the Supporting Information).

■ CONCLUSION

In conclusion, we have synthesized a *C*-glycoside analogue of *β*-GalCer **2** in a stereoselective manner starting from readily available lactone **3** via Sharpless dihydroxylation and olefin cross-metathesis as key steps. The strategy offers two branching points for introducing diversity, as shown in Figure 2. The synthesis proceeds through the *C*-glycoside analogue of psychosine, which can be coupled with various fatty acids of different lengths and unsaturation patterns. The lipid chain length can be modulated by using different olefins in the cross metathesis step. The simple and straightforward route is expected to give ready access to various *β*-*C*-GalCer analogues for biological studies.

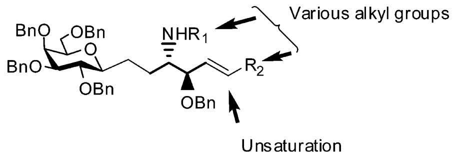


Figure 2. Branching points in the synthetic route to introduce diversity.

■ EXPERIMENTAL SECTION

All reactions were conducted under a dry nitrogen atmosphere. Solvents (CH_2Cl_2 >99%, THF 99.5%, acetonitrile 99.8%, DMF 99.5%) were purchased in capped bottles and dried under sodium or CaH_2. All other solvents and reagents were used without further purification. All glassware used was oven-dried before use. TLC was performed on precoated aluminum plates of silica gel 60 F254 (0.25 mm, E. Merck). Developed TLC plates were visualized under a short-wave UV lamp and by heating plates that were dipped in ammonium molybdate/cerium(IV) sulfate solution. Silica gel column chromatography was performed using silica gel (100−200 mesh) and employed a solvent polarity correlated with TLC mobility. NMR experiments were conducted on a 400 MHz instrument using $CDCl_3$ (D, 99.8%) solvent. Chemical shifts are relative to the deuterated solvent peaks and are in parts per million (ppm). High-resolution mass spectra were acquired in ESI mode using a Q-TOF analyzer. Melting points were determined by a capillary apparatus. Specific rotation experiments were measured at 589 nm (Na) and 25 or 20 °C. IR spectra were recorded on an FT-IR spectrometer using CsCl plates.

1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-butene (4). A solution of lactone **3** (10.4 g, 19.31 mmol) in THF (60 mL) was cooled to −78 °C and treated with a solution of homoallylmagnesium bromide in THF (1.0 M, 65 mL, 65 mmol). After it was stirred for 45 min, the solution was warmed to 0 °C. The reaction mixture was quenched by solid NH_4Cl (6.0 g) and diluted with CH_2Cl_2 (50 mL). Water (20 mL) was added, and to the so formed white turbidity was added $NaHSO_4$ (15 mL) until the two layers separated. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2) and dried over anhydrous Na_2SO_4. The combined organic layers were concentrated on a rotary evaporator to give the corresponding hemiketal. This hemiketal was dissolved in CH_3CN (80 mL) and cooled to −40 °C. Then $BF_3\cdot Et_2O$ (4.9 mL, 38.62 mmol) and Et_3SiH (6.1 mL, 38.62 mmol) were sequentially added into the reaction mixture and stirred for 30 min. The reaction was quenched by saturated aqueous $NaHCO_3$ (5 mL). The reaction mixture was diluted with EtOAc (40 mL) and washed with water (15 mL) and brine (10 mL). The separated aqueous layer was washed with EtOAc (30 mL × 2) and dried over anhydrous Na_2SO_4. The combined organic layers were concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (7% ethyl acetate/petroleum ether) to afford **4** (6.7 g, 60% over two steps) as a viscous liquid. ^1H and ^{13}C NMR data of compound **4** are in agreement with the reported data.[16]

Ethyl-2-ene-5-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)-pentanoate (5). To a stirred solution of alkene **4** (7.1 g, 12.3 mmol) in H_2O (75 mL) and THF (75 mL) were added sodium periodate (19.3 g, 90 mmol), and 2.5 wt % osmium tetroxide in *tert*-butyl alcohol (3.8 mL, 0.37 mmol) at room temperature. The reaction mixture was stirred for 2.5 h at room temperature. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with water (15 mL) and brine (10 mL). The separated aqueous layer was washed with CH_2Cl_2 (30 mL × 2) and dried over anhydrous Na_2SO_4. The combined organic layers were concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (25% ethyl acetate/petroleum ether) to give the corresponding one carbon less aldehyde. The obtained aldehyde (7.0 g, 12.11 mmol) was dissolved in dry benzene (60 mL). A portion of 60% NaH (1.45 g, 60.44 mmol) was dissolved in dry benzene (10 mL), and to this was added triethyl phosphonoacetate (5.3 mL, 26.63 mmol). The resulting solution was added dropwise to the aldehyde-containing reaction flask at room temperature. After 5 min, the reaction mixture was refluxed at 80−85 °C for 2 h. The reaction was quenched with 5% citric acid (5 mL), diluted with CH_2Cl_2 (30 mL), and washed with water (15 mL). The separated aqueous layer was washed with CH_2Cl_2 (30 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (14% ethyl acetate/petroleum ether) to give **5** (4.9 g, 61% over two steps) as a viscous liquid: $[\alpha]^{25}_{D} = -1.4°$ (*c* 4.4, $CHCl_3$); IR ($CHCl_3$) ν 3617, 3018, 2976, 2893, 2400, 1712, 1525, 1421, 1218, 1046, 918, 877, 770, 669, 626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.26 (m, 20H), 6.97 (dt, *J* = 8.0, 15.6 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.96 (d, *J* = 11.6 Hz, 1H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 13.1 Hz, 1H), 4.68 (s, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.49, 4.45 (ABq, *J* = 11.8 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.01 (d, *J* = 2.4 Hz, 1H), 3.70 (t, *J* = 9.2 Hz, 1H), 3.62 (dd, *J* = 2.4, 9.2 Hz, 1H), 3.59−3.51 (m, 3H), 3.23 (td, *J* = 2.4, 9.2 Hz, 1H), 2.47−2.38 (m, 1H), 2.29−2.22 (m, 1H), 2.04−1.97 (m, 1H), 1.7−1.60 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 149.1, 138.8, 138.43, 138.38, 138.1, 128.6, 128.40, 128.37, 128.3, 128.0, 127.9, 127.81, 127.75, 127.70, 121.5, 84.9, 79.0, 78.8, 75.7, 74.6, 73.72, 73.66, 72.4, 69.2, 60.3, 30.2, 28.4, 14.4; HRMS-ESI $[M + H]^+$ calcd for $C_{41}H_{47}O_7$ 651.3322, found 651.3349.

Ethyl (2*S*,3*R*)-2,3-Dihydroxy-5-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)pentanoate (6). A solution of AD mix-*β* (5.3 g) in 1:1 *tert*-butyl alcohol and water (45 mL) was added to a stirred solution of **5** (2.4 g, 3.73 mmol) in 1:1 *tert*-butyl alcohol and water (15 mL) at 0 °C. Potassium osmate dihydrate (6.2 mg, 19 μmol) and methanesulfonamide (426 mg, 4.48 mmol) were added, and the reaction mixture was stirred at 5 °C for 50 h. The reaction mixture was quenched by adding sodium sulfite (5.6 g) and kept at room temperature for 20 min. It was diluted with CH_2Cl_2 (40 mL) and washed with water (10 mL). The separated aqueous layer was washed with CH_2Cl_2 (30 mL × 2) and dried over anhydrous Na_2SO_4. The combined organic layers were concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (28% ethyl acetate/petroleum ether) to afford **6** (2.25 g, 88%) as a viscous liquid: $[\alpha]^{25}_{D} = +5.2°$ (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν 3620, 3433, 3019, 2400, 1732, 1217, 1046, 928, 877, 770, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.23 (m, 20H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.93 (d, *J* = 11.7 Hz, 1H), 4.74, 4.67 (ABq, *J* = 11.7 Hz, 2H), 4.65 (d, *J* = 10.8 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.44, 4.40 (ABq, *J* = 11.8 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.00 (d, *J* = 2.8 Hz, 1H), 3.95 (d, *J* = 2.7 Hz, 1H), 3.91−3.85 (m, 1H), 3.70 (t, *J* = 9.3 Hz, 1H), 3.58 (dd, *J* = 2.8, 9.3 Hz, 1H), 3.56−3.49 (m, 2H), 3.46 (dd, *J* = 4.4, 6.0 Hz, 1H), 3.28 (td, *J* = 2.5, 9.3 Hz, 1H), 3.14 (br s, 1H), 2.59 (br s, 1H), 2.09−2.02 (m, 1H), 1.77−1.71 (m, 2H), 1.68−1.60 (m, 1H), 1.27 (t, *J* = 7.1, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 138.7, 138.5, 138.4, 137.9, 128.6, 128.5, 128.4, 128.30, 128.0, 127.92, 127.86, 127.8, 127.72, 127.67, 84.9, 79.60, 78.8, 77.4, 77.1, 75.6, 74.6, 73.7, 73.6, 72.7, 72.4, 69.1, 61.9, 30.0, 28.1, 14.3; HRMS-ESI $[M + H]^+$ calcd for $C_{41}H_{49}O_9$ 685.3377, found 685.3369.

(3*R*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-pentane-3,4,5-triol (7). The diol **6** (2.5 g, 3.67 mmol) was dissolved in THF (28 mL) and cooled to 0 °C. Vacuum-dried $LiAlH_4$ (210 mg, 5.51 mmol) was added portionwise into the reaction mixture and slowly warmed to room temperature. After 2.5 h, the reaction mixture was quenched with 10% NaOH (5 mL) and diluted with EtOAc (30 mL). The so-formed white turbidity was filtered through a pad of silica gel, washed with a mixture of MeOH and $CHCl_3$ (25%, 50 mL), and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (65% ethyl acetate/petroleum ether) to give **7** (2.36 g, 88%) as a white solid: $[\alpha]^{25}_{D} = +0.7°$ (*c* 0.66, $CHCl_3$); mp 68−69 °C; IR ($CHCl_3$) ν 3617, 3445, 3019, 2976, 2401, 1524, 1391, 1216, 1046, 928, 877, 759, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.25 (m, 20H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.94 (d, *J* = 11.6 Hz, 1H), 4.75, 4.69 (ABq, *J* = 11.8 Hz, 2H), 4.65 (d, *J* = 10.8 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.45, 4.40 (ABq, *J* = 11.7 Hz, 2H), 3.92 (d, *J* = 3.7 Hz, 1H), 3.72 (t, *J* = 9.4 Hz, 1H), 3.64 (dd, *J* = 3.7, 9.4 Hz, 1H), 3.62−3.51 (m, 5H, H-5), 3.43 (dd, *J* = 4.6, 8.7 Hz, 1H), 3.40 (dd, *J* = 4.6, 7.6 Hz, 1H), 3.30−3.35 (m, 1H), 2.99 (br s, 1H), 2.64 (br s, 1H), 2.05−1.70 (m, 3H), 1.68−1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.40, 138.35, 137.8, 128.60, 128.57, 128.4, 128.3, 128.1, 128.0, 127.93, 127.86, 127.7, 84.9, 79.9, 78.4, 75.7, 74.6, 73.9, 73.8, 73.7, 72.5, 72.4, 69.4, 64.7, 30.1, 27.6; HRMS-ESI $[M + H]^+$ calcd for $C_{39}H_{47}O_8$ 643.3271, found 643.3244.

(3*R*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3,5-*O*-*p*-methoxybenzylidenepentane-3,4,5-triol (8). (±)-Camphorsulfonic acid (0.24 g, 1.0 mmol) and anisaldehyde dimethyl acetal (2.1 mL, 12.6 mmol) were sequentially added at room temperature to a clear solution of triol **7** (1.35 g, 2.1 mmol) in CH_3CN (15 mL) and stirred at the same temperature for 1 h. The reaction mixture was quenched by Et_3N (0.5 mL), the solution was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (23% ethyl acetate/petroleum ether) to give the 1,3-benzylidene-protected compound **8** (0.72 g, 45%) as a viscous liquid: $[\alpha]^{20}_{D} = -0.4°$ (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) ν 3437, 3015, 2963, 2927, 2855, 1724, 1518, 1260, 1216, 1098, 759, 698, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.24 (m, 22H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.46 (s, 1H), 4.94 (d, *J* = 11.6 Hz, 1H), 4.93 (d, *J* = 10.6 Hz, 1H), 4.75, 4.68 (ABq, *J* = 11.7 Hz, 2H), 4.64 (d, *J* = 10.6 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.46, 4.42 (ABq, *J* = 11.8 Hz, 2H), 4.15 (dd, *J* = 1.7, 11.8 Hz, 1H), 3.98−3.94 (m, 2H), 3.82−3.71 (m, 1H), 3.79 (s, 3H), 3.68 (t, *J* = 9.2 Hz, 1H), 3.59−3.50 (m, 5H), 3.40 (d, *J* = 9.9 Hz, 1H), 3.23 (dt, *J* = 2.4, 9.2 Hz, 1H), 2.58 (d, *J* = 10.9 Hz, 1H), 2.13−2.08 (m, 1H), 1.86−1.82 (m, 2H), 1.59−1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 138.9, 138.6, 138.1, 130.8, 128.6, 128.5, 128.4, 128.1, 127.9, 127.80, 127.75, 127.7, 127.4, 113.7, 101.3, 84.9, 80.2, 79.9, 79.2, 77.4, 77.1, 75.7, 74.7, 73.9, 73.7, 72.9, 72.4, 69.1, 65.5, 55.5, 27.9, 27.5; HRMS-ESI $[M + Na]^+$ calcd for $C_{47}H_{52}NaO_9$ 783.3504, found 783.3502.

(3*R*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-4-benzyloxy-3,5-*O*-*p*-methoxybenzylidenepentane-3,5-diol (9). The 2° alcohol **8** (0.76 mg, 1.0 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. A portion of 60% NaH (0.13 g, 5.5 mmol) was added and stirred for 10 min. BnBr (260 μL, 2.2 mmol) was added at 0 °C, and the reaction mixture was refluxed at 65 °C for 2 h. The reaction mixture was quenched with MeOH (1.5 mL), diluted with EtOAc (40 mL), and washed with brine (10 mL). The separated aqueous layer was washed with EtOAc (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (15% ethyl acetate/petroleum ether) to afford **9** (612 mg, 72%) as a white solid: $[\alpha]^{25}_{D} = -6.5°$ (*c* 0.54, $CHCl_3$); mp 129−130 °C; IR ($CHCl_3$) ν 3019, 2916, 1614, 1518, 1454, 1216, 1094, 928, 758, 699, 628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.21 (m, 27H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.54 (s, 1H), 5.02 (d, *J* = 11.6 Hz, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.83 (d, *J* = 12.5 Hz, 1H), 4.82, 4.74 (ABq, *J* = 11.7 Hz, 2H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 12.5 Hz, 1H), 4.53, 4.50 (ABq, *J* = 11.8 Hz, 2H), 4.43 (d, *J* = 12.5 Hz, 1H), 4.08 (d, *J* = 1.8 Hz, 1H), 3.87−3.84 (m, 3H), 3.83 (s, 3H), 3.69−3.63 (m, 5H), 3.18 (s, 1H), 3.28 (dt, *J* = 2.0, 8.8 Hz, 1H), 2.16−2.09 (m, 1H), 1.99−1.89 (m, 2H), 1.52−1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 138.9, 138.5, 138.3, 138.1, 131.2, 128.54, 128.53, 128.4, 128.3, 128.20, 128.1, 128.0, 127.90, 127.71, 127.69, 127.66, 127.63, 127.56, 113.5, 101.2, 84.9, 79.8, 79.4, 75.6, 74.7, 73.90, 73.6, 72.3, 70.9, 70.8, 68.9, 68.10, 55.4, 27.80, 27.70; HRMS-ESI $[M + H]^+$ calcd for $C_{54}H_{59}O_9$ 851.4159, found 851.4196.

(3*R*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-(*p*-methoxybenzyloxy)-4-benzyloxy-5-pentanol (10). Compound **9** (0.6 g, 0.72 mmol) was dissolved in dry toluene (8.8 mL) and cooled to −10 °C. A 25 wt % solution of DIBAL-H in toluene (2.9 mL, 4.32 mmol) was added dropwise at −10 °C over 5 min, and the mixture was stirred for 2 h. The reaction vessel was brought to 0 °C and the mixture quenched by adding MeOH (1 mL) and 10% KOH (1 mL); the desired product was extracted with Et_2O (40 mL). The separated aqueous layer was washed with Et_2O (20 mL × 2), and the combined organic layers were dried over anhydrous Na_2SO_4. The solution was filtered and concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (25% ethyl acetate/petroleum ether) to afford **10** (572 mg, 93%) as a viscous liquid: $[\alpha]^{25}_{D} = -2.0°$ (*c* 0.66, $CHCl_3$); IR ($CHCl_3$) ν 3618, 3436, 3018, 2400, 1515, 1219, 1046, 928, 771, 670, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.23 (m, 25H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.97 (d, *J* = 11.6 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.77, 4.69 (ABq, *J* = 11.3 Hz, 2H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 2H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.48 (d, *J* = 9.3 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 2H), 4.01 (d, *J* = 2.0 Hz, 1H), 3.80−3.73 (m, 1H), 3.77 (s, 3H), 3.66−3.51 (m, 8H), 3.20 (dt, *J* = 1.8, 9.1 Hz, 1H), 2.18 (br s, 1H), 2.13−2.07 (m, 1H), 1.99−1.93 (m, 1H), 1.52−1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.30 138.9, 138.6, 138.50, 138.46, 138.1, 130.5, 129.8, 128.59, 128.55, 128.5, 128.38, 128.36, 128.1, 128.0, 127.9, 127.8, 113.90, 84.9, 79.9, 79.8, 79.51, 79.47, 77.1, 75.6, 74.6, 73.8, 73.7, 72.8, 72.6, 72.4, 69.2, 61.9, 55.4, 28.6, 26.6; HRMS-ESI $[M + H]^+$ calcd for $C_{54}H_{61}O_9$ 853.4316, found 853.4331.

Ethyl (2*S*,3*R*)-2,3-*O*-*p*-Methoxybenzylidene-5-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)pentane-2,3-diol (11). The diol **6** (1.9 g, 2.75 mmol) was dissolved in CH_3CN (22 mL). (±)-Camphorsulfonic acid (0.32 g, 1.37 mmol) and anisaldehyde dimethyl acetal (2.8 mL, 16.47 mmol) were sequentially added at room temperature and stirred for 1 h. The reaction mixture was quenched by Et_3N (0.5 mL), the solution was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (20% ethyl acetate/petroleum ether) to give the corresponding benzylidene-protected compound **11** (2.05 g, 93%) in a 5:2 ratio of inseparable regioisomers as a yellowish viscous liquid: IR ($CHCl_3$) ν 3018, 2857, 1748, 1615, 1518, 1454, 1251, 1217, 1101, 1028, 759, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.23 (m, 25H), 6.91−6.86 (m, 2H), 5.94 (s, 1H), 5.93 (s, 1H), 4.94 (d, *J* = 9.4 Hz, 1H), 4.93 (d, *J* = 9.8 Hz, 1H), 4.75 (d, *J* = 11.8 Hz, 1H), 4.74 (d, *J* = 9.4 Hz, 1H), 4.67 (d, *J* = 12.3 Hz, 2H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.46, 4.42 (ABq, *J* = 11.8 Hz, 2H), 4.29−4.17 (m, 3H), 4.16−4.13 (m, 2H), 3.98 (d, *J* = 2.6 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.68 (t, *J* = 9.2 Hz, 1H), 3.60−3.50 (m, 4H), 3.32−3.20 (m, 1H), 2.22−2.10 (m, 1H), 1.90−1.75 (m, 1H), 1.70−1.52 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 160.6, 138.7, 138.4, 138.3, 138.0, 128.7, 128.50, 128.45, 128.40, 128.35, 128.30, 128.26, 128.2, 127.97, 127.85, 127.8, 127.71, 127.68, 128.6, 113.7, 104.9, 104.1, 84.8, 81.0, 80.8, 79.5, 79.4, 79.2, 78.8, 76.8, 75.6, 74.6, 73.7, 73.6, 72.3, 69.13, 69.06, 61.44, 61.39, 55.3, 30.2, 29.4, 28.3, 28.2, 14.3, 14.2; HRMS-ESI $[M + Na]^+$ calcd for $C_{49}H_{54}NaO_{10}$ 825.3609, found 825.3602.

(3*R*, 4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-*p*-methoxybenzyloxypentane-4,5-diol (12). Ester **11** (0.47 g, 588 μmol) was dissolved in dry toluene (5.2 mL) and cooled to −76 °C. A 25 wt % solution of DIBAL-H in toluene (4.7 mL, 7.05 mmol) was added dropwise at −76 °C over a period of 5 min, and the mixture was stirred for 40 min. The reaction vessel was immediately brought to 0 °C and the mixture stirred for 3 h at 0 °C. After complete consumption of starting material, the reaction mixture was quenched by adding MeOH (1 mL) and 10% KOH (1 mL), and extracted with Et_2O (40 mL). The separated aqueous layer was washed with Et_2O (20 mL × 2). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The organic phase was concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (50% ethyl acetate/petroleum ether) to give **12** (323 mg, 77%) as a white solid: $[\alpha]^{20}_{D} = -17.3°$ (*c* 1.01, $CHCl_3$); mp 78−79 °C; IR ($CHCl_3$) ν 3436, 3008, 2933, 2861, 2773, 1881, 1723, 1612, 1514, 1454, 1250, 1216, 1111, 914, 756, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.17 (m, 22H), 6.81−6.79 (m, 2H), 4.94 (d, *J* = 11.1 Hz, 2H), 4.75, 4.68 (ABq, *J* = 11.7 Hz, 2H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.46, 4.41 (ABq, *J* = 11.8 Hz, 2H), 4.33 (d, *J* = 10.9 Hz, 1H), 3.97 (d, *J* = 2.6 Hz, 1H), 3.75 (s, 3H), 3.67 (t, *J* = 9.2, Hz, 1H), 3.64−3.56 (m, 4H), 3.55−3.49 (m, 3H), 3.44 (q, *J* = 5.7 Hz, 1H), 3.20 (dt, *J* = 2.3, 9.2 Hz, 1H), 2.36 (s, 2H), 2.01−1.97 (m, 1H), 1.92−1.88 (m, 1H), 1.64−1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 138.8, 138.5, 138.4, 138.0, 130.3, 129.8, 128.58, 128.55, 128.4, 128.3, 128.25, 128.1, 127.94, 127.9, 127.8, 127.75, 127.7, 114.0, 84.9, 79.7, 79.4, 79.1, 77.2, 75.6, 74.6, 73.9, 73.7, 72.9, 72.4, 72.1, 69.3, 64.1, 55.4, 27.6, 26.5; HRMS-ESI $[M + Na]^+$ calcd for $C_{47}H_{54}NaO_9$ 785.3660, found 785.3654.

(2*R*)-4-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-2-*p*-methoxybenzyloxy-1-butanal (13). To a stirred solution of diol **12** (80 mg, 105 μmol) in THF (1.2 mL) was added sodium periodate (0.11 g, 524 μmol) at room temperature, and the mixture was stirred for 3 h at the same temperature. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with H_2O (10 mL). The separated aqueous layer was washed with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (20% ethyl acetate/petroleum ether) to give **13** (61 mg, 80%) as a viscous liquid: $[\alpha]^{20}_{D} = +5.5°$ (*c* 1.56, $CHCl_3$); IR ($CHCl_3$) ν 3030, 2924, 2856, 1731, 1612, 1514, 1454, 1366, 1249, 1111, 1028, 754, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, *J* = 1.8 Hz, 1H), 7.29−7.14 (m, 22H), 6.73 (d, *J* = 8.6 Hz, 2H), 4.85 (d, *J* = 12.3 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.66, 4.59 (ABq, *J* = 11.8 Hz, 2H), 4.55 (d, *J* = 10.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.35 (d, *J* = 13.1 Hz, 2H), 4.34 (s, 1H), 3.89 (d, *J* = 2.5 Hz, 1H), 3.68 (s, 3H), 3.68−3.64 (m, 1H), 3.56 (t, *J* = 9.2 Hz, 1H), 3.49 (dd, *J* = 2.5, 9.1 Hz, 1H), 3.47−3.39 (m, 3H), 3.11 (dt, *J* = 2.1, 9.2 Hz, 1H), 2.05−1.96 (m, 1H), 1.90−1.81 (m, 1H), 1.57 (dddd, *J* = 4.7, 8.8, 18.5 Hz, 1H), 1.48−1.38 (m,, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 159.6, 138.8, 138.5, 138.1, 129.8, 129.7, 128.6, 128.5, 128.35, 128.3, 128.0, 127.92, 127.85, 127.8, 127.7, 127.69, 114.0, 84.9, 83.5, 79.6, 79.2, 79.1, 77.4, 77.1, 75.6, 74.6, 73.8, 73.6, 72.4, 72.3, 69.2, 55.4, 27.6, 26.5; HRMS-ESI $[M + Na]^+$ calcd for $C_{46}H_{50}NaO_8$ 753.3398, found 753.3393.

(3*R*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-(*p*-methoxybenzyloxy)-4-benzyloxy-5-pentanol (10). To a stirred solution of diol **12** (0.2 g, 260 μmol) in dry THF (2.5 mL) at 0 °C were added 60% NaH (52 mg, 1.3 mmol) and TBDPSCl (0.1 mL, 390 μmol). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with MeOH (1.5 mL) and diluted with EtOAc (20 mL) and brine (10 mL). The separated aqueous layer was washed with EtOAc (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator, and the crude product was passed through a pad of silica gel to give the corresponding primary silylated product. The silylated product was dissolved in dry THF (2.3 mL) and cooled to 0 °C. A portion of 60% NaH (52 mg, 1.3 mmol) and BnBr (68 μL, 570 μmol) were sequentially added into the reaction mixture, and the reaction mixture was refluxed at 65 °C for 2 h. The reaction mixture was quenched with MeOH (1.5 mL), diluted with EtOAc (25 mL), and washed with brine (10 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator, and the crude product was passed through a pad of silica gel to give the corresponding benzylated product. The benzylated product was dissolved in dry THF (2.0 mL), TBAF in THF (520 μL, 520 μmmol) was added at room temperature, and the mixture was stirred for 6 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with H_2O (10 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (25% ethyl acetate/petroleum ether) to give **10** (96 mg, 43% over three steps) as a viscous liquid.

(3*R*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-(*p*-methoxybenzyloxy)-4-benzyloxy-5-hexene (14). $NaHCO_3$ (0.34 g, 4.09 mmol) was added to a clear solution of **10** (0.34 g, 0.41 mmol) in dry CH_2Cl_2 (8.5 mL). To this milky white solution was added Dess−Martin periodinane (0.4 g, 0.94 mmol). The white suspension was stirred for 70 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 (2 mL), saturated aqueous $NaHCO_3$ (5 mL) and saturated $Na_2S_2O_3$ (5 mL) were added, and the mixture was stirred until the two layers separated. The separated aqueous layer was washed with CH_2Cl_2 (10 mL × 2), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the corresponding aldehyde. Methyltriphenylphosphonium bromide (1 g, 2.46 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. A 1.6 M solution of *n*-BuLi in hexane (1.6 mL, 2.56 mmmol) was added to it, until the reddish orange color persisted. The ice bath was removed, the mixture was stirred at room temperature for 1 h, and the so-formed ylide was added to a solution of the aldehyde (obtained in an earlier step) in THF (3 mL) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL), diluted with CH_2Cl_2 (25 mL), and washed with brine (10 mL). The separated aqueous layer was washed with CH_2Cl_2 (10 mL × 2), the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated on arotary evaporator, and the crude product was purified by column chromatography on silica gel (10% ethyl acetate/petroleum ether) to afford **14** (273 mg, 79%) as a viscous liquid: $[\alpha]^{25}_{D}$ = −2.8° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) *ν* 3683, 3019, 2400, 1523, 1453, 1216, 1089, 928, 759, 699, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.56−7.25 (m, 25H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.80 (ddd, *J* = 7.8, 8.8, 16.4 Hz, 1H), 5.26 (dd, *J* = 10.5, 16.4 Hz, 2H), 4.97 (d, *J* = 11.9 Hz, 1H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.76, 4.70 (ABq, *J* = 11.2 Hz, 2H), 4.68 (d, *J* = 10.8 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 2H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 10.7 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 4.0 (d, *J* = 1.7 Hz, 1H), 3.85 (t, *J* = 6.7 Hz, 1H), 3.76 (s, 3H), 3.65 (t, *J* = 9.1 Hz, 1H), 3.60−3.57 (m, 3H), 3.53 (dd, *J* = 4.7, 10.8 Hz, 1H), 3.51−3.42 (m, 1H), 3.19 (t, *J* = 7.2 Hz, 1H), 2.15 (t, *J* = 9.2 Hz, 1H), 1.96−1.91 (m, 1H), 1.43 (t, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.1, 138.9, 138.8, 138.63, 138.59, 138.20, 135.7, 131.2, 129.8, 128.54, 128.46, 128.42, 128.39, 128.3, 128.1, 128.0, 127.8, 127.72, 127.68, 127.50, 118.7, 113.8, 84.9, 83.1, 81.4, 80.2, 79.7, 75.6, 74.6, 73.9, 73.7, 73.2, 72.4, 70.60, 69.3, 55.4, 28.7, 27.6; HRMS-ESI $[M + H]^+$ calcd for $C_{55}H_{61}O_8$ 849.4366, found 849.4382.

(3*R*,4*R*,5*E*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-(*p*-methoxybenzyloxy)-4-benzyloxy-5-nonadecene (15). Alkene **14** (0.2 g, 0.23 mmol) and 1-pentadecene (310 μL, 1.15 mmol) were dissolved in dry CH_2Cl_2 (4 mL). Grubbs' second-generation catalyst (40 mg, 46 μmol) was added, and the mixture was refluxed at 45 °C for 48 h. The reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (8% ethyl acetate/petroleum ether) to give **15** (0.21 g, 88%) as a yellowish viscous liquid: $[\alpha]^{25}_{D}$ = −6.6° (*c* 3.5, $CHCl_3$); IR ($CHCl_3$) *ν* 3684, 3437, 3019, 1514, 1391, 1216, 1047, 928, 877, 849, 770, 699, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.52−7.25 (m, 25H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.63 (dt, *J* = 8.4, 15.4 Hz, 1H), 5.39 (dd, *J* = 8.3, 15.4 Hz, 1H), 4.97 (d, *J* = 11.7 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 10.8 Hz, 2H), 4.66 (d, *J* = 10.5 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 12.4 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 4.46 (d, *J* = 15.4 Hz, 2H), 4.39 (d, *J* = 12.4 Hz, 1H), 4.0 (s, 1H), 3.79 (t, *J* = 8.0, Hz, 1H), 3.75 (s, 3H), 3.64 (t, *J* = 9.2, Hz, 1H), 3.61−3.50 (m, 4H), 3.50−3.40 (m, 1H), 3.19 (dt, *J* = 2.5, 9.2, Hz, 1H), 2.15 (t, *J* = 9.0, Hz, 1H), 2.04 (q, *J* = 7.1 Hz, 2H), 1.95−1.91 (m, 1H), 1.50−1.30 (m, 2H), 1.29 (s, 22H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.1, 139.1, 138.9, 138.64, 138.59, 138.1, 136.0, 131.4, 129.8, 128.54, 128.46, 128.4, 128.3, 128.1, 128.0, 127.84, 127.79, 127.71, 127.67, 127.4, 127.3, 113.7, 84.9, 83.1, 81.7, 80.2, 79.7, 77.1, 75.6, 74.60, 73.9, 73.7, 73.2, 72.40, 70.1, 69.20, 55.3, 32.5, 32.1, 29.9, 29.8, 29.7, 29.5, 29.40, 29.36, 28.7, 27.7, 22.8, 14.3; HRMS-ESI $[M + Na]^+$ calcd for $C_{68}H_{86}NaO_8$ 1053.6215, found 1053.6224.

(3*R*,4*R*,5*E*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-hydroxy-4-benzyloxy-5-nonadecene (16). DDQ (33 mg, 0.15 mmol) was added to a solution of **15** (0.1 g, 104 μmol) in a mixture of CH_2Cl_2 (2.9 mL) and H_2O (0.3 mL). After 45 min, the reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2. The resulting solution was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (20% ethyl acetate/petroleum ether) to afford compound **16** (68 mg, 72%) as a viscous liquid: $[\alpha]^{20}_{D}$ = −8.0° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) *ν* 3568, 3029, 2925, 2853, 2736, 1730, 1603, 1454, 1363, 1216, 1098, 756, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.39−7.26 (m, 25H), 5.67 (dt, *J* = 8.5, 15.4 Hz, 1H), 5.31 (dd, *J* = 7.9, 15.4 Hz, 1H), 4.96 (d, *J* = 11.7 Hz, 1H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.76, 4.69 (ABq, *J* = 11.8 Hz, 2H), 4.68 (d, *J* = 10.8 Hz, 1H), 4.65 (d, *J* = 13.4 Hz, 1H), 4.62 (d, *J* = 13.4 Hz, 1H), 4.48, 4.42 (ABq, *J* = 11.7 Hz, 2H), 4.33 (d, *J* = 11.7 Hz, 1H), 3.99 (d, *J* = 2.6 Hz, 1H), 3.68 (t, *J* = 9.2 Hz, 1H), 3.60 (dd, *J* = 2.6, 9.2 Hz, 1H), 3.57−3.50 (m, 5H), 3.24 (dt *J* = 2.0, 9.2 Hz, 1H), 2.75 (br s, 1H), 2.20−2.15 (m, 1H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.82 (dt, *J* = 2.8, 9.2 Hz, 2H), 1.59−1.50 (m, 1H), 1.28 (s, 22H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 138.9, 138.7, 138.61, 138.60, 138.2, 137.5, 128.57, 128.55, 128.50, 128.38, 128.35, 128.3, 128.1, 127.99, 127.91, 127.77, 127.75, 127.70, 127.0, 85.1, 84.2, 80.1, 79.6, 75.7, 74.6,74.1, 73.9, 73.7, 72.5, 70.0, 69.3, 32.6, 32.10, 29.9, 29.8, 29.7, 29.5, 29.40, 29.3, 29.20, 28.5, 22.9, 14.3; HRMS-ESI $[M + H]^+$ calcd for $C_{60}H_{79}O_7$ 911.5826, found 911.5835.

(3*S*,4*R*,5*E*)-1-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-azido-4-benzyloxy-5-nonadecene (17). To a stirred solution of **16** (72 mg, 79.8 μmol) in CH_2Cl_2 (2.0 mL) at 0 °C were added pyridine (38 μL, 0.48 mmol) and MsCl (14 μL, 0.18 mmol) sequentially. The reaction mixture was stirred at room temperature for 3 h, and then it was diluted with CH_2Cl_2 (30 mL). The organic phase was washed with $NaHCO_3$ (15 mL), H_2O (10 mL), and brine (5 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (20% ethyl acetate/petroleum ether) to give the corresponding mesylate. This was dissolved in DMF (2.2 mL), and NaN_3 (11 mg, 0.16 mmol) was added. The reaction mixture was heated at 100 °C for 7 h. After complete consumption of starting material, it was diluted with $CHCl_3$ (30 mL) and washed with H_2O (10 mL) and brine (10 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator, and the crude product was purified by column chromatography on silica gel (10% ethyl acetate/petroleum ether) to afford **17** (60 mg, 80%) as a viscous liquid: $[\alpha]^{20}_{D}$ = −22.4° (*c* 0.775, $CHCl_3$); IR ($CHCl_3$) *ν* 3019, 2927, 2854, 2102, 1966, 1717, 1604, 1366, 1216, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.38−7.22 (m, 25H), 5.65 (dt, *J* = 6.6, 15.4 Hz, 1H), 5.40 (dd, *J* = 8.5, 15.4 Hz, 1H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.93 (d, *J* = 10.7 Hz, 1H), 4.75, 4.67 (ABq, *J* = 11.8 Hz, 2H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.61 (d, *J* = 10.7 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.45, 4.40 (ABq, *J* = 11.8 Hz, 2H), 4.32 (d, *J* = 12.0 Hz, 1H), 3.98 (d, *J* = 2.7 Hz, 1H), 3.71 (dd, *J* = 4.4, 8.4 Hz, 1H), 3.65 (t, *J* = 9.2 Hz, 1H), 3.57 (dd, *J* = 2.7, 9.2 Hz, 1H), 3.55−3.53 (m, 2H), 3.49 (dd, *J* = 5.4, 7.6 Hz, 1H), 3.45 (dd, *J* = 4.4, 9.0 Hz, 1H), 3.18 (td, *J* = 2.5, 9.2 Hz, 1H), 2.05 (q, *J* = 7.6 Hz, 2H), 1.92−1.82 (m, 1H), 1.64−1.56 (m, 3H), 1.25 (s, 22H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 138.9, 138.5, 138.1, 138.0, 128.60, 128.58, 128.5, 128.4, 128.34, 128.29, 128.1, 127.9, 127.80, 127.71, 127.65, 127.56, 126.0, 85.0, 82.7, 79.1, 79.0, 75.7, 74.7, 73.9, 73.7, 72.4, 69.9, 69.1, 65.7, 32.6, 32.10, 29.9, 29.8, 29.7, 29.5, 29.4, 29.3, 28.4, 26.60, 22.9, 14.3; HRMS-ESI $[M + Na]^+$ calcd for $C_{60}H_{77}N_3NaO_6$ 958.5705, found 958.5695.

(3*S*,4*R*,5*E*)-4-*O*-Benzyl-1-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)-3-*N*-(pentadecanoylamino)-5-nonadecene (2a). To a stirred solution of azide **17** (61 mg, 65.7 μmol) in THF (2.5 mL) were added PPh_3 (36 mg, 0.14 mmol), H_2O (0.5 mL, 27.8 mmol), and pyridine (0.5 mL, 1.24 mmmol) at room temperature, and the reaction mixture was refluxed at 65 °C for 13 h. The reaction mixture was concentrated in vacuo and coevaporated several times with toluene. Palmitic acid (22 mg, 85.8 μmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (22 mg, 114.8 μmol), and HOBt·H_2O (17 mg, 111 μmol) were sequentially added at room temperature to a mixture of DMF (2 mL) and Et_3N (0.02 mL). The resulting solution was added to the crude amine in DMF (1.5 mL) at room temperature, and the reaction mixture was stirred for 6 h. The reaction mixture was partitioned between EtOAc (30 mL) and H_2O (10 mL). The separated aqueous layer was washed with EtOAc (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (25% ethyl acetate/petroleum ether) to afford **2a** (49 mg, 65% over two steps) as a viscous liquid: $[\alpha]^{20}_{D} = -12.6°$ (c 0.65, $CHCl_3$); IR ($CHCl_3$) ν 3424, 2928, 2854, 1737, 1660, 1515, 1105, 929, 763, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.26 (m, 25H), 5.68 (dt, J = 8.2, 15.4 Hz, 1H), 5.51 (d, J = 9.4 Hz, 1H), 5.35 (dd, J = 7.8, 15.4 Hz, 1H), 4.93 (d, J = 11.7 Hz, 1H), 4.90 (d, J = 10.8 Hz, 1H), 4.74, 4.68 (ABq, J = 11.8 Hz, 2H), 4.63 (d, J = 11.8 Hz, 1H), 4.60 (d, J = 10.8 Hz, 1H), 4.56 (d, J = 12.1 Hz, 1H), 4.47, 4.42 (ABq, J = 11.8 Hz, 1H), 4.24 (d, J = 12.1 Hz, 2H), 4.01−3.90 (m, 1H), 3.98 (d, J = 2.1 Hz, 1H), 3.76 (dd, J = 3.8, 7.6 Hz, 1H), 3.62 (t, J = 9.2 Hz, 1H), 3.59−3.48 (m, 4H), 3.16 (m, 2H), 2.07−1.90 (m, 4H), 1.33−1.28 (m, 5H), 1.25 (s, 46H), 0.88 (t, J = 8.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 138.9, 138.6, 138.2, 136.2, 128.62, 128.55, 128.5, 128.4, 128.1, 127.95, 127.92, 127.8, 127.72, 127.66, 127.20, 85.0, 82.1, 79.80, 79.5, 75.7, 74.7, 73.9, 73.70, 72.5, 70.4, 69.1, 52.7, 46.1, 37.20, 32.6, 32.1, 29.9, 29.8, 29.73, 29.65, 29.6, 29.5, 28.7, 25.9, 25.2, 22.9, 14.3, 8.9; HRMS-ESI $[M + Na]^+$ calcd for $C_{76}H_{109}NNaO_7$ 1170.8096, found 1170.8084.

(3*S*,4*R*,5*E*)-4-*O*-Acetyl-1-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-3-*N*-(pentadecanoylamino)-5-nonadecene (2b). Sodium (130 mg) was added to pure ammonia gas which was liquified (~15 mL) at −50 °C in a three-neck round-bottom flask. A solution of **2a** (25 mg, 18.3 μmol) in dry THF (3 mL) was added at a rate so that the blue color persisted. The deep blue solution was stirred at −40 °C for 2.5 h. The reaction mixture was quenched with MeOH (2 mL), and excess NH_3 was allowed to evaporate at room temperature. The solution was concentrated, the residue was dissolved in pyridine (2.5 mL) and Ac_2O (2.5 mL), and the solution was stirred at room temperature for 14 h. The reaction mixture was quenched with MeOH (1 mL) at 0 °C. The reaction mixture was concentrated in vacuo, and the obtained residue was dissolved in H_2O (10 mL) and diluted with EtOAc (15 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (28% ethyl acetate/petroleum ether) to afford **2b** (10.3 mg, 52% over two steps) as a yellowish viscous liquid. ^1H and ^{13}C NMR data of compound **2b** are in complete agreement with the reported data:[12] $[\alpha]^{20}_{D} = -6.0°$ (c 0.5, $CHCl_3$); IR ($CHCl_3$) ν 3271, 3154, 2926, 2854, 2253, 1745, 1661, 1599, 1467, 1378, 1261, 1096, 908, 734, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (dt, J = 8.0, 15.4 Hz, 1H), 5.42−5.38 (m, 1H), 5.35 (dd, J = 8.5, 15.4 Hz, 1H), 5.31−5.28 (m, 1H), 5.18 (dd, J = 4.4, 6.7 Hz, 1H), 5.05 (t, J = 9.0 Hz, 1H), 5.03−4.98 (m, 1H), 4.20−4.10 (m, 2H), 4.05 (dd, J = 6.6, 11.2 Hz, 1H), 3.85 (app. t, J = 6.1, 6.6 Hz, 1H), 3.44 (dt, J = 2.9, 9.0 Hz, 1H), 2.37−2.25 (m, 1H), 2.20−1.98 (m, 4H), 2.14 (s, 3H), 2.05 (s, 6H), 2.03 (s, 3H), 1.97 (s, 3H), 1.70−1.50 (m, 5H), 1.25 (s, 46H), 0.87 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 170.7, 170.43, 170.36, 170.3, 136.9, 124.0, 77.4, 74.30, 72.3, 69.1, 67.9, 61.8, 50.8, 37.1, 32.6, 32.1, 29.9, 29.73, 29.67, 29.60, 29.55, 29.48, 29.5, 29.2, 27.5, 26.1, 25.4, 22.9, 21.40, 21.0, 20.9, 20.8, 14.3; HRMS-ESI $[M + Na]^+$ calcd for $C_{51}H_{89}NNaO_{12}$ 930.6277, found 930.6278. *Note*: a comparison of our data with reported data is given on pages S35 (^1H) and S36 (^{13}C) of the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^1H and ^{13}C NMR spectra of **2a,b** and **4−17**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for S.S.K.: suvarn@chem.iitb.ac.in.

Notes

The authors declare no competing financial interest.

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