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C-Galactosylceramide Diastereomers via Sharpless Asymmetric Epoxidation Chemistry[&]

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In the early 90's, researchers at Kirin Pharma reported the results of their studies of glycolipid extracts of *Agelas Mauritianus*, an Okinawan sponge. An optimized synthetic material, α -galactosylceramide **1** (Figure 1, also known as KRN7000 and α -Galcer), a slightly simplified version of the active materials found in the sponge extracts, displayed potent *anti*-tumor activity in a whole animal murine assay.ⁱ

An intensive series of biological experiments in the ensuing decade unveiled the activity of the α -Galcer as stemming from its immunostimulant activity.ⁱⁱ Thus, α -Galcer is *not* cytotoxic, and high-throughput cell-based assays would not have revealed its activity. The molecular basis for α -Galcer stimulation of the immune system is its initial binding to a protein receptor, named CD1d, found on the surface of antigen presenting cells. The complex between the receptor and the α -Galcer has been crystallized and analyzed by X-ray diffraction and shows that two lipid chains of the ceramide are buried in two hydrophobic channels of the protein and that the 2,3 hydroxyls of galactose and the 3 hydroxyl of the phytosphingosine side-chain participate in hydrogen bonds with the protein.ⁱⁱⁱ This binding motif leaves the 4 and 6 hydroxyls of the α -Galcer available to be recognized by receptors on natural killer T cells. In a very recent disclosure, the crystal structure of the triple complex of CD1d/ α -galcer/NKT receptor shows the binding of the gal-4-OH to the NKT, but the 6-OH seems to be free.^{iv} The effect of the second protein molecule's recognition of the initial complex is to produce a powerful surge of cytokines interferon- γ , (IFN γ), interleukin-4 (IL-4) and interleukin-12 (IL-12) which then signal for the eventual cytotoxic immune response. Extensive analog studies in the O-glycoside series revealed the importance of the galactose configuration and the free hydroxyls. The only allowed substitution of the galactose OH's is N-acyl at the 6-position of galactose. Variation of lipid chain length and degrees of unsaturation in both the phytosphingosine and N-acyl side-chains are permissible.^v In most cases, small changes in cytokine levels are the result; but in one striking example, shortening the lipid of the phytosphingosine from 14 to 5 carbons (Figure 1, compound **2**, named as **OCH**) stimulates almost exclusive production of IL-4 with a great diminution of IFN γ and IL-12. In immunology terms, this change is said to favor a TH2 immune response whereas the reverse, a decrease in IL-4 and an increase in the other cytokines is called a TH1 response. In the mouse, the TH2

[&]Dedicated to the memory of Professor Giuseppe Capozzi (1941–2008), Dipartimento di Chimica Organica, Università di Firenze, a friend and colleague.

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effect offers protection against autoimmune diseases while the TH1 pathway protects against “foreign” pathogens.

The investigation of α -Galcer in our laboratory began with the concept that the C-glycoside **3** might provide a more deep-seated change in the structure-activity profile. Aside from the obvious stability to enzymatic hydrolysis provided by replacement of anomeric O by CH₂, the important changes are (i) the loss of one hydrogen-bond acceptor and (ii) the destabilization of the galactose chair through replacement of axial O-anomeric stabilization with axial CH₂ steric repulsion. In the event, the C-glycoside **3** was prepared and we were rewarded with striking enhancement of *in vivo* activity in blocking malaria and melanoma in mice. Assay for cytokines revealed that IFN γ and IL-12 levels were about the same as for the O-glycoside while the IL-4 titre was dramatically reduced. We also studied the E and Z alkene analogs **4** and **5** and found that the E material **4** was active whereas the Z analog **5** was essentially inert in our assays (Figure 1).^{vi}

Since stereochemistry in both the galactose and in the linker region had been found to be a critical element for activity, we deemed it worthwhile to examine the effects of stereoisomers in the phytosphingosine chain. There had been an early report of a study in the O-series where the 4 possible stereoisomers **6** bearing the 4-deoxyphytosphingosine chain were studied.^{vii} Interestingly, the only isomer other than the natural 2S, 3R to show tumor growth inhibitory effects was **7** with the phytosphingosine in the unnatural, enantiomeric 2R, 3S form. Also, there has been a recent evaluation of the natural 4-deoxy series with the exact analogs of both α -Galcer and OCH. The activities **6** and **8** in the 4-deoxy series were similar to those of the parent materials (Figure 2).^{viii}

Since our earlier preparations of C-glycoside **3** had been convergent and involved coupling of intact phytosphingosines with galactose, they would not be suitable for our proposed stereoisomerism study. Thus, we embarked on a scheme where the phytosphingosine was elaborated from a pre-formed C-glycoside which we now describe.^{ix}

The known aldehyde **10** was obtained in 5 steps from commercially available β -D-galactose pentaacetate **9** according to a literature procedure (Scheme 1).¹⁰ Homologation of **10** via Wadsworth-Horner-Emmons reaction afforded (*E*)- α , β unsaturated ester **11**. DIBAL-H reduction gave the (*E*)-allylic alcohol **12** in 92% yield. Sharpless asymmetric epoxidation (SAE)¹¹ using substoichiometric amount of catalysts (50 mol% TTIP, 60 mol% D-(-)-DIPT) ensured conversion of **12** to (2*R*, 3*R*) epoxy alcohol **13** in high enantiomeric excess (*ee*>95%). Opening the (2*R*, 3*R*) epoxy alcohol **13** using NaN₃/NH₄Cl in a simple S_N2 conversion provided an inseparable mixture of desired 3-azido-1,2 vicinal diol **14** and by-product 1,3 diol **15** in 90% yield.¹² The 8/1 ratio of **14/15** was determined at a later stage. Thus, the mixture of azides was reduced with P(Me)₃ to provide amine intermediate,¹³ which was then protected with (*t*-Boc)₂O to afford an inseparable mixture of regioisomers **16** and **17**. To our delight, selective protection of the primary hydroxyl group as its TBS ether gave a separable mixture of **18** and **19** in a ratio of 8/1 in 90% yield. To assign their structures, **18** and **19** were deprotected with TBAF and the products were treated with NaIO₄. Only a compound derived from 1,2 diol could be cleaved by NaIO₄ to give the corresponding aldehyde while the 1,3 diol could not be cleaved by NaIO₄. In this way, **18** was confirmed to be the 1,2-vicinal diol.

Protection of the secondary hydroxyl of compound **18** with MOM and removal of the TBS group gave primary alcohol **21** in high yield. Oxidation of alcohol to aldehyde **22** proceeded without epimerization at the neighboring α stereocenter using either Dess-Martin periodinane or a novel Kirschning solid phase oxidant,¹⁴ both procedures taking place in high yield without causing epimerization at the α position. Inverse addition of the crude aldehyde **22** to freshly prepared tetradecyl magnesium bromide (C₁₄H₂₉MgBr) provided a separable mixture of **23**

and **24** in a ratio of 5:1 and in 60% combined yield for two steps. Based on the “Cram chelation control rule”,¹⁵ the stereochemistry of **23** and **24** was tentatively assigned as (3*S*, 4*S*, 5*S*) and (3*S*, 4*S*, 5*R*) respectively with the minor isomer **24** proposed as the desired, or natural, (3*S*, 4*S*, 5*R*) configuration at the three contiguous stereocenters. The structure assignment was confirmed later by correlation with the corresponding final products (Scheme 2)

Acidic hydrolysis of **24** removed MOM and Boc groups in one step and the resulting amine was converted to amide **25** in 80% yield. Hydrogenation of amide **25** using Pearlman's catalyst (Pd(OH)₂/C) in THF/EtOH solution afforded the fully deprotected C-glycoside analogue of KRN7000 **3**. Its NMR spectra matched with those of the previously synthesized C-glycoside analogue of KRN7000 (see supporting information). Similarly, the major isomer **23** was converted to the corresponding C-glycoside analogue **26**, which is a 5-OH epimer of the target C-glycoside analogue of the KRN7000 (Scheme 3)

As described above, the key step of opening of epoxide **13** by sodium azide was not a very clean reaction, requiring extended reaction time in refluxing MeOH. Furthermore, about 10% of the regioisomeric azide (at C-4) which was obtained required separation via careful chromatography at a later stage. Therefore, we adopted the Ti(O-*i*-Pr)₂(N₃)₂ conditions described by Sharpless.¹⁶ In our case, treatment of the (2*R*, 3*R*) epoxy alcohol **13** with Ti(O-*i*-Pr)₂(N₃)₂ gave a single product which we assigned as the desired *anti*-3-azido-2-OH **14** on the basis of the hypothesis that ring opening of the oxirane was a single S_N2 reaction as in the sodium azide experiment. Spectral comparison with authentic **14** was not definitive because the batch obtained in the sodium azide experiment was a mixture. In actual fact, the Ti(O-*i*-Pr)₂(N₃)₂ single product was ultimately revealed to be 3-azido-1, 2 vicinal diol **27**. As our synthesis proceeded via duplication of the sequence described above, detailed comparison of the final products derived from the Ti(O-*i*-Pr)₂(N₃)₂ opening of the epoxy alcohol **13** did not match with those compounds derived from NaN₃ opening. The correct structure assignment in this section (Scheme 4) reveals a series that is diastereomeric to those obtained from the sodium azide opening. The (2*S*, 3*R*) epoxy alcohol **27** was converted to aldehyde **32** in an identical manipulation sequence as described in the previous section. Grignard reaction between the aldehyde **32** and C₁₄H₂₉MgBr gave a separable mixture, and the ratio of the major isomer **33** and minor isomer **34** was 1.3:1. The stereochemical assignment was based on the “Cram-chelation control” model as was shown to be operative in the epimeric series (Scheme 4).

Both major isomer **33** and minor isomer **34** were converted to the corresponding C-glycoside analogues **36** and **38** respectively (Scheme 5). The revelation that neither of the NMR spectra of these two final products (see supporting information) matched with those of the α-C-Galcers from the sodium azide sequence forced us to assign their stereochemistries and to account for a divergence from the expected stereochemical outcome.

In fact, the C-glycoside analog **38**, the minor isomer derived from the Ti-catalyzed sequence, was identical to the C-3 epimer **42** which had been obtained in earlier work from our group. This material arose from the linking of a phytosphingosine derivative **40**, epimeric at C-3, to a galactose **39** via cross metathesis. The epimeric configuration of the amino group was unambiguous because it derived from natural phytosphingosine in which the primary alcohol had been oxidized to an aldehyde which had then been treated to form an epimeric mixture at the N-bearing carbon (Scheme 6)

The nmr spectrum of epimer **38** also closely matched the spectrum of the C-glycoside **48**, a material of the same configuration prepared by Annoura, differing only in carbon chain length (Scheme 7).¹⁸

Therefore, it must have been the case that the Ti-aided azide-opening of epoxide **13** had occurred with retention of the 3-N stereo center. To obtain diagnostic NMR confirmation of stereochemistry, the *trans*- amino alcohol **18** and *cis*-amino alcohol **29**, derived from opening of epoxide **13** with NaN₃ and Ti-aided azide respectively, were transformed to the corresponding *cis* 5-membered oxazolidine benzoyl ester **51** and *trans* benzoyl ester **54** (Scheme 8).

In its NOESY spectrum, strong correlation between H₂, H₂' and H₅, H₅' of the *p*-bromo benzoyl ester **51** clearly demonstrated the *cis* relationship of these groups, therefore the corollary *cis* relationship of H₃ and H₄, thus establishes the *anti* relationship of the corresponding H₃ and H₄ in the 1,2-diol **14** before the heterocycle is formed (Figure 3).

While for the *p*-bromo benzoyl ester **54**, which was derived from Ti(O-*i*-Pr)₂(N₃)₂ opening of epoxide **13**, two sets of correlation between H₂, H₂' and H₄ protons, H₃ and H₅, H₅' protons were observed. No correlation between H₃ and H₄ was detected, which was anticipated for a *trans* five-membered cyclic ring system (Figure 4). In this way, the stereochemical relationship between the 3-azide and 2-hydroxy of 1,2-diol **27** was proved to be *syn*, thus, the 3-C stereo center was proved unambiguously to be retained during Ti(O-*i*-Pr)₂(N₃)₂ opening of epoxide **13**.

This epoxide opening with retention can be rationalized by invoking Ti-catalyzed intramolecular participation by the pyranosidic O or 2-BnO to form an intermediate oxonium ion (Scheme 9, path A or B, respectively), inverting the epoxide center, reminiscent of earlier work of Fraser-Reid.¹⁹ This would be followed by an intermolecular azide opening with a second inversion, i.e., net retention, to afford azido alcohol **27**. It is also possible to rationalize the stereochemistry result by invoking a Ti-catalyzed epoxide opening/intramolecular delivery of azide from the Ti complex as suggested by Tan (path C) (Scheme 9).²⁰ There is no simple experiment that will distinguish between these two retention pathways.

Immunostimulant Activity

Our collaborating immunology group conducted in vitro assays for cytokine production using a system 3 separate NKT cell hybridomas paired with a CD1d antigen-presenting HeLa cell. With NKT line 829, the stereoisomers described (compound **26**, **36** and **38**) produced 40-fold less IFN γ than the positive control of α -Galcer. With NKT 912, our stereoisomers were 7-fold less productive and with NKT 926, they were 50-fold less productive. Further, there was no significant difference among these unnatural stereoisomers.²¹

In summary, the C-glycoside analog **3** of α -galactosylceramide **1** (KRN7000) was synthesized in 19 linear steps in 3.3% overall yield through the Sharpless Asymmetric Epoxidation method as the controller of stereochemistry. Sodium azide opening of epoxide **13** gave *anti* vicinal azido diol **14** with inverted stereo center at C-3 but Ti(O-*i*-Pr)₂(N₃)₂ opening of epoxide **13** provided *syn* vicinal azido diol **27** with retention of the C-3 configuration. This unusual phenomenon could be rationalized by related pathways which find literature precedent; and therefore this result should serve as a cautionary note for researchers planning to use Ti catalysis for epoxide opening.

Experimental

Instruments and Materials

NMR spectra were recorded with a QE 300MHz (¹H) and 75 MHz (¹³C) with a TECMAG data system or Bruker 500 MHz (¹H) and 125 MHz (¹³C) in deuterated solvents. The assignment of proton and carbon NMR peaks was supported by routine COSY and HSQC

spectra and for some cases by NOESY spectra. Melting points were determined on a Fisher-Johns apparatus and were uncorrected. Electrospray ionization (ESI) mass spectra experiments were performed at the Hunter College Mass Spectrometry Facility on an Agilent Technologies 1100 LC/MSD. Typical ESI method: solvent: 1/1 acetonitrile/water + 0.1% HOAc + 50 μ l NH₄Ac, flow: 0.5 ml/min, positive ion mode, fragmentor voltage: 30–200V, drying gas at 175° C. All air–moisture sensitive reactions were performed under a positive pressure of dry N₂ gas. All solvents and reagents were purified prior to use according to standard laboratory procedures. Low temperatures were recorded as bath temperatures. Thin layer chromatography analysis was carried out on precoated aluminium sheets of silica gel 60 F 254. UV light and vanillin, phosphomolybdic acid spray or DNP spray were used to visualize the components on the TLC plates. Flash column chromatography was carried out with silica gel 60 (230–400 mesh) purchased from ChemAbsorb, using ACS reagent grade petroleum ether, hexane, ethyl acetate, methylene chloride, chloroform, and methanol as eluents.

5-(3,4,5-Tris-benzyloxy-6-benzyloxymethyl-tetrahydro-pyran-2-yl)-pent-2-enoic acid methyl ester (11)

To a solution of crude 3-(3,4,5-Tris-benzyloxy-6-benzyloxymethyl-tetrahydro-pyran-2-yl)-propionaldehyde (**10**) (1.3 g, 2.3 mmol) in anhydrous MeCN (30 mL) was added methyl (triphenylphosphoronylidene)acetate (1.5 g, 4.5 mmol) in one portion at room temperature under N₂. The solution was stirred overnight at room temperature. The mixture was diluted with CH₂Cl₂ (50 mL), washed with H₂O (20 mL), extracted with CH₂Cl₂ (3 $\times$ 50 mL), dried over Na₂SO₄ (anhydrous), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with 30 % ethyl acetate/petroleum ether provided α,β unsaturated ester **11** (1.27 g, 89% yield) as yellow oil. M/S: m/z 654 (M⁺+NH₄⁺). HRMS calcd for C₄₀H₄₄O₇ 636.3087, found 636.3085. ¹H NMR (500MHz, CDCl₃): δ 7.45–7.20 (m, 20H, Ph), 7.0–6.9 (d, t, *J*=15.6, 6.9Hz, 1H, CH=), 5.80 (d, *J* = 15.5 Hz, 1H, =CH), 4.76–4.78 (m, 8H, CH₂Ph), 4.05–3.90 (m, 4H), 3.85–3.75 (m, 5H), 3.70–3.65 (m, 1H), 2.40–2.30 (m, 1H), 2.25–2.10 (m, 1H), 1.90–1.80 (m, 1H), and 1.65–1.55 (m, 1H). ¹³C NMR (125MHz, CDCl₃): δ 167.2, 149.1, 138.7, 138.6, 138.5, 138.4, 128.6, 128.6, 128.5, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 121.4, 77.4, 77.1, 76.8, 74.5, 73.4, 73.3, 73.2, 72.4, 67.8, 51.5 and 28.7.

5-(3,4,5-Tris-benzyloxy-6-benzyloxymethyl-tetrahydro-pyran-2-yl)-pent-2-en-1-ol (12)

α,β unsaturated ester **11** (1.20 g, 1.89 mmol) was dissolved in anhydrous CH₂Cl₂ (10 mL) and was cooled to –78 °C under N₂. DIBAL-H (5.7 mL, 5.7 mmol, 1 M in hexane) was added dropwise over 10 min. After completion of addition, the reaction mixture was slowly warmed up to room temperature and was stirred for 2 h at room temperature. The solution was cooled to 0°C and MeOH (10 mL) was added dropwise followed by addition of *satd.* potassium sodium tartate solution (30 mL). The solution was stirred vigorously until two clear phases appeared. The mixture was extracted with ethyl acetate (3 $\times$ 50 mL). The combined organic layer was dried with Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with 30–50% ethyl acetate/petroleum ether afforded the allylic alcohol **12** (1.03 g, 90% yield) as pale yellow oil. M/S: m/z 626 (M⁺+NH₄⁺). HRMS calcd for C₃₉H₄₄O₆ 608.3138, found 608.3134. ¹H NMR (500MHz, CDCl₃): δ 7.35–7.20 (m, 20H, Ph), 5.71–5.65 (m, 2H, –CH=CH–), 4.75–4.52 (m, 8H, CH₂Ph), 4.05 (m, 2H, –CH₂OH), 3.99–3.90 (m, 3H), 3.85–3.75 (m, 2H), 3.73–3.67 (m, 1H), 3.65–3.3.0 (dd, *J*=10.3, 4.5 Hz, 1H), 2.20 (m, 1H), 2.05–1.99 (m, 1H), 1.74–1.70 (m, 1H), and 1.60–1.50 (br, 1H). ¹³C-NMR (125MHz, CDCl₃): δ 138.8, 138.7, 138.5, 138.5, 132.7, 129.6, 128.6, 128.6, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 77.0, 76.9, 74.7, 73.5, 73.4, 73.4, 73.3, 73.1, 72.3, 68.0, 63.8 and 28.7.

(3'*R*,4'*R*)-1-(3',4'-oxiran-5'-hydroxy-pentanyl)-(2,3,4,6-tetra-O-benzyl- α -D-galactopyranoside (13)

A 100 mL round bottom flask containing powdered 4Å molecular sieves (4 g) was heated with a heating gun *in vacuo* for 10 min and was cooled down to room temperature under N₂. The flask was then filled with dry CH₂Cl₂ (10 mL) and was cooled to -20°C. Titanium (IV) isopropoxide (0.4 mL, 1.35 mmol) and diisopropyl D-(-)-tartrate (0.28 mL, 1.62 mmol) were then added. The solution was stirred for 30 min at -20°C. *tert*-butyl hydroperoxide (0.54 mL, 2.7 mmol, 5 M in toluene) was added dropwise over a period of 10 min. The solution was stirred for another 30 min at -20°C. Allylic alcohol **12** (0.82 g, 1.35 mmol, predried with 4Å MS for 30 min) in dry CH₂Cl₂ (5 mL) was added dropwise. The solution was stirred at -20°C for 18 h (stored in freezer overnight) and was cooled to 0°C. H₂O (10 mL) was added and the mixture was stirred for 30 min at 0°C, then 30% NaOH solution saturated by NaCl (10 mL) was added and the solution was stirred for 30 min at 0°C. The mixture was filtered through a pad of celite and the celite was washed with CH₂Cl₂ (50 mL). The organic phase was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL). The organic phase was combined and washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with 50% ethyl acetate/petroleum ether to provide epoxide **13** (0.50 g, 70% yield) as pale yellow oil. M/S: m/z 642 (M⁺+NH₄⁺). HRMS calcd for C₃₉H₄₄O₇ 624.3087, found 624.3082. ¹H NMR (300MHz, C₆D₆): δ 7.0 (m, 20H, Ph), 4.45-4.10 (m, 8H, CH₂Ph), 3.95-3.85 (m, 2H), 3.83-3.80 (m, 1H), 3.80-3.75 (m, 1H, -CH₂OH), 3.70-3.60 (m, 1H, -CH₂OH), 3.50-3.45 (m, 1H), 3.35-3.31 (m, 3H), 2.70 (m, 1H), 2.55-2.45 (m, 1H), 1.80-1.46 (m, 3H), and 1.40-1.11 (m, 2H). ¹³C NMR (125MHz, CDCl₃): δ 138.7, 138.5, 138.4, 138.2, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 76.9, 74.6, 73.7, 73.5, 73.4, 73.3, 73.2, 72.4, 68.0, 61.8, 58.5, 55.6, 28.2 and 23.4.

3-azido-1, 2 diol **14 and 2-azido-1, 3 diol **15****

The (2*R*, 3*R*) epoxide **13** (23.8 g, 38 mmol) was dissolved in a mixed solution of MeOH/H₂O (400 mL/50 mL, 8:1). NaN₃ (12.4 g, 190 mmol) and NH₄Cl (4.5 g, 84 mmol) were added in one portion. The solution was refluxed at 80°C under N₂ for 16 h. The solution was cooled down to room temperature and the solvent was removed under reduced pressure. The mixture was diluted with ethyl acetate (200 mL), washed with H₂O (200 mL). The aqueous layer was separated from organic layer and was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over Na₂SO₄ (anhydrous), filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with 30–50% ethyl acetate/petroleum ether to afford a mixture of 1, 2 diol **14** and 1, 3 diol **15** (23.6 g, 93% yield) as yellow oil. M/S: m/z 685 (M⁺+NH₄⁺). HRMS calcd for C₃₉H₄₅N₃O₇, 667.3258, found 667.3256. ¹H NMR (500MHz, CDCl₃): δ 7.34-7.24 (m, 20H, Ph), 4.74-4.49 (m, 8H, CH₂Ph), 4.03-3.86 (m, 4H), 3.82-3.71 (m, 2H), 3.66-3.61 (m, 1H), 3.58-3.53 (m, 3H), 3.52-3.48 (m, 1H), 2.71 (br s, 1H, -OH), 1.96 (br s, 1H, -OH), 1.85-1.78 (m, 1H), 1.74-1.68 (m, 2H) and 1.51-1.42 (m, 1H). ¹³C NMR (125MHz, CDCl₃): δ 138.5, 138.4, 138.2, 138.1, 128.5, 128.5, 128.4, 128.4, 128.1, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 74.4, 73.8, 73.3, 73.3, 73.2, 72.4, 67.7, 64.4, 63.2 and 27.1.

1, 2-diol **16 and 1, 3-diol **17****

The mixture of 1,2 diol **14** and 1,3 diol **15** (24.6 g, 37 mmol) was dissolved in anhydrous THF (400 mL). A solution of P(Me)₃ (220 mL, 221 mmol, 1 M in THF) was added dropwise at 0°C under N₂ over 30 min. The solution was then stirred at room temperature overnight. A solution of NaOH (200 mL, 0.4 mol, 2 M) was added and the solution was stirred for 2 h. The mixture was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over Na₂SO₄ (anhydrous), filtered and concentrated *in vacuo*. The crude amine was

dissolved in a solution of THF/1, 4-dioxane (100 mL/100 mL, 1:1). A *satd.* solution of NaHCO₃ (50 mL) was added followed by addition of (*t*-Boc)₂O (11.1 mL, 48.1 mmol). The solution was stirred for 24 h at room temperature. The mixture was concentrated to a total volume of 50 mL under reduced pressure. The solution was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over Na₂SO₄ (anhydrous), filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with 30–50% ethyl acetate/petroleum ether to afford a mixture of 1, 2 diol **16** and 1, 3 diol **17** (21.3 g, 78% combined yield) as yellow oil. M/S: *m/z* 759 (M⁺+NH₄⁺). HRMS calcd for C₄₄H₅₅NO₉, 741.3877, found 741.3874. ¹H NMR (500MHz, CDCl₃): δ 7.32–7.25 (m, 20H, Ph), 4.921 (d, *J*=8.4 Hz, 1H, NH), 4.71–4.44 (m, 8H, CH₂Ph), 4.05 (bs, 1H), 3.97–3.93 (m, 3H), 3.74–3.73 (br s, 1H), 3.69 (br s, 1H), 3.59 (dd, *J*=10.4 Hz, 3.52 Hz, 1H), 3.54–3.42 (m, 3H), 3.21–3.19 (br s, 1H), 3.12 (br s, 1H), 2.66 (broad peak, OH), 2.41 (broad peak, OH), 1.87–1.86 (m, 1H), 1.71–1.69 (m, 1H), 1.58–1.55 (m, 1H), 1.43 (s, 9H, (CH₃)₃), and 1.36–1.28 (m, 1H). ¹³C NMR (125MHz, CDCl₃): δ 157.5, 138.7, 138.5, 138.4, 138.4, 128.6, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 80.1, 76.5, 74.6, 74.5, 73.4, 73.3, 73.2, 73.2, 72.4, 67.5, 63.1, 53.9 (NHCO), 53.1 (NHCO), 29.1, 28.5, 27.0, 24.6 and 20.9.

(3'S,4'S)-1-{3'-*N*-tertbutylcarbamate-4'-hydroxy-5'-(tert-Butyl-dimethyl-silanyloxy)-pentanyl}-(2,3,4,6-tetra-*O*-benzyl-α-*C*-D-galactopyranoside (18**)**

The mixture of compounds **16** and **17** (11.8 g, 15.9 mmol) was dissolved in anhydrous CH₂Cl₂ (200 mL) at room temperature under N₂. Imidazole (3.3 g, 48.0 mmol) and *t*-butyldimethylsilyl chloride (3.2 g, 20.7 mmol) were added in one portion. The solution was stirred for 1h at room temperature. The mixture was washed with *satd.* NH₄Cl solution (200 mL), extracted with CH₂Cl₂ (3 × 150 mL). The combined organic layers were dried over Na₂SO₄ (anhydrous), filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with 10–20% ethyl acetate/petroleum ether to get the first fraction **19** (1.3 g, 10% yield) and the second fraction **18** (10.6 g, 78% yield), which is the desired product as yellow oil. M/S: *m/z* 873(M⁺+NH₄⁺). HRMS calcd for: C₅₀H₆₉NO₉Si, 855.4742, found 855.4738. ¹H NMR (500 MHz, CDCl₃): δ 7.33–7.20 (m, 20H, Ph), 4.99–4.97 (d, *J*=8.9 Hz, 1H, NH), 4.67–4.44 (m, 8H, CH₂), 4.02–3.95 (bs, 1H), 3.92–3.91 (m, 1H), 3.87–3.86 (m, 1H), 3.81–3.77 (m, 1H), 3.72 (bs, 1H), 3.68–3.66 (m, 1H), 3.61–3.53 (m, 4H), 3.49–3.39 (m, 1H), 1.74–1.64 (m, 4H), 1.38 (s, 9H, (CH₃)₃), 0.89–0.70 (s, 9H, CH₃), 0.02 (s, 6H, CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 156.4, 138.8, 138.7, 138.6, 138.5, 128.6, 128.5, 128.5, 128.5, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 79.3, 77.1, 74.7, 73.4, 73.4, 73.3, 72.3, 67.9, 64.7, 53.9, 28.6, 27.9, 26.1, 18.4, –5.2 and –5.3.

(3'S,4'S)-1-{3'-*N*-tert butyl carbamate-4'-methoxymethoxy-5'-(tert-Butyl-dimethyl-silanyloxy)-pentanyl}-(2,3,4,6-tetra-*O*-benzyl-α-*C*-D-galactopyranoside (20**)**

The TBS protected ether **18** (5.8 g, 6.8 mmol) was dissolved in anhydrous CH₂Cl₂ (200 mL). Freshly distilled diisopropylethylamine (11.8 mL, 67.9 mmol) was added at 0°C under N₂. Methoxymethyl chloride (2.1 mL, 27.2 mmol) was then added dropwise over 10 min. The solution was stirred at room temperature for 18 h. The reaction was quenched by addition of *satd.* NH₄Cl solution (100 mL), extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried over Na₂SO₄ (anhydrous), filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with 10–20% ethyl acetate/petroleum ether to get the fully protected compound **20** (5.79 g, 95%) as yellow oil. M/S: 917 *m/z* (M⁺+NH₄⁺). HRMS calcd for C₅₂H₇₃NO₁₀Si, 899.5004, found 899.5007. ¹H NMR (500MHz, CDCl₃): δ 7.31–7.26 (m, 20H, Ph), 5.52–5.23 (d, *J*=8.5 Hz, 1H, NH), 4.69–4.47 (m, 10H, CH₂Ph and OCH₂O), 3.97 (br s, 2H), 3.89 (br s, 1H), 3.77–3.76 (m, 3H), 3.73–3.70 (m, 2H), 3.67–3.64 (m, 2H), 3.57–3.56 (m, 1H), 3.35 (s, 3H, OCH₃), 1.68 (bs, 3H), 1.53 (s, 1H), 1.42 (s, 9H, (CH₃)₃), 0.89 (s, 9H, CH₃), 0.05 (s, 3H, CH₃), 0.04 (s, 3H, CH₃). ¹³C NMR (125MHz,

CDCl₃): δ 156.0, 138.7, 138.6, 138.5, 138.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.7, 127.6, 127.5, 127.5, 127.2, 96.5, 79.4, 78.8, 77.4, 77.1, 74.8, 73.6, 73.4, 73.3, 73.2, 72.2, 68.0, 64.2, 55.8, 52.2, 28.7, 27.9, 18.4 and -5.9.

(3'S,4'S)-1-{3'-N-tert butyl carbamate-4'-methoxymethoxy-5'-hydroxy-pentanyl}-(2,3,4,6-tetra-O-benzyl- α -C-D-galactopyranoside (21)

The fully protected compound **20** (4.6 g, 5.2 mmol) was dissolved in anhydrous THF (100 mL) and the solution was cooled to 0°C under N₂. A solution of tetrabutylammonia fluoride (10.3 mL, 10.3 mmol, 1 M THF solution) was added. The mixture was stirred for 2.5 h at room temperature. The solution was washed with *satd.* NH₄Cl solution (100 mL), extracted with ethyl acetate (3 $\times$ 100 mL). The combined organic layers were dried over Na₂SO₄ (anhydrous), filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with 20–60% ethyl acetate/petroleum ether to get the primary alcohol **21** (4.0 g, 100% yield) as white solid. M/S: 803 m/z (M⁺+NH₄⁺). HRMS calcd for C₄₆H₅₉NO₁₀, 785.4139, found 785.4135. ¹H NMR (500 MHz, CDCl₃): δ 7.33–7.26 (m, 20H, Ph), 4.88 (*d*, *J*=8.9 Hz, 1H, NH), 4.71–4.47 (m, 10H, CH₂Ph and OCH₂O), 4.02 (br s, 1H), 3.96 (br s, 1H), 3.95–3.3.85 (m 2H), 3.72 (br s, 2H), 3.69–3.62 (m, 1H), 3.61–3.54 (m, 2H), 3.54–3.48 (m, 1H), 3.36 (s, 3H, OCH₃), 3.35 (broad peak, 1H), 3.28 (m, 1H), 1.78 (br s, 1H), 1.71–1.69 (br s, 1H), 1.61–1.55 (br s, 1H), 1.43 (s, 9H, (CH₃)₃), 1.29–1.26 (br s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 156.6, 138.8, 138.7, 138.5, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.8, 127.8, 127.7, 96.9, 82.7, 79.7, 77.4, 77.1, 76.7, 74.7, 73.3, 73.3, 72.2, 67.8, 62.3, 55.9, 51.6, 28.6 and 26.9.

(3'S,4'S,5'S)-1-{3'-N-tert-butylcarbamate-4'-methoxymethoxy-5'-hydroxynonadecanyl}-(2,3,4,6-tetra-O-benzyl)- α -C-D-galactopyranoside 23

The primary alcohol **21** (0.6 g, 0.77 mmol) was dissolved in anhydrous CH₂Cl₂ (10 mL) under N₂. Dess-Martin periodinane (0.42 g, 1 mmol) was added in one portion at room temperature. The solution was stirred for 45 min at room temperature and was diluted with CH₂Cl₂ (20 mL) followed by addition of *satd.* NaHCO₃ solution (10 mL) and *satd.* Na₂S₂O₃ solution (10 mL). The mixture was stirred until two clear phases appeared. The solution was extracted with CH₂Cl₂ (3 $\times$ 60 mL). The combined organic layers were dried over Na₂SO₄ (anhydrous), filtered and concentrated *in vacuo*. The crude product was coevaporated with anhydrous toluene (3 $\times$ 10 mL) and was then put under high vacuum to afford the crude aldehyde **22** (0.55 g), which was used in the next step without further purification.

Kirschning Oxidation¹⁴: A mixture of the primary alcohol **21** (0.8 g, 0.8 mmol) and a polymer bound resin prepared according to literature procedure¹⁴ (1.4 g, 4.9 mmol) in dry CH₂Cl₂ (10 mL) with catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) under nitrogen was stirred at room temperature for 2h. After disappearance of starting material, the resin was washed with CH₂Cl₂ (3 $\times$ 30 mL) and the combined organic washings and filtrate was concentrated under reduced pressure to afford the crude aldehyde **22** (0.97 g), which was used in the next step without further purification. The aldehyde **22** was dissolved in anhydrous THF (5 mL) and the solution was added dropwise to a solution of freshly prepared tetradecyl magnesium bromide (C₁₄H₂₉MgBr, 2.3 mmol) in anhydrous THF (5 mL) at 0°C under N₂ over 10 min. The mixture was stirred at 0°C for 30 min and was then stirred for 2 h at room temperature. The reaction was quenched by addition of *satd.* NH₄Cl solution (20 mL) and the mixture was stirred for 10 min. The mixture was extracted with ethyl ether (3 $\times$ 50 mL). The combined organic layers were dried over Na₂SO₄ (anhydrous), filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography eluting with ethyl acetate/petroleum ether (polarity increased from 5% to 20%) to get the major isomer **23** (0.36 g, 48% yield) as the first fraction and the minor isomer **24** (72 mg, 10% yield) as the second fraction.

The major isomer **23**: M/S: 999 m/z ($M^+ + NH_4^+$). HRMS calcd for $C_{60}H_{87}NO_{10}$, 981.6330, found 981.6322. 1H NMR (500MHz, $CDCl_3$): δ 7.35-7.29 (m, 20H, Ph), 5.26 (d, $J=9.1$ Hz, 1H, NH), 4.76-4.48 (m, 10H, CH_2Ph and OCH_2O), 3.99 (bs, 2H), 3.96 (m, 1H), 3.86-3.74 (m, 4H), 3.65-3.63 (m, 2H), 3.41 (s, 3H, OCH_3), 3.31 (m, 1H), 2.76 (d, $J=5.2$ Hz, 1H), 1.71-1.66 (m, 4H), 1.57-1.54 (m, 2H), 1.45 (s, 9H, $(CH_3)_3$), 1.33-1.19 (br s, 24H, CH_2), 0.91 (t, $J=6.9$ Hz, 3H, CH_3). ^{13}C NMR (125MHz, $CDCl_3$): δ 156.4, 138.8, 138.7, 138.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 97.9, 83.9, 79.3, 77.4, 77.3, 76.8, 76.8, 74.8, 73.5, 73.5, 73.3, 72.2, 67.9, 56.3, 52.1, 34.0, 32.1, 30.0, 29.9, 29.8, 29.6, 28.6, 27.4, 25.8, 22.9 and 14.3.

(3'S,4'S,5'R)-1-{3'-N-tert-butylcarbamate-4'-methoxymethoxy-5'-hydroxynonadecanyl}-(2,3,4,6-tetra-O-benzyl)- α -C-D-galactopyranoside **24**

M/S: 999 m/z ($M^+ + NH_4^+$). HRMS calcd for $C_{60}H_{87}NO_{10}$, 981.633, found 981.6320. 1H NMR (500MHz, $CDCl_3$): δ 7.37-7.29 (m, 20H, Ph), 4.89 (d, $J=9.4$ Hz, 1H, NH), 4.75-4.48 (m, 10H, CH_2Ph and OCH_2O), 3.99-3.96 (m, 3H), 3.84-3.77 (m, 3H), 3.75 (d, $J=5.2$ Hz, 1H), 3.61-3.59 (m, 1H), 3.56 (dd, $J=10.6, 3.8$ Hz, 1H), 3.39 (s, 3H, OCH_3), 3.34 (t, $J=5.0$ Hz, 1H), 2.73 (d, $J=6.1$ Hz, 1H), 1.91 (m, 1H), 1.71 (m, 2H), 1.62-1.59 (m, 2H), 1.53 (m, 1H), 1.45 (s, 9H, $(CH_3)_3$), 1.38-1.27 (m, 24H, CH_2), 0.91 (t, $J=6.6$ Hz, 3H, CH_3). ^{13}C NMR (125MHz, $CDCl_3$): δ 155.9, 138.9, 138.7, 138.6, 138.5, 128.6, 128.6, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 98.6, 87.5, 79.3, 77.1, 76.9, 76.5, 74.9, 73.6, 73.4, 73.3, 71.8, 68.4, 56.2, 51.8, 33.0, 32.1, 29.9, 29.8, 29.6, 28.7, 27.1, 26.4, 22.9 and 14.3.

(3'S,4'S,5'R)-3'-N-hexacosanoyl-4',5'-dihydroxynonadecacyl- α -C-D-galactopyranoside **3**

To a solution of the minor isomer **24** (45 mg, 0.046 mmol) in MeOH/1,4-dioxane (1 mL/1 mL) was added HCl solution (2 mL, 12 mmol, 6 M in MeOH) and the solution was stirred at room temperature overnight. The solution was concentrated to dryness under reduced pressure. The mixture was dissolved in THF (5 mL) and was neutralized with *satd.* ammonia hydroxide solution (5 mL). The mixture was extracted with $CHCl_3$ (3×20 mL). The combined organic layers were dried over Na_2SO_4 (anhydrous), filtered and concentrated *in vacuo*. The crude compound was coevaporated with anhydrous toluene (3×10 mL) and was then put under high vacuum pump for 1 h to afford crude amine (40 mg) as yellow oil.

The amine was dissolved in anhydrous THF (2 mL). The activated ester $C_{25}H_{51}COOPhNO_2$ (55 mg, 0.091 mmol) and DMAP (3 mg) were added at room temperature under N_2 . The mixture was stirred at room temperature overnight. 0.5 g of celite 545 was added and the solvent was removed *in vacuo* to get powder. Flash chromatography purification eluting with 10% ethyl acetate/ petroleum ether to remove the excess amount of ester and using 20–30% ethyl acetate/petroleum ether to give the amide **25** (0.04 g, 72% yield).

The amide **25** (0.04 g, 0.033 mmol) was dissolved in a solvent of THF/EtOH (3 mL/3 mL, 1:1). $Pd(OH)_2/C$ (0.10 g, 20% by weight) was added in one portion. The solution was degassed three times and was stirred under H_2 balloon (1 atm) for 24 h. At the end of the reaction, a white precipitate formed. The solution was filtered through a pad of celite, which was washed with 50% $CHCl_3$ /MeOH solution (30 mL) followed by pyridine (20 mL). The solvent was removed *in vacuo* and the solid was dissolved in pyridine (2 mL). Celite 545 (0.5 g) was added and the solvent was removed *in vacuo*. The powder was put to the top of the column. Flash chromatography separation eluting with $CHCl_3$, 5%, 10% and 20% MeOH/ $CHCl_3$ afforded the target C-glycoside **3** (0.016 g, 42%, 30% yield for three steps) as a white solid. Mp 176–179°C; HRMS calcd for $C_{51}H_{101}N_1O_8$, 855.7527, found 855.7514. 1H NMR (500MHz, C_5D_5N): δ 8.49 (d, $J=8.9$ Hz, 1H, NH), 4.73 (dd, $J=8.8, 5.5$ Hz, 1H), 4.52 (m, 3H), 4.37 (dd, $J=11.2, 4.5$ Hz, 1H), 4.25 (m, 4H), 3.97 (s, 1H, impurity), 2.72 (m, 1H), 2.55 (m, 1H), 2.48 (m, 3H), 2.33 (m, 2H), 2.20 (m, 1H), 2.05 (m, 5H, impurity), 1.96 (m, 2H), 1.86 (m, 3H), 1.69 (m, 1H),

1.57 (m, 5H), 1.31 (m, 56H), 1.03 (m, 3H), 0.89 (t, $J=6.9$ Hz, 6H, CH₃). ¹³C NMR (125MHz, C₅D₅N): δ 173.9, 78.9, 77.5, 74.3, 73.2, 72.7, 71.1, 70.9, 63.2, 53.2, 37.3, 34.8, 32.4, 30.7, 30.5, 30.3, 30.3, 30.2, 30.2, 30.2, 30.1, 29.9, 29.9, 26.8, 26.7, 23.2, 23.0 and 14.6.

(3'S,4'S,5'S)-3'-N-hexacosanoyl-4',5'-dihydroxynonadecacyl- α -C-D-galactopyranoside 26

This material was obtained from major isomer **23** (35% overall yield for three steps) following the same procedures as described for processing isomer **24**. Mp 170-175°C; HRMS calcd for C₅₁H₁₀₁N₁O₈, 855.7527, found 855.7515. ¹H NMR (500MHz, C₅D₅N): δ 6.80 (broad peak, OH), 6.51 (broad peak, OH), 6.33 (broad peak, OH), 6.09 (broad peak, OH), 5.72 (broad peak, OH), 4.77-4.73 (m, 2H), 4.66 (s, 1H), 4.53 (s, 2H), 4.48 (s, 1H), 4.31-4.29 (m, 2H), 4.20 (s, 1H), 3.79 (s, 1H), 2.89 (br s, 1H), 2.63 (bs, 1H), 2.48 (t, $J=7.2$ Hz, 2H), 2.31-2.24 (m, 3H), 2.22-2.14 (m, 1H), 2.09-1.97 (m, 1H), 1.91-1.73 (m, 7H), 1.71-1.59 (m, 2H), 1.39-1.26 (m, 58H), 0.92-0.87 (m, 6H). ¹³C NMR (125MHz, C₅D₅N): δ 175.5, 77.3, 74.3, 72.6, 71.4, 70.7, 62.7, 53.4, 37.1, 34.6, 32.4, 37.1, 34.6, 32.4, 30.6, 30.5, 30.3, 30.2, 30.1, 30.1, 29.9, 29.9, 29.1, 27.2, 26.8, 23.3, 23.1 and 14.6.

(3'R,4'S)-1-{3'-azido-4',5'-dihydroxy-pentanyl}-(2,3,4,6-tetra-O-benzyl- α -C-D-galactopyranoside (27)

Titanium (IV) isopropoxide (0.22 mL, 0.73 mmol) and azido trimethylsilane (0.2 mL, 1.5 mmol) were added to anhydrous benzene (10 mL) and the solution was refluxed at 80°C under N₂ for at least 5 h. Epoxide **13** (0.30 g, 0.48 mmol) was dissolved in anhydrous benzene (10 mL) and was added to the solution in one portion. The mixture was stirred for 15–30 min at 80°C and was cooled to room temperature. The solvent was removed under reduced pressure. Diethyl ether (20 mL) was added followed by addition of 5% H₂SO₄ (10 mL, V/V). The solution was stirred at room temperature until two clear phases appeared. The mixture was extracted with CH₂Cl₂ (3 $\times$ 30 mL). The organic phase was dried with Na₂SO₄, filtered and concentrated *in vacuo*. Flash chromatography purification eluting with 50% ethyl acetate/petroleum ether afforded 3-azido-1, 2 diol **27** (0.21 g, 64% yield) as yellow oil. M/S: m/z 685.3 (M⁺+NH₄⁺). HRMS calcd for C₃₉H₄₅N₃O₇, 667.3258, found 667.3254. IR (KBr): 3435.98, 2873.99, 2100.89, 763.72 cm⁻¹. ¹H NMR (300MHz, CDCl₃): δ 7.30 (m, 20H), 4.8-4.4 (m, 8H), 4.01-3.83 (m, 4H), 3.77-3.69 (m, 2H), 3.60-3.45 (m, 4H), 3.42-3.34 (m, 1H), 2.5-2.4 (br, OH), 2.25-2.15 (br, OH), 1.90-1.75 (m, 1H), and 1.74-1.50 (m, 3H). ¹³C NMR (75MHz, CDCl₃): δ 138.7, 138.6, 138.5, 138.3, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 77.4, 76.9, 74.7, 74.0, 73.8, 73.5, 73.5, 73.4, 72.5, 70.5, 68.1, 64.0, 63.5, 26.9 and 23.9.

(3'R,4'S)-1-{3'-N-tert butyl carbamate-4',5'-dihydroxy-pentanyl}-(2,3,4,6-tetra-O-benzyl- α -C-D-galactopyranoside (28)

The following materials were obtained from azidodiols **27** via the procedures used for azidodiols **13**. Yield: 91% yield for two steps from **27**. M/S: m/z 742.3 (M⁺+H⁺). HRMS calcd for C₄₄H₅₅NO₉, 741.3877, found 741.3869. ¹H NMR (500 MHz, CDCl₃): δ 7.35-7.22 (m, 20H, Ph), 4.75-4.50 (m, 8H, CH₂Ph), 4.05-3.98 (br, 1H), 3.98-3.95 (br, 2H), 3.93-3.88 (m, 1H), 3.76-3.72 (m, 2H), 3.69-3.63 (m, 1H), 3.62-3.56 (m, 2H), 3.55-3.48 (m, 1H), 3.44-3.39 (m, 1H), 3.10-3.00 (br, 1H, -OH), 2.18-2.10 (br, 1H, -OH), 1.80-1.72 (m, 1H), 1.69-1.62 (m, 1H), 1.62-1.52 (m, 1H), 1.52-1.47 (m, 1H), and 1.46-1.42 (s, 9H, (CH₃)₃). ¹³C NMR (125 MHz, CDCl₃): δ 157.5, 138.8, 138.6, 138.5, 138.4, 128.6, 128.6, 128.5, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 80.1, 77.2, 76.8, 74.7, 74.6, 73.5, 73.4, 73.4, 73.3, 72.5, 68.1, 63.6, 51.6, 28.6 and 24.1.

(3'R,4'S)-1-{3'-N-tert butyl carbamate-4'-hydroxy-5'-(tert-Butyl-dimethyl-silanyloxy)-pentanyl}-(2,3,4,6-tetra-O-benzyl- α -C-D-galactopyranoside (29)

Yield: 99%. M/S: m/z 873.3 ($M^+ + NH_4^+$). HRMS calcd for $C_{50}H_{69}NO_9Si$, 855.4742, found 855.4736. 1H NMR (500MHz, $CDCl_3$): δ 7.35-7.22 (m, 20H, Ph), 4.75-4.50 (m, 8H, CH_2Ph), 4.05-3.95 (m, 3H), 3.85-3.80 (m, 1H), 3.78-3.73 (m, 1H), 3.73-3.70 (m, 1H), 3.65-3.60 (m, 3H), 3.55-3.50 (m, 1H), 3.48-3.45 (m, 1H), 2.65-2.60 (br, 1H, -OH), 1.76-1.65 (m, 2H), 1.60-1.50 (m, 2H), 1.45-1.40 (s, 9H, $(CH_3)_3$), 0.92 (s, 9H, CH_3), 0.06 (s, 6H, CH_3). ^{13}C NMR (125MHz, $CDCl_3$): δ 156.2, 138.8, 138.7, 138.6, 138.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 79.1, 76.9, 76.8, 74.6, 73.3, 73.2, 73.1, 73.0, 72.4, 67.8, 65.0, 50.9, 29.0, 28.5, 26.0, 18.4, -5.2 and -5.3.

(3'R,4'S)-1-{3'-N-tert butyl carbamate-4'-methoxymethoxy-5'-(tert-Butyl-dimethyl-silanyloxy)-pentanyl}-(2,3,4,6-tetra-O-benzyl- α -C-D-galactopyranoside (30)

Yield: 99%. M/S: m/z 917 ($M^+ + NH_4^+$). HRMS calcd for $C_{52}H_{73}NO_{10}Si$, 899.5004, found 899.5004. 1H NMR (500MHz, $CDCl_3$): δ 7.35-7.22 (m, 20H, Ph), 4.83 (d, $J=9.7$ Hz, 1H, NH), 4.75-4.50 (m, 10H, $4CH_2$ and OCH_2O), 4.05-3.96 (m, 3H), 3.80-3.70 (m, 3H), 3.70-3.65 (m, 1H), 3.65-3.55 (m, 4H), 3.29 (s, 3H, OCH_3), 1.76-1.74 (m, 1H), 1.70-1.55 (m, 2H), 1.56-1.48 (m, 1H), 1.42 (s, 9H, $(CH_3)_3$, Boc), 0.85 (s, 9H, CH_3), and 0.05 (s, 6H, CH_3). ^{13}C NMR (125MHz, $CDCl_3$): δ 155.9, 138.9, 138.8, 138.7, 138.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 97.9, 79.5, 78.9, 77.2, 74.7, 73.4, 73.2, 72.4, 67.9, 63.9, 55.9, 50.9, 29.1, 28.6, 26.1, 18.4 and -5.4.

(3'R,4'S)-1-{3'-N-tert butyl carbamate-4'-methoxymethoxy-5'-hydroxy-pentanyl}-(2,3,4,6-tetra-O-benzyl- α -C-D-galactopyranoside (31)

Yield: 92%. M/S: m/z 803 ($M^+ + NH_4^+$). HRMS calcd for $C_{52}H_{73}NO_{10}Si$, 785.4139, found 785.4133. 1H NMR (500MHz, $CDCl_3$): δ 7.34-7.24 (m, 20H, Ph), 4.73-4.45 (m, 10H, $-CH_2Ph$ and OCH_2O), 3.97-3.93 (m, 3H), 3.85-3.79 (m, 2H), 3.74-3.37 (m, 2H), 3.65-3.57 (m, 3H), 3.51-3.48 (m, 1H), 3.42-3.40 (m, 1H), 3.33-3.31 (s, 3H, OCH_3), 1.76-1.71 (m, 1H), 1.68-1.66 (m, 1H), 1.56-1.53 (m, 2H), and 1.42 (s, 9H, $-C(CH_3)_3$). ^{13}C NMR (125MHz, $CDCl_3$): δ 156.9, 138.5, 138.4, 138.3, 138.1, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 97.0, 81.0, 79.5, 77.3, 76.9, 74.4, 73.2, 73.1, 72.9, 72.8, 72.3, 70.5, 67.8, 61.8, 55.6, 50.3, 28.3 and 28.2.

(3'R,4'S,5'R)-1-{3'-N-tert-butyl carbamate-4'-methoxymethoxy-5'-hydroxy-nonadecanyl}-(2,3,4,6-tetra-O-benzyl)- α -C-D-galactopyranoside (33)

Major isomer: yield: 28% for two steps from **31**. M/S: m/z 999 ($M^+ + NH_4^+$). HRMS calcd for $C_{60}H_{87}NO_{10}$, 981.6330, found 981.6322. 1H NMR (500MHz, $CDCl_3$): δ 7.35-7.21 (m, 20H, Ph), 4.74-4.49 (m, 10H, CH_2Ph and OCH_2O), 4.05-3.96 (m, 3H), 3.85-3.74 (m, 3H), 3.74-3.69 (m, 1H), 3.65-3.60 (dd, $J=3.9$, 10.3 Hz, 1H), 3.55-3.52 (br s, 1H), 3.34 (s, 3H, OCH_3), 3.21 (d, $J=6.9$ Hz, 1H), 3.05 (d, $J=2.3$ Hz, -OH), 1.76-1.51 (m, 4H), 1.42 (s, 9H, Boc), 1.35-1.22 (m, 26H), and 0.90 (t, $J=6.7$ Hz, 3H, CH_3). ^{13}C NMR (125MHz, $CDCl_3$): δ 155.8, 138.9, 138.8, 138.7, 138.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 99.2, 87.4, 79.3, 77.1, 76.6, 76.4, 76.4, 74.7, 73.5, 73.3, 73.3, 73.1, 71.6, 68.1, 56.3, 50.8, 32.9, 32.2, 30.0, 29.9, 29.9, 29.8, 29.6, 28.6, 25.8, 22.9 and 14.3.

(3'R,4'S,5'S)-1-{3'-N-tert-butyl carbamate-4'-methoxymethoxy-5'-hydroxynonadecanyl}-(2,3,4,6-tetra-O-benzyl)- α -C-D-galactopyranoside (34)

Minor isomer, yield: 22% for two steps from **31**. M/S: m/z 999 ($M^+ + NH_4^+$). HRMS calcd for $C_{60}H_{87}NO_{10}$, 981.6330, found 981.6325. 1H NMR (500 MHz, $CDCl_3$): δ 7.51-7.24 (m, 20H, Ph), 4.76-4.48 (m, 10H, $4CH_2$ and OCH_2O), 4.05-3.90 (m, 4H), 3.90-3.85 (m, 1H), 3.85-3.74 (m, 2H), 3.74-3.70 (m, 1H), 3.65-3.60 (m, 1H), 3.31 (s, 3H, OCH_3), 3.19 (m, 1H), 1.78-1.51

(m, 4H), 1.50-1.45 (m and s, 11H), 1.45-1.21 (m, 24H), and 0.90 (t, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 157.5, 138.9, 138.7, 138.6, 138.5, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 98.7, 85.2, 80.0, 76.9, 76.6, 74.8, 73.6, 73.5, 73.4, 73.3, 73.2, 70.8, 68.1, 56.5, 50.8, 32.8, 32.1, 30.1, 29.9, 29.6, 29.1, 28.5, 26.1, 22.9 and 14.3.

(3'R,4'S,5'S)-3'-N-hexacosanoyl-4',5'-dihydroxynonadecacyl-α-C-D-galactopyranoside (36)

Yield: 54% for three steps from **33**. Mp 183-185°C; HRMS calcd for C₅₁H₁₀₁N₁O₈, 855.7527, found 855.7522. ¹H NMR (500MHz, C₅D₅N): δ 8.05 (d, *J*=9.2 Hz, 1H, NH), 6.65 (br, OH), 6.40 (br, OH), 6.20 (br, OH), 5.80 (br, OH), 4.76-4.72 (m, 1H), 4.72-4.66 (m, 2H), 4.54-4.48 (m, 1H), 4.45-4.34 (m, 2H), 4.32-4.27 (m, 1H), 4.12-4.06 (m, 1H), 4.01-3.94 (m, 1H), 2.49-2.35 (m, 5H), 2.27-2.23 (m, 1H), 2.16-2.10 (m, 1H), 1.91-1.77 (m, 5H), 1.52-1.21 (m, 66H), and 0.87 (t, 6H, CH₃). ¹³C NMR (125MHz, C₅D₅N): δ 173.7, 77.5, 75.8, 74.7, 73.0, 72.7, 71.0, 70.7, 62.8, 50.9, 37.3, 32.6, 32.5, 30.8, 30.7, 30.6, 30.5, 30.4, 30.4, 30.3, 30.3, 30.2, 30.0, 30.0, 27.0, 27.0, 23.4 and 14.7.

(3'R,4'S,5'R)-3'-N-hexacosanoyl-4',5'-dihydroxynonadecacyl-α-C-D-galactopyranoside (38)

Yield: 55% for three steps from **34**. Mp 178-182°C; HRMS calcd for C₅₁H₁₀₁N₁O₈, 855.7527, found 855.7523. ¹H NMR (500MHz, C₅D₅N): δ 8.65 (d, *J*=9.0 Hz, 1H, NH), 6.65 (br, OH), 6.40 (br, OH), 6.20 (br, OH), 5.80 (br, OH), 5.02-5.01 (m, 1H), 4.76-4.72 (m, 1H), 4.72-4.66 (br s, 1H), 4.59-4.56 (m, 1H), 4.42 (m, 1H), 4.38 (m, 1H), 4.33 (m, 1H), 4.19 (br, 1H), 3.94 (m, 1H), 3.89 (m, 1H), 3.63 (d, *J*=4.7 Hz, less than 1H), 2.49-2.35 (m, 5H), 2.27-2.23 (m, 1H), 2.16-2.10 (m, 1H), 1.91-1.769 (m, 5H), 1.52-1.21 (m, 66H), and 0.87 (m, 6H, CH₃). ¹³C NMR (125MHz, C₅D₅N): δ 175.2, 77.8, 76.3, 74.5, 72.8, 72.7, 71.0, 70.9, 63.1, 51.5, 37.1, 34.9, 32.7, 32.7, 30.9, 30.8, 30.8, 30.7, 30.6, 30.6, 30.5, 30.5, 30.4, 30.3, 30.2, 30.1, 29.6, 27.3, 27.2, 23.5, 23.3 and 14.8.

(3'S,4'S)-1-{5'-(tert-Butyl-dimethyl-silanyloxy)-2',2'-dimethyl-4'-propyl-oxazolidine-3'-N-tertbutylcarbamate-pentanyl}-(2,3,4,6-tetra-O-benzyl-α-C-D-galactopyranoside 49

The TBS ether compound **18** (0.51 g, 0.6 mmol) was dissolved in anhydrous CH₂Cl₂ (10 mL). 2,2-dimethoxy-propane (1 mL) was added followed by addition of *p*-TsOH (7 mg) at 0°C under N₂. The solution was then stirred at room temperature for 1 h. The solution was washed with satd. NaHCO₃ solution (10 mL), extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with 10-30% ethyl acetate/petroleum ether to afford the cyclic compound **49** (0.41 g, 75% yield) as yellow oil. M/S: m/z 913 (M⁺+NH₄⁺) (calcd: for C₅₃H₇₃NO₉Si, 895). ¹H NMR (500MHz, CDCl₃): δ 7.32-7.25 (m, 20H, Ph), 4.79-4.37 (m, 8H, CH₂Ph), 4.09-4.05 (m, 2H), 3.97-3.94 (br s, 2H), 3.91-3.86 (m, 3H), 3.79-3.75 (m, 1H), 3.73 (d, *J*=7.5 Hz, 1H), 3.67-3.55 (m, 2H), 1.82-1.79 (m, 2H), 1.66-1.63 (m, 1H), 1.59-1.55 (br s, 4H), 1.51 (s, 3H, CH₃), 1.44 (s, 3H, CH₃), 1.39 (s, 6H, CH₃), 0.87 (s, 9H, CH₃), 0.05 (s, 3H, CH₃), and 0.03 (s, 3H, CH₃). ¹³C NMR (125MHz, CDCl₃): δ 152.7, 152.2, 138.9, 138.9, 138.8, 138.7, 138.6, 138.4, 128.8, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.7, 127.6, 93.4, 92.9, 79.9, 79.7, 77.3, 77.1, 76.6, 74.9, 73.8, 73.6, 73.5, 73.4, 73.1, 71.6, 68.5, 68.2, 61.3, 58.8, 28.7, 28.6, 28.3, 27.5, 27.4, 27.0, 26.1, 25.3, 23.9, 23.7, 18.5, -5.0 and -5.1 (Note: Because the existence of two conformers of amide, the carbon peaks become to two series of peaks).

(3'S,4'S)-1-{2',2'-dimethyl-4'-propyl-oxazolidine-3'-N-tertbutylcarbamate-5'-hydroxy-pentanyl}-(2,3,4,6-tetra-O-benzyl-α-C-D-galactopyranoside 50

To a solution of cyclic compound **49** (0.40 g, 0.45 mmol) in anhydrous THF (5 mL) was added tetrabutylammonia fluoride (1.4 mL, 1.4 mmol, 1 M in THF) dropwise at 0°C under N₂. The

solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography eluting with 10–30% ethyl acetate/petroleum ether to afford the primary alcohol **50** (0.34 g, 95% yield) as yellow oil. M/S: m/z 799 ($M^+ + NH_4^+$) (*calcd*: for $C_{47}H_{59}NO_9$, 781). 1H NMR (500MHz, $CDCl_3$): δ 7.33–7.23 (m, 20H, Ph), 4.74–4.49 (m, 8H, CH_2Ph), 4.13–4.11 (br s, 1H), 3.93–3.83 (m, 5H), 3.82–3.62 (m, 4H), 3.62–3.53 (br s, 1H), 1.79 (br s, 2H), 1.67 (br s, 2H), 1.55 (br s, 6H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (125MHz, $CDCl_3$): δ 152.1, 138.9, 138.8, 138.7, 138.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.8, 127.7, 93.6, 93.0, 79.8, 77.9, 76.8, 76.5, 76.3, 74.9, 73.8, 73.6, 73.3, 72.3, 71.9, 69.1, 68.5, 61.1, 58.8, 28.7, 28.3, 27.6, 25.3, 24.3 and 23.9.

(3'S,4'S)-1-{2',2'-dimethyl-4'-propyl-oxazolidine-3'-N-tertbutylcarbamate-5'-(4-Bromobenzoyloxymethyl)-pentanyl}-(2,3,4,6-tetra-O-benzyl- α -C-D-galactopyranoside 51

To a solution of alcohol **50** (0.33 g, 0.42 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) was added anhydrous pyridine (0.5 mL) and para-bromobenzoyl chloride (0.18 g, 0.84 mmol) at 0°C under N_2 . The solution was stirred at room temperature for 2 h. The solution was washed with *satur.* NH_4Cl solution (20 mL), extracted with CH_2Cl_2 (3 $\times$ 50 mL). The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with 10–20% ethyl acetate/petroleum ether to afford benzoyl ester **51** (0.34 g, 82% yield) as yellow oil. M/S: m/z 981 ($M^+ + NH_4^+$) (*calcd*: for $C_{54}H_{62}BrNO_{10}$, 963). 1H NMR (500MHz, $CDCl_3$): δ 7.88–7.86 (d, $J=8.4$ Hz, 2H), 7.52–7.51 (d, $J=8.4$ Hz, 2H), 7.33–7.23 (m, 20H, Ph), 4.72–4.43 (m, 8H, $-CH_2Ph$), 4.31–4.30 (dd, $J=11.2, 5.8$ Hz, 2H, CH_2OCO), 4.17–4.16 (s, 1H, CHO), 4.02–3.90 (m, 4H), 3.73 (br s, 1H), 3.69–3.68 (br s, 1H), 3.65–3.62 (dd, $J=9.9, 4.8$ Hz, 1H), 1.96–1.91 (m, 1H), 1.73–1.54 (br s, 5H), 1.53–1.49 (br s, 4H), 1.49–1.42 (m, 9H, $C(CH_3)_3$). ^{13}C NMR (125MHz, $CDCl_3$): δ 165.6, 152.6, 152.0 (amide CO), 138.8, 138.6, 138.2, 131.9, 131.5, 128.9, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 126.8, 126.5, 93.9, 93.3 ($OC(CH_3)_2N$), 80.3, 80.0, 77.9, 76.6, 76.4, 74.9, 74.3, 73.8, 73.6, 73.2, 72.2, 71.9, 68.6, 68.5, 63.1, 58.8, 28.6, 28.2, 27.7, 27.6, 27.3, 25.4, 24.2 and 23.9.

(3'R,4'S)-1-{5'-(tert-Butyl-dimethyl-silanyloxy)-2',2'-dimethyl-4'-propyl-oxazolidine-3'-N-tertbutylcarbamate-pentanyl}-(2,3,4,6-tetra-O-benzyl- α -C-D-galactopyranoside 52

Yield: 91% from TBS ether compound **29**. M/S: m/z 913 ($M^+ + NH_4^+$) (*calcd*: for $C_{53}H_{73}NO_9Si$, 895). 1H NMR (500MHz, $CDCl_3$): δ 7.33–7.24 (m, 20H, Ph), 4.735–4.43 (m, 8H, CH_2Ph), 3.98 (s, 1H), 3.93–3.91 (m, 2H), 3.85–3.71 (m, 4H), 3.69 (dd, $J=7.9, 2.5$ Hz, 1H), 3.65 (dd, $J=10.0, 5.3$ Hz, 1H), 3.59 (s, 2H), 1.91–1.89 (m, 1H), 1.57–1.52 (s, 6H, CH_3 and CH_2), 1.49 (s, 3H, CH_3), 1.42 (s, 9H, $(CH_3)_3$), 0.88 (s, 9H, CH_3), 0.07 (s, 3H, CH_3), 0.04 (s, 3H, CH_3). ^{13}C NMR (125MHz, $CDCl_3$): δ 152.1, 138.9, 138.8, 138.7, 128.5, 128.4, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.3, 94.7, 94.4, 80.9, 79.8, 79.1, 76.9, 76.6, 76.3, 74.7, 73.5, 73.2, 72.1, 68.0, 64.8, 59.6, 28.7, 27.7, 26.2, 23.7, 18.5, -5.1 and -5.2 .

(3'R,4'S)-1-{2',2'-dimethyl-4'-propyl-oxazolidine-3'-N-tertbutylcarbamate-5'-hydroxy-pentanyl}-(2,3,4,6-tetra-O-benzyl- α -C-D-galactopyranoside 53

Yield: 90%. M/S: m/z 799 ($M^+ + NH_4^+$) (*calcd*: for $C_{47}H_{59}NO_9$, 781). 1H NMR (500MHz, $CDCl_3$): δ 7.33–7.24 (m, 20H, Ph), 4.74–4.45 (m, 8H, CH_2Ph), 4.05–3.81 (m, 6H), 3.73–3.69 (s, 2H), 3.66–3.55 (m, 2H), 3.47–3.42 (bs, 2H), 1.94–1.85 (m, 1H), 1.67–1.59 (m, 3H), 1.54 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), and 1.42 (s, 9H, $(CH_3)_3$). ^{13}C NMR (125MHz, $CDCl_3$): δ 152.1, 138.8, 138.6, 138.5, 128.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 79.9, 77.4, 77.1, 74.5, 73.7, 73.6, 73.3, 63.9, 58.4 and 28.7 (note: C $(CH_3)_3$ peak at 94 ppm was too small).

(3'*R*,4'*S*)-1-{2',2'-dimethyl-4'-propyl-oxazolidine-3'-*N*-tertbutylcarbamate-5'-(4-bromo-benzoyloxymethyl)-pentanyl}-(2,3,4,6-tetra-*O*-benzyl- α -C-D-galactopyranoside 54

Yield: 90%. M/S: m/z 981 ($M^+ + NH_4^+$). HRMS calcd for $C_{54}H_{62}BrNO_{10}$, 963.3557, found 963.3550. 1H NMR (500MHz, $CDCl_3$): δ 7.92-7.90 (d, J = 8.42 Hz, 2H), 7.57-7.55 (d, J =8.4 Hz, 2H), 7.37-7.29 (m, 20H, Ph), 4.76-4.47 (m, 8H, CH_2), 4.35-4.34 (m, 2H), 4.22-4.19 (m, 1H), 4.01 (m, 4H), 3.82 (br s, 2H), 3.74-3.72 (m, 1H), 3.69-3.66 (dd, J =10.2, 4.6 Hz, 1H), 2.00-1.98 (m, 1H), 1.62 (br s, 5H), 1.56 (br s, 4H), 1.47 (s, 9H). ^{13}C NMR (125MHz, $CDCl_3$): δ 165.7, 152.1, 138.7, 138.6, 138.4, 131.9, 131.4, 128.9, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.8, 127.7, 95.3, 94.5, 80.2, 77.4, 76.7, 76.4, 74.6, 73.5, 73.3, 59.7 and 28.7.

Supplementary Material

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1, α -galactosylceramide
(KRN7000, α -Galcer)

2, OCH, truncated side
chain analog of KRN7000

3, C-glycoside analog of KRN7000

4, *E* alkene analog
5, *Z* alkene analog

Figure 1.
 α -galactosylceramide **1** (KRN7000) and its analogues

Figure 2.
4-deoxy analogs **6**, **7** and **8** of α-Galcer and OCH

Figure 3.
NOESY effect of **51**, derived from NaN_3 opening of epoxide **13**

Figure 4.
NOESY effect of **54**, derived from $\text{Ti}(\text{O-}i\text{-Pr})_2(\text{N}_3)_2$ opening of epoxide **13**

Scheme 1.

Reagents and conditions: (a). $(\text{MeO})_2\text{POCHCO}_2\text{Me}$, MeCN, r.t., overnight, 89%. (b). DIBAL-H, CH_2Cl_2 , -78°C , 2h, 90%. (c). TTIP, D-(-)-DIPT, TBHP, 4 Å MS, CH_2Cl_2 , -20°C , 18h, 70%. (d). $\text{NaN}_3/\text{NH}_4\text{Cl}$, MeOH/ H_2O (8:1), 80°C , overnight, 93%. (e). i. $\text{P}(\text{Me})_3$, THF, overnight; ii. 1N NaOH, 2h; iii. $(t\text{-Boc})_2\text{O}$, *satd.* NaHCO_3 , THF/1, 4-dioxane(1:1), r.t., overnight, 78% for three steps. (f). TBSCl, imidazole, CH_2Cl_2 , r.t., 88%.

Scheme 2.

Reagents and conditions: (a). MOMCl, DIPEA, CH₂Cl₂, 0°C -r.t., 12h, 95%. (b). TBAF, THF, r.t., 2 h, 100%. (c). Kirschning reagent, TEMPO(*cat.*), CH₂Cl₂, rt, 2h, or Dess-Martin oxidation, CH₂Cl₂, rt, 1h, quantitative. (d). C₁₄H₂₉MgBr, THF, 0°C-r.t., 2h, 58% for two steps.

Scheme 3.

Reagents and conditions: (a). i. HCl, THF/MeOH, 1,4-dioxane (1:1:1), r.t. overnight; ii. $\text{CH}_3(\text{CH}_2)_{24}\text{COOPhNO}_2$, DMAP, THF, r.t., 24 h, 72% for two steps. (b). H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, THF/EtOH (1:1), 24h, 42%. For compound **26**, 35% for three steps.

Scheme 4.

Reagents and conditions: (a) $\text{Ti}(i\text{-OPr})_2(\text{N}_3)_2$, Benzene, 70 °C, 10 min, 64%. (b) i. $\text{P}(\text{Me})_3$, THF, r.t., 18h; ii. 1N NaOH, 2h; iii. $(t\text{-Boc})_2\text{O}$, THF/1,4 -dioxane(1:1), *satd.* NaHCO_3 , r.t., 12h; 91% for 3 steps. (c) TBSCl, imidazole, CH_2Cl_2 , r.t., 2 h, 99%. (d) MOMCl, DIPEA, CH_2Cl_2 , 0°C-r.t., 24h, 99%. (e) TBAF, THF, 0°C-r.t., 2h, 92%. (f) Dess-Martin oxidation, CH_2Cl_2 , r.t., 2h. (g) $\text{C}_{14}\text{H}_{29}\text{MgBr}$, THF, 0°C-r.t., 2 h, 50% combined yield for 2 steps.

Scheme 5.

Reagents and conditions: (a) i. 6N HCl, THF/MeOH (1:1) overnight; ii. CH₃(CH₂)₂₄COOPhNO₂, DMAP, THF, 24h. (b) Pd(OH)₂/C, THF/ EtOH (1:1), H₂, 24h. 54% for **36**, three steps from **33**; 55% for **38**, three steps from **34**.

Scheme 6. Alternative synthesis of C-3 epimer **42** (Guangwu Chen, Hunter College)

Scheme 7.

Annoura *et al.*'s synthesis of C-glycoside analog of OCH and its C-3 epimer

Scheme 8.

Reagents and conditions: (a). 2,2-dimethoxy propane, *p*-TsOH, CH₂Cl₂, 0°C-r.t.; 75% for **49**, 91% for **52**. (b). TBAF, THF, 0°C-r.t.; 95% for **50**, 90% for **53**. (c). 4-BrPhCOCl, pyridine, CH₂Cl₂, r.t.; 82% for **51**, 90% for **54**.

Scheme 9.
Mechanism for the retention of configuration of 3-N stereo center