Synthesis of β-D-Galactosyl Ceramide Methylene Isostere

Alessandro Dondoni,* Daniela Perrone, and Elisa Turturici

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, Via Borsari 46, 44100 Ferrara, Italy

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The methylene isostere of the glycosphingolipid β-D-galactosyl *N*-palmitoyl C_{18} ceramide has been synthesized by a linear reaction sequence starting from a β-linked D-galactopyranosyl aldehyde. First, this sugar aldehyde was converted into a methylenephosphorane which in turn was coupled with *N*-Boc serinal acetonide. The double bond of the resulting olefin was reduced and the oxazolidine ring was cleaved and oxidized to give a *C*-glycosyl *N*-Boc α-amino butanal (three-carbon chain elongation). Then, an additional C_{15} carbon chain was installed by addition of lithium 1-pentadecyne to the above glycosyl amino aldehyde. The syn/anti ratio (70:30) of the resulting mixture of amino alcohols was reversed (5:95) by an oxidation−reduction sequence to achieve the same stereochemistry as in the hydrophilic head of D-*erythro*-sphingosines. The major product was subjected to the reduction of the triple bond with $LiAlH_4$ to give the olefin with *E* geometry. Finally the *N*-amide group was installed by reaction with palmitoyl chloride and the *O*-benzyl protective groups of the sugar moiety were removed by treatment with lithium in liquid NH_3−THF. The final product was characterized as the *O*-acetyl derivative.

The simplest modification that can be made in natural oligosaccharides and glycoconjugates to obtain chemically and enzymatically resistant analogues is the replacement of the oxygen atom of the glycosidic linkage with a methylene group.[1,2] These isosteres are precious tools for the studies at molecular level of the role that carbohydrates play in numerous biological processes[3] and for the explorative work in drug discovery.[4] Quite surprisingly this concept has been much less applied to glycosphingolipids (GSLs). Natural glycosphingolipids constitute a large family of *O*-glycoconjugates most of which can be represented by the general formula shown in Figure 1. These molecules contain two basic structural motifs: a ceramide, i.e., a sphingoid base (sphingosine or sphinganine) *N*-acylated with a fatty acid chain (stearoyl or palmitoyl), and an oligosaccharide, among which D-glucose, D-galactose, D-lactose, and sialic acid are the most common components. The structural variation in all these portions gives rise to a great variety of chemically distinct glycosphingolipids.[5] The biological role of

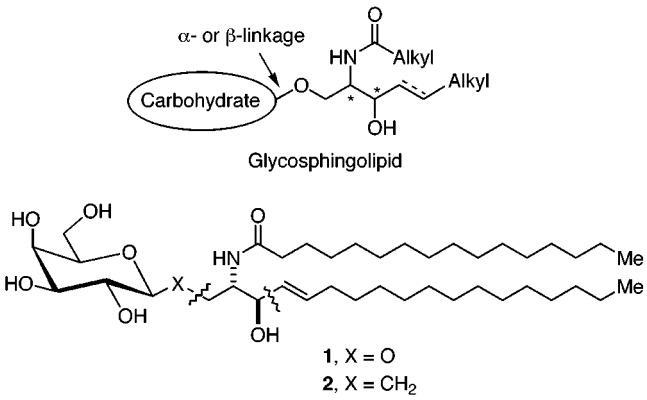

Figure 1.

glycosphingolipids as cell membrane main constituents has been recognized in "essentially all aspects of cell regulations"[6] including cell growth and differentiation, cell−cell recognition, and adhesion.[5a,7] Glycosphingolipids are also known to be involved in various lipid storage diseases.[8] To further explore the functions of these compounds as well as find new therapeutic approaches and because of the difficulty of isolation from natural sources in homogeneous form, various glycosphingolipids have been prepared in recent years.[9] Also, the synthesis

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(2) For *C*-glycosyl amino acids, see: Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1999**, *64*, 933−944 and references therein.

(3) (a) Varki, A. *Glycobiology* **1993**, *3*, 97−130. (b) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321−327. (c) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720.

(4) Mulligan, M. S.; Paulson, J. C.; De Frees, S.; Zheng, Z.-L.; Lowe, J. B., Ward, P. A. *Nature* **1993**, *364*, 149−151.

(5) (a) Hakomori, S.-I. Sphingolipid Biochemistry. In *Handbook of Lipid Research*; Kanfer, J. N., Hakomori, S., Eds.; Plenum: New York, 1983; Vol. 3, pp 1−150. (b) Li, Y.-T.; Li, S.-C. *Adv. Carbohydr. Chem. Biochem.* **1882**, *40*, 235.

(6) Merrill, A. H., Jr.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins and Membranes*; Vance, D. E., Vance, J. E., Eds.; Elsevier Science B. V.: Amsterdam, The Netherlands, 1996; Chapter 12, pp 309−339.

(7) (a) Hakamori, S.-I. *Biochem. Soc. Trans.* **1993**, *21*, 583−595. (b) Merrill, A. H., Jr.; Hannun, Y. A.; Bell, R. M. In *Advances in Lipid Research, Vol. 25, Sphingolipids Part A: Functions and Breakdown Products*; Bell, R. M., Hannun, Y. A., Merrill, A. H., Jr., Eds.; Academic Press: San Diego, CA, 1993; pp 1−23. (c) Schwarz, A.; Rapaport, E.; Hirschberg, K.; Futerman, A. H. *J. Biol. Chem.* **1995**, *270*, 10990−10998.

(8) For instance, Tay-Sachs desease is a hereditary human desease in which at least one step in sphingolipid degradation is deficient thus leading to the accumulation of lipids in the lysosomes of the cells and to their destruction. For a short account, see: Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1955−1959.

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of GSL analogues[10] is a topic of current interest because these compounds have proven to be potent enzyme inhibitors. Nevertheless no syntheses of genuine methylene isosteres of glycosphingolipids have been reported so far. The compound constituted by glucopyranose α-linked to a long-chain saturated amino alcohol recently described by Gurjar and Reddy[11] should be considered a nonisosteric analogue of a *C*-glucosylsphinganine since the carbon tether holding the sugar and the saturated aglycone moiety is lacking one carbon atom in respect to the natural products. The *C*-lactosylceramide reported by Schmidt and co-workers[12] shows a carbon−carbon bond between the two monosaccharide moieties while the natural *O*-glycosidic linkage still holds the ceramide. Hence, we report here on the total synthesis of the methylene isostere (Gal-CH_2−Cer, **2**) of the natural glycosphingolipid β-D-galactosyl *N*-palmitoyl C_{18} ceramide (Gal-*O*-Cer, **1**). Since **1** has recently been shown to be a receptor for HIV binding in cells lacking the principal CD4 cellular receptor,[13] the methylene isostere **2** may act as an inhibitor against HIV infection. A nonisosteric analogue of **1** that proved to block efficiently the interaction of recombinant HIV-1 gp 120 with **1** was considered to be a potential inhibitor of the first step of the infection process.[14]

Results and Discussion

Natural *O*-glycosylceramides as well as glycosphingolipids in general are currently prepared by *O*-glycosylation of either suitably protected sphingosine or ceramide derivatives.[9] This convergent approach takes advantage of the availability of sphingosines with many structural variations[15] and the numerous and well-established methods of *O*-glycoside synthesis.[16] The same approach may not be equally practical for *C*-glycosylceramide synthesis. This would require the transformation of the primary hydroxy group of sphingosine into a functional group capable of a fair degree of reactivity toward a sugar derivative to give either an α- or β-*C*-glycosidic linkage. These manipulations may especially affect the quite sensitive allylic alcohol function of sphingosine[17] to produce partially epimerized mixtures. Therefore, suitable protection of the amino and the secondary hydroxy group of sphingosine is crucial. A second point of concern is the stereocontrol at the anomeric center of the sugar, a nontrivial problem in *C*-glycoside synthesis.[18] Guided by the bond disconnection shown in Figure 1, we planned a synthetic approach to **2** through two sequential carbon-chain elongation reactions starting from a C1-functionalized galactose derivative. To this aim we considered the *O*-tetrabenzyl formyl *C*-galactoside **3** readily available from the corresponding galactolactone by the thiazole-based formylation methodology developed in our laboratory.[19,20] We envisaged an initial assembly via Wittig olefination of **3** with a methylenephosphorane bearing a group that was susceptible of conversion into a glycinal moiety (Scheme 1). The configurational stability of **3** under the Wittig coupling conditions[14,21] secured the β-linked stereochemistry at the anomeric carbon of the galactoside moiety. The coupling of **3** with the oxazolidinone methylenephosphorane derived from **4**, a β-alanyl anion equivalent described by Sibi and Renhowe,[22] afforded in our hands the alkene **5** as a mixture of *E* and *Z* isomers in lower yield (20%) than that reported by others (34%).[14] A similar reaction carried out with the ylide derived from the oxazoline bearing phosphonium salt[23] **6**, afforded the corresponding alkene **7** in a more satisfactory chemical yield (50%). The complexity of the NMR spectrum of this product suggested the presence of a mixture of compounds, presumably olefins with *E* and *Z* geometry and epimers with opposite configuration at the stereocenter of the heterocyclic ring. Accordingly, subsequent reduction of the olefin carbon−carbon double bond with diimide,[24] opening of the oxazoline ring by HCl promoted hydrolysis, and acetylation of the resulting alcohol with Ac_2O−pyridine−DMAP gave the ester **8** which proved to be a mixture of *R* and *S* epimers in 1:1 ratio by NMR analysis.

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(15) For recent syntheses of sphingosines and excellent reviews of the earlier literature, see: (a) Dondoni, A.; Perrone, D.; Turturici, E. *J. Chem. Soc., Perkin Trans.* **1997**, 2389−2393. (b) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510−520. (c) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3979−3985. (d) Kumar, P.; Schmidt, R. R. *Synthesis* **1998**, 33−35. (d) Andrés, J. M.; Pedrosa, R. *Tetrahedron: Asymmetry* **1998**, *9*, 2493−2498. (e) Hertweck, C.; Goerls, H.; Boland, W. *J. Chem. Soc., Chem. Commun.* **1998**, 1955−1956.

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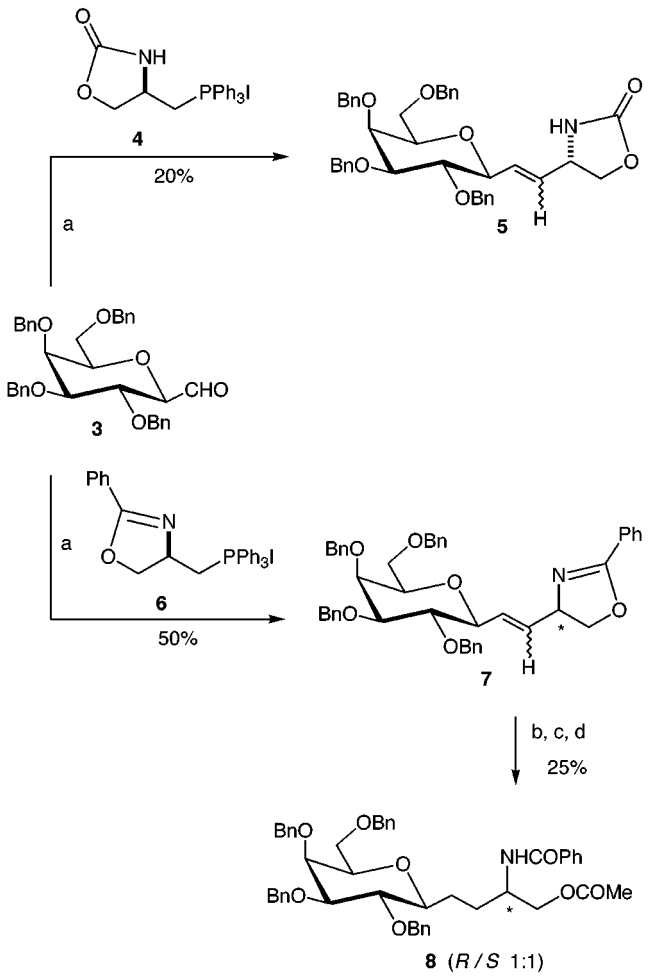
(22) Sibi, M. P.; Renhowe, P. A. *Tetrahedron Lett.* **1990**, *31*, 7407−7410.

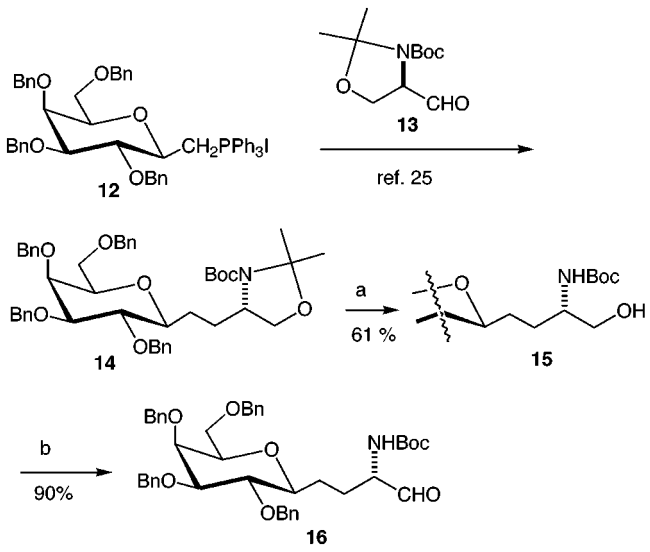
Scheme 1[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C. (b) $TsNHNH_2$, AcONa, DME, 85 °C. (c) HCl (2 M), THF. (d) Ac_2O, pyridine, DMAP.

Because of the above unsatisfactory results, we decided to capitalize on a more efficient Wittig olefination that was recently reported from our laboratory[25] as the result of a parallel research. This involved the ylide of the sugar phosphonium iodide **12** (Scheme 2) and the quite common protected D-serinal **13**. The phosphonium salt **12** was prepared[25] from the formyl *C*-galactoside **3** (three steps, 66% yield) while the aldehyde **13** was obtained from D-serine by a recently improved method.[26] Thus, coupling of these reagents and diimide reduction of the double bond of the resulting mixture of *E* and *Z* olefins as described,[25] afforded the alkyloxazolidine **14** in ca. 50% yield. The removal of the acetonide protective group under standard conditions ($AcOH-H_2O$, 4:1) transformed **14** into the *N*-Boc amino alcohol **15** which in turn was converted into the aldehyde **16** by Swern oxidation.[27] While the Wittig coupling between **12** and **13** worked well on a small scale (1 mmol) as reported,[25] the same reaction carried out with 5 mmol or more of reagents (1.5 g of **13**) followed by deacetonization, afforded the *S* amino alcohol **15** containing 10−15% of the *R* isomer as shown by ^1H NMR analysis.[28] The isolation of pure **15** was carried out by conversion of the mixture of amino alcohol epimers into *p*-nitrobenzoyl esters and separation by medium-pressure column chromatography. The alcohol **15** was liberated from the ester in almost quantitative yield by basic treatment and then oxidized to the aldehyde **16**. The stereochemical purity of **16** was confirmed by reduction ($NaBH_4$, 0 °C, 90%yield) to the alcohol **15** and analysis of the NMR spectrum of the latter.

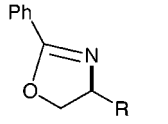
Scheme 2[a]



[a] Reagents and conditions: (a) AcOH, H_2O. (b) $(COCl)_2$, DMSO, *i*-Pr_2EtN, CH_2Cl_2, −78 °C.

Having developed a gram-scale synthesis of the α-amino aldehyde **16**, we turned out to the next step of the synthetic plan that involved the attachment of the lipophilic unsaturated carbon-chain corresponding to the sphingosine moiety. For this purpose we initially considered adding of a lithium alkylacetilide to **16** and reducing the triple to a double bond as described in various sphingosine syntheses.[29] We were aware that because of the single protection of the amino group of **16**, the addition of the organometal would very likely proceed with syn selectivity[30] to give the undesired amino alcohol as major product. In the event, we were ready to

(23) The phosphonium iodide **6** was prepared from the 4-(carbomethoxy)-2-phenyloxazoline **9** through alcohol **10** and iodide **11** (see the Experimental Section). In turn, compound **9** was prepared starting from D-serine as described for its L-enantiomer (Tkaczuk, P.; Thornton, E. R. *J. Org. Chem.* **1981**, *46*, 4393−4398).



9, R = CO_2Me
10, R = CH_2OH
11, R = CH_2I
6, R = CH_2PPh_3I

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(28) The two epimers could not be revealed by ^1H NMR analysis at room temperature since the spectrum was very complex due to the presence of geometrical isomers and rotamers. A less complex spectrum was obtained at 120 °C due to the coalescence of signals.

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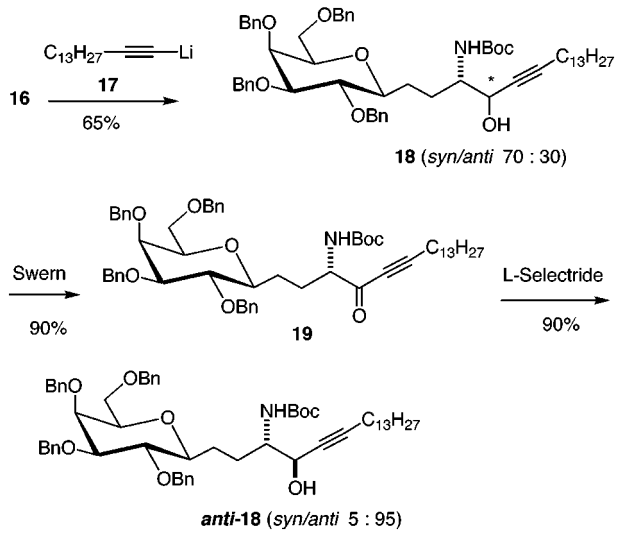
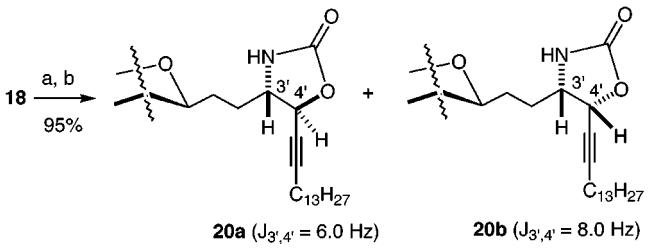
Scheme 3



apply an oxidation−reduction sequence for hydroxy group inversion developed in our laboratory some years ago.[31,32] This synthetic scheme had to be adopted because several attempts to prepare an amino aldehyde of type **16** with a double protected amino group that could undergo anti selective organometal addition[30] were unsuccessful. For example, the acetylation of **15** with Ac_2O−pyridine−DMAP at 90 °C gave after 6 h the *O*-acetyl ester while the *N*HBoc group remained unaltered.

Thus, the addition of excess lithium 1-pentadecyne **17** to the α-amino aldehyde **16** (Scheme 3) afforded the alcohol **18** (65% yield) as a mixture of *S* (syn adduct) and *R* isomer (anti adduct) in 70:30 ratio as judged by ^{1}H NMR analysis. The same ratio of isomers was obtained on carrying the reaction in the presence of the complex-destroying agent hexamethylphosphoramide (HMPA),[33] while the overall yield dropped to a lower value (35%). The stereochemistry of these isomers was assigned following the conversion of crude **18** into a mixture of oxazolidinones **20a** and **20b** (70:30 ratio) and comparison of the H-3′ and H-4′ coupling constant values as well as by NOE measurements (Scheme 4). Being the amino alcohol **18** constituted by a mixture of diastereomers with a predominance of the undesired syn product, we turned to the hydroxy group inversion. For this purpose crude **18** was oxidized to the ketone **19** (90% yield) by the Swern method, and the carbonyl of the resulting ynone was subjected to reduction by various metal hydrides (Table 1). The optimal reagent was found to be lithium tri-*sec*-butylborohydride (L-selectride) which afforded the desired amino alcohol ***anti*-18** with high diastereoselectivity (dr ≥ 95%) and high isolated chemical yield (90%). The stereochemistry of this compound was unequivocally assigned through its oxazolidinone derivative **20b**.

Scheme 4[a]



[a] Reagents and conditions: (a) HCl/dioxane (4.8 M). (b) Im_2CO, THF.

Table 1. Reduction of the Ketone 19 with Metal Hydrides to *anti*-18 and *syn*-18 Amino Alcohols[a]

hydride (equiv)	additive (equiv)	solvent	temp. °C	yield (%)[b]	**18** (anti:syn)[c]
$NaBH_4$ (5)		THF/MeOH 4:1	−60	60	60:40
$NaBH_4$ (5)	$CeCl_3$ (1)	EtOH	−60	90	73:27
Red-Al (1)[d]		THF	−78	60	70:30
LABOH (1)[e]		THF	−78	24	48:52
DIBAH (3)[f]		THF	−78	43	78:22
L-Selectride (2)[g]		THF	−78	90	95:5
L-Selectride (2)[g]	$ZnBr_2$ (1)	THF	−78	65	85:15

[a] All reactions were carried out with 50 mg of ketone **19**. [b] Isolated chemical yields of mixtures of ***anti*-18** and ***syn*-18**. [c] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude mixture. [d] Sodium bis(2-methoxyethoxy)aluminum hydride. [e] Lithium tri-*tert*-butoxyaluminum hydride. [f] Diisobutylaluminum hydride. [g] Litium tri-*sec*-butylborohydride.

With the alkyne ***anti*-18** in hand, the stereoselective hydrogenation of the triple bond and the replacement of the *N*Boc with the *N*-palmitoyl group remained to be carried out. Thus, removal of the *tert*-butoxycarbonyl group with HCl in dioxane gave the amino alcohol **21** in 90% isolated yield (Scheme 5). Given the conditions employed for the reduction of the triple bond in earlier sphingosine syntheses involving alkyne intermediates,[29a,b] we first considered the reduction of **21** with lithium in liquid ammonia. It was expected that under these conditions also deprotection of the benzyl ether groups of the galactose moiety would take place. Hence the hydrogenation of **21** was carried out with excess lithium in liquid ammonia/THF at −45 °C for 2 h. After the evaporation of ammonia, the crude residue was treated with palmitoyl chloride in the presence of sodium acetate to complete the construction of the ceramide moiety. Acetylation of the crude reaction mixture with Ac_2O in pyridine afforded a mixture of products constituted by the peracetylated galactosyl ceramide isostere **2a** and an unseparable byproduct in 45% overall yield from **21**. We looked for improved conditions in this final stage of the synthesis. Mindful of the excellent results of Liotta and co-workers in a classical sphingosine synthesis,[29d] the reduction of the triple bond of **21** was carried out using lithium aluminum hydride in refluxing dimethoxyethane (DME). After 3 h we could consistently obtain a yield of 65% of isolated *O*-tetrabenzyl galactopsychosine isostere **22**.[34] The elaboration of this compound allowed the isolation of two differentially protected target products **2a** and **2b**. The installation of the palmitoyl chain on the amino group of **22** afforded the *O*-tetrabenzylgalactosyl ceramide isostere **2b** (80% yield) whose debenzylation and

(30) It has been amply documented that addition reactions of organometals to chiral α-amino aldehydes lead to syn or anti amino alcohols depending on whether the amino group is singly or doubly protected, respectively. For reviews of our research in this area and leading references to the work of other groups, see: ref 20. Dondoni, A.; Perrone, D. *Aldrichimica Acta* **1997**, *30*, 35−46.

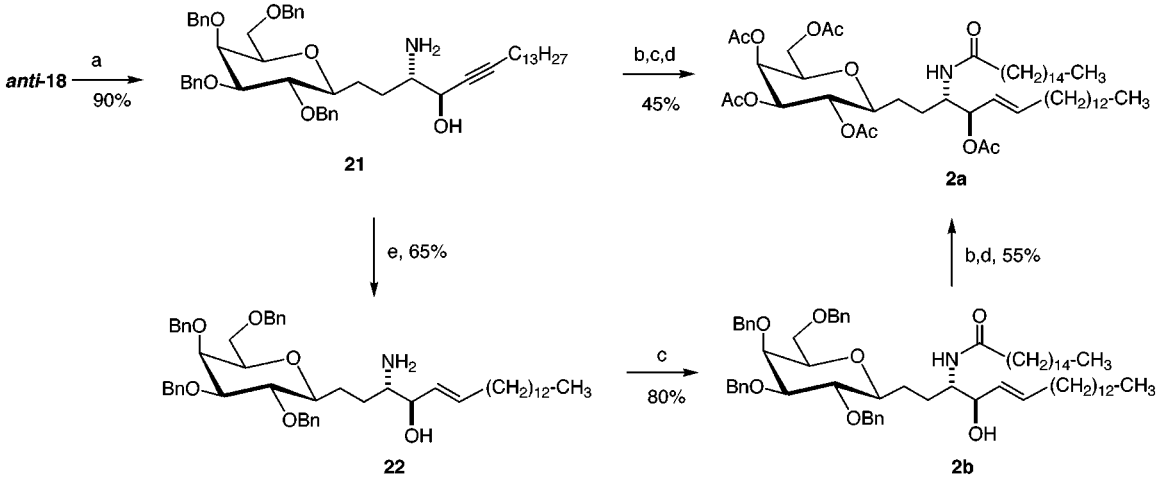
(31) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 702−706.

(32) For a recent application of this method in rare sugar synthesis, see: Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1997**, *62*, 6261−6267.

(33) Mulzer, J.; Pietschmann, C.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1997**, *62*, 3938−3943.

(34) Interest for debenzylated galactosylpsychosine isostere may arise from the potential inhibitory activity of rgp120-GalCer binding as shown by the *O*-linked analogue. See ref 14.

Scheme 5[a]



[a] Reagents and conditions: (a) HCl/dioxane (4.8 M). (b) Li/NH_3, THF, −45 °C. (c) $C_{15}H_{31}COCl$, AcONa, THF. (d) Ac_2O, pyridine. (e) $LiAlH_4$, DME, 85 °C.

exhaustive acetylation produced pure **2a** in 55% isolated yield. Key structural features of **2a** and **2b** that were substantiated by ^{1}H NMR analysis were the β-anomeric linkage ($J_{1,2}$ = 9.0 Hz) and the olefin with *E* geometry (*J* = 15.0 Hz). The absolute and relative configuration at the stereocenters bearing the amino and hydroxy groups were sufficiently demonstrated in the precursors of these compounds.

In conclusion, the first synthesis of a carbon-linked isostere of natural galactosyl ceramide was accomplished in 12 steps from the sugar phosphorane **12** in 4% overall yield. The linear synthetic scheme constitutes a model that should be amenable to the preparation of an array of galactosyl ceramides by changing either the alkyne in the condensation reaction with the aldehyde **16** or the fatty acid chloride in the amide bond formation. Moreover since other sugar phospshoranes are available in our laboratory, a combinatorial approach to various glycosyl ceramide isosteres may become of interest.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agent[35] and freshly distilled prior to use. Flash column chromatography[36] was performed on silica gel 60 (230−400 mesh), under positive pressure from a compressed air line. Medium-pressure chromatography was performed on silica gel 60 (230−240 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with alcoholic solutions of ninhydrin or sulfuric acid. After extractive workup, organic solutions were dried over Na_2SO_4, filtered through a cotton plug, and evaporated under reduced pressure. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C. IR spectra were recorded using a Perkin-Elmer 1310 spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded at room temperature in $CDCl_3$ solutions, unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix.

(*S*)-4-(Hydroxymethyl)-2-phenyl-2-oxazoline (10). To a cold (−50 °C) suspension of $LiAlH_4$ (0.35 g, 9.12 mmol) in anhydrous THF (14.0 mL) was added a solution of **9**[37] (1.70 g, 8.28 mmol) in anhydrous THF (10.0 mL). The mixture was stirred for 15 min, warmed to room temperature, and then treated with an aqueous phosphate buffer (pH 7, 15.0 mL) and filtered through Celite. The aqueous phase was extracted with AcOEt, and the combined organic phases were dried and concentrated to give **10** (1.10 g, 80%) as a white solid: mp 100−101 °C; $[\alpha]_D$ −82 (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 3.20 (s, 1 H, O*H*), 3.67 (dd, 1 H, *J* = 3.6, 11.6 Hz), 3.99 (dd, 1 H, *J* = 2.9, 11.6 Hz), 4.35 (dd, 1 H, *J* = 5.4, 6.2 Hz), 4.38−4.48 (m, 1 H), 4.49 (dd, 1 H, *J* = 5.4, 8.7 Hz), 7.30−7.50 (m, 3 H), 7.80−7.90 (m, 2 H); ^{13}C NMR δ 63.4, 68.7, 68.1, 126.9, 128.1, 131.3, 165.5. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.59; H, 6.27; N, 7.87.

(*R*)-4-(Iodomethyl)-2-phenyl-2-oxazoline (11). A mixture of alcohol **10** (1.00 g, 5.64 mmol), PPh_3 (4.30 g, 16.4 mmol), imidazole (1.50 g, 22.4 mmol), and iodine (3.57 g, 14.0 mmol) in anhydrous toluene (200 mL) was heated to 80 °C for 30 min. The resulting suspension was filtered, and the solution was washed with 5% aqueous $Na_2S_2O_3$ and with saturated aqueous $NaHCO_3$. The organic phase was dried, filtered, and concentrated. Chromatography on silica gel of the crude residue with toluene/AcOEt (100:5) gave **11** (1.30 g, 80%) as a yellow syrup: $[\alpha]_D$ +50.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR δ 3.24 (dd, 1 H, *J* = 7.8, 10.1 Hz), 3.50 (dd, 1 H, *J* = 3.9, 10.1 Hz), 4.18−4.26 (m, 1 H), 4.46−4.58 (m, 2 H), 7.28−7.55 (m, 3 H), 7.90−8.00 (m, 2 H); ^{13}C NMR δ 10.8, 67.2, 73.2, 127.3, 128.4, 131.7, 133.8, 165.2. Anal. Calcd for $C_{10}H_{10}NOI$: C, 41.81; H, 3.51; N, 4.88. Found: C, 41.73; H, 3.52; N, 4.84.

(*R*)-4-(2-Phenyl-2-oxazolininyl)methyltriphenylphosphonium iodide (6). A mixture of **11** (1.20 g, 4.18 mmol) and PPh_3 (4.39 g, 16.7 mmol) was heated to 120 °C for 1 h; then, to the still hot reaction mixture was added toluene (10.0 mL). After the reaction was cooled to room temperature, Et_2O (10.0 mL) was added. The precipitate was filtered, washed with Et_2O, and dried under vacuum to give the phosphonium salt **6** (2.00 g, 90%) as a white solid: mp 104−105 °C; $[\alpha]_D$ −18.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 3.25−4.42 (m, 1 H), 4.69−4.85 (m, 3 H), 5.10 (dt, 1 H, *J* = 3.0, 15.0 Hz), 7.20−8.00 (m, 20 H); ^{13}C NMR δ 31.2, 61.5, 73.8, 118.2, 119.4, 126.5, 128.2, 130.2, 131.9, 133.9, 134.8, 164.7. Anal. Calcd for $C_{28}H_{25}NOPI$: C, 61.21; H, 4.58; N, 2.54. Found: C, 61.39; H, 4.57; N, 2.54.

Methyl-5,9-anhydro-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-1-*O*-acetyl-2-*N*-benzoylamino-D-*threo*-L-*galacto*-(and L-*talo*)-deconate (8). To a stirred, cold (−78 °C) mixture of phosphonium salt **6** (0.60 g, 1.08 mmol), powdered 4-Å molecular sieves (0.50 g) and anhydrous THF (10.0 mL) was added *n*-BuLi (0.68 mL, 1.08 mmol of a 1.6 M solution in hexanes).

(35) Perrin, D. D.; Armarego, W. L. *Purification of Laboratory Chemicals*; Pergamon: New York, 1988.

(36) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(37) See the reference cited in note 23.

After 15 min, the resulting red-colored suspension was treated with a solution of the aldehyde **3**[19] (0.2 g, 0.36 mmol) in anhydrous THF (2.0 mL). The mixture was allowed to warm to −20 °C in a period of 2 h and then treated with aqueous phosphate buffer (pH 7) and filtered through Celite. The organic phase was dried and concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (3:1) containing Et_3N (1‰) gave the olefin **7** (0.13 g, 50%). To a stirred and warmed (85 °C) solution of this mixture (0.12 g, 0.17 mmol) and *p*-toluensulfonhydrazide (0.06 g, 0.34 mmol) in dimethoxyethane (2.0 mL) was added an aqueous solution of AcONa (1 M, 0.5 mL) in four portions over 2 h. After an additional 4 h at 85 °C, the reaction mixture was diluted with H_2O (2.0 mL) and extracted with Et_2O. The organic phase was concentrated, and the crude residue was dissolved in aqueous HCl (2 M, 2.0 mL) and stirred for 16 h at room temperature. The solution was extracted with Et_2O, and the combined organic phases were washed with H_2O, dried, and concentrated. To a solution of the crude residue in pyridine (2.0 mL) and Ac_2O (2.0 mL) was added DMAP (cat.). The resulting mixture was stirred at room temperature for 14 h and then concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (4:1) gave **8** (0.06 g, 50%) as a mixture of 2*S* and 2*R* epimers in ca. 1:1 ratio (by ^{1}H NMR analysis): ^{1}H NMR (selected data) δ 5.85 (d, 0.5 H, J = 8.2 Hz, N*H*), 5.95 (d, 0.5 H, J = 8.2 Hz, N*H*); MALDI-TOF MS 781.1 (M^+ + Na), 797.1 (M^+ + K).

5,9-Anhydro-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-decitol (15). The reaction was carried out as described in ref 25 starting from the phosphonium salt **12** (6.0 g, 6.50 mmol) and the aldehyde **13** (1.50 g, 6.50 mmol) to give the oxazoline derivative **14** (2.80 g, 52%) as a syrup. A solution of this compound (5.0 g, 6.65 mmol) in AcOH/H_2O (5:1, 42.0 mL) was stirred at room temperature for 24 h and then concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (2:1) containing Et_3N (1‰) afforded compound **15** (4.25 g, 90%) contaminated by its 2*R* epimer (85:15 ratio by ^{1}H NMR analysis). Attempts to separate these epimers by flash chromatography failed. To a solutions of these epimers (4.25 g) in anhydrous pyridine (45.0 mL) was added *p*-nitrobenzoyl chloride (1.83 g, 9.88 mmol). The mixture was stirred for 14 h at room temperature and then concentrated. Purification of the crude residue by medium-pressure chromatography (6 atm) with toluene/AcOEt (10:1) gave as the first eluate the *p*-nitrobenzoyl ester of **15** (2.69 g, 76%) as a light yellow solid: mp 80−81 °C; $[\alpha]_D$ −8.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 1.40 (s, 9 H), 1.56−1.80 (m, 3 H), 1.80−1.98 (m, 1 H), 3.22 (ddd, 1 H, $J_{4a,5} = J_{5,6} = 8.0$, $J_{4b,5} = 2.8$ Hz, H-5), 3.47−3.71 (m, 5 H), 3.98 (dd, 1 H, $J_{7,8} = 2.5$, $J_{8,9} = 0.5$ Hz, H-8), 3.96−3.99 (m, 1 H, H-2), 4.22 (dd, 1 H, $J_{1a,2} = 5.0$, $J_{1a,1b} = 11.0$ Hz, H-1a), 4.29 (dd, 1 H, $J_{1b,2} = 4.5$, H-1b), 4.40 and 4.43 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.53 (d, 1 H, J = 9.0 Hz, N*H*), 4.64 and 4.94 (2 d, 2 H, J = 11.3 Hz, PhCH_2), 4.68 and 4.76 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.65 and 4.95 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 7.20−7.40 (m, 20 H), 8.15−8.29 (m, 4 H); ^{13}C NMR δ 27.6, 27.9, 28.3, 30.0, 49.4, 69.1, 72.2, 73.5, 73.6, 75.4, 76.6, 78.6, 79.1, 79.4, 84.4, 123.1, 127.7, 128.0, 128.4, 135.4, 137.9, 138.2, 155.5. Anal. Calcd for $C_{50}H_{56}N_2O_{11}$: C, 69.75; H, 6.56; N, 3.25. Found: C, 69.56; H, 6.77; N, 3.29. The second eluate was the 2*R* epimer (0.53 g, 13%) as a syrup: ^{1}H NMR δ 1.40 (s, 9 H), 1.40−1.45 (m, 1 H), 1.61−1.82 (m, 2 H), 1.90−2.10 (m, 1 H), 3.20 (ddd, 1 H, $J_{4a,5} = J_{5,6} = 8.0$, $J_{4b,5} = 2.8$ Hz, H-5), 3.45−3.71 (m, 5 H), 3.97 (dd, 1 H, $J_{7,8} = 2.5$, $J_{8,9} = 0.5$ Hz, H-8), 3.96−3.98 (m, 1 H, H-2), 4.20 (dd, 1 H, $J_{1a,1b} = 12.0$, $J_{1a,2}$ = 6.5 Hz, H-1a), 4.30 (dd, 1 H, $J_{1b,2} = 5.0$ Hz, H-1b), 4.42 and 4.45 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.63 and 4.93 (2 d, 2 H, J = 11.3 Hz, PhCH_2), 4.67−4.69 (m, 1 H, N*H*), 4.68 and 4.77 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.65 and 4.95 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 7.22−7.40 (m, 20 H), 8.15−8.25 (m, 4 H); ^{13}C NMR δ 27.7, 28.3, 29.7, 49.6, 70.0, 72.2, 74.4, 74.5, 75.5, 76.1, 76.6, 78.7, 79.2, 84.8, 120.8, 126.6, 127.8, 128.4, 131.5, 137.9, 138.6, 144.4, 155.4.

To a suspension of the *p*-nitrobenzoyl ester of **15** (2.69 g, 3.12 mmol) in anhydrous MeOH (50.0 mL) was added at room temperature a solution of MeONa (5%, 0.72 g of Na, 31.2 mmol) in MeOH (14.4 mL). The solution was stirred for 15 min and then diluted with AcOH (2.40 mL) and concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (2:1) containing Et_3N (1‰) gave the alcohol **15** (2.22 g, 90%) as a white solid: mp 92−93 °C; $[\alpha]_D$ −11.8 (*c* 1.8, $CHCl_3$); ^{1}H NMR δ 1.42 (s, 9 H), 1.50−1.52 (m, 3 H), 1.72−1.93 (m, 1 H, H-3b), 2.61−2.70 (s, 1 H, O*H*), 3.20 (ddd, 1 H, $J_{4a,5} = J_{5,6} = 8.0$, $J_{4b,5} = 2.7$ Hz, H-5), 3.43−3.70 (m, 8 H), 3.88 (dd, 1 H, $J_{7,8} = 2.6$, $J_{8,9} = 0.5$ Hz, H-8), 4.41 and 4.47 (2d, 2 H, J = 12.0 Hz, PhCH_2), 4.64 and 4.94 (2d, 2 H, J = 11.3 Hz, PhCH_2), 4.65−4.70 (m, 1 H, N*H*), 4.68 and 4.76 (2d, 2 H, J = 12.0 Hz, PhCH_2), 4.65 and 4.95 (2d, 2 H, J = 11.3 Hz, PhCH_2), 7.40 and 7.80 (m, 20 H); ^{13}C NMR δ 27.0, 27.8, 28.3, 53.0, 60.4, 66.5, 69.1, 72.2, 73.4, 73.6, 74.4, 75.4, 77.2, 78.6, 79.3, 84.8, 127.6, 127.8, 127.9, 128.2, 128.4, 137.8, 138.2, 138.6, 156.7. Anal. Calcd for $C_{43}H_{53}O_8N$: C, 72.54; H, 7.50; N, 1.96. Found: C, 72.79; H, 7.58; N, 2.20.

5,9-Anhydro-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-decitose (16). To a cold (−78 °C) solution of oxalyl chloride (0.16 g, 1.26 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added a solution of DMSO (0.20 g, 2.52 mmol) in anhydrous CH_2Cl_2 (1.20 mL). The mixture was stirred for 30 min at −78 °C; then, a solution of alcohol **15** (0.60 g, 0.84 mmol) in anhydrous CH_2Cl_2 (1.80 mL) was added. The reaction was stirred for 1 h, and then *N*,*N*-diisopropylethylamine (0.88 mL, 5.05 mmol) was added. After warming the reaction to 0 °C over 10 min, the mixture was treated with cold (0 °C) aqueous HCl (1 M, 3.0 mL). The solution was extracted with CH_2Cl_2, and the combined organic phases were washed with aqueous phosphate buffer (pH 7), dried, and concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (3:1) containing Et_3N (1‰) gave the aldehyde **16** (0.54 g, 90%) as a syrup: $[\alpha]_D$ +7.3 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.40 (s, 9 H), 1.40−1.96 (m, 4 H), 3.25 (ddd, 1 H, $J_{4a,5} = J_{5,6} = 9.0$, $J_{4b,5}$ = 2.8 Hz, H-5), 3.50−3.66 (m, 4 H), 3.69 (dd, 1 H, $J_{6,7} = 9.0$, $J_{7,8}$ = 3.0 Hz, H-7), 3.78−3.87 (m, 1 H, H-2), 4.40 (dd, 1 H, $J_{8,9}$ = 0.5 Hz, H-8), 4.47 and 4.53 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.56 and 4.84 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.63 and 4.82 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.66 and 4.78 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 6.63 (d, 1 H, J = 7.5 Hz, N*H*), 7.20−7.40 (m, 20 H), 9.45 (d, 1 H, J = 0.7 Hz, H-1); ^{13}C NMR δ 25.1, 28.3, 31.0, 59.5, 69.1, 72.2, 73.5, 73.6, 74.4, 75.4, 76.6, 76.9, 78.4, 79.1, 127.5, 127.6, 127.8, 127.9, 128.2, 128.4, 137.8, 138.2, 156.0, 200.5; MALDI-TOF MS 733.1 (M^+ + Na), 749.1 (M^+ + K). Anal. Calcd for $C_{43}H_{51}NO_8$: C, 72.75; H, 7.24; N, 1.97. Found: C, 72.73; H, 7.22; N, 2.10.

3′(*S*)-*N*-(*tert*-Butoxycarbonylamino)-4′(*S*)(and (*R*))-nonadec-5′-yn-4′-olyl 2,3,4,6-Tetra-*O*-benzyl-β-*C*-D-galactopyranoside (18). To a stirred, cold (−20 °C) mixture of 1-pentadecyne (0.23 g, 3.53 mmol), powdered 4-Å molecular sieves (0.20 g), and anhydrous THF (18.0 mL) was added *n*-BuLi (2.20 mL, 3.52 mmol of a 1.6 M solution in hexanes). The resulting white suspension was stirred at this temperature for 30 min and then cooled to −50 °C over a period of 10 min. A solution of the aldehyde **16** (0.50 g, 0.70 mmol) in anhydrous THF (3.0 mL) was added dropwise, and the resulting mixture was stirred at −50 °C for 2 h and then quenched with aqueous phosphate buffer (pH 7) and allowed to warm to room temperature. The white suspension was filtered through a pad of Celite, and the phases were separated. The aqueous phase was extracted with AcOEt, and the combined organic layers were dried and concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (3:1) gave **18** (0.65 g, 65%) as a 70:30 mixture of epimers ***syn*-18** and ***anti*-18** (by ^{1}H NMR analysis): ^{1}H NMR δ 0.82−0.87 (m, 3 H), 1.20−1.50 (m, 20 H), 1.40−1.52 (m, 11 H), 1.54−1.70 (m, 3 H), 1.88−2.00 (m, 1 H), 2.15 (dt, 1 H, J = 1.0, 4.5 Hz), 2.70 (d, 0.7 H, J = 4.6 Hz, O*H*), 3.08 (d, 0.3 H, J = 6.4 Hz, O*H*), 3.40−3.70 (m, 5 H), 3.97 (dd, 1 H, $J_{3,4} = 2.4$, $J_{4,5} = 0.5$ Hz, H-4), 4.25−4.33 (m, 0.7 H, H-4′), 4.41 and 4.47 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.38−4.42 (m, 0.3 H, H-4′), 4.43 and 4.94 (2 d, 2 H, J = 12.0

Hz, PhCH_2), 4.64 and 4.94 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.68 and 4.75 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 7.20−7.40 (m, 20 H); ^{13}C NMR δ 14.3, 18.8, 22.7, 28.1, 29.2, 29.4, 30.0, 56.3, 65.8, 69.1, 72.3, 73.5, 73.7, 75.5, 76.7, 79.1, 79.4, 84.8, 86.2, 127.6, 127.8, 127.9, 128.2, 128.4, 137.9, 138.3, 138.7, 156.5.

Oxazolidinones 20a and 20b. The mixture of epimers **18** (0.13 g, 0.14 mmol) was dissolved in a solution of HCl in dioxane (4.8 M, 3.0 mL) and water (0.50 mL). The solution was stirred at room temperature for 14 h and then concentrated. To the residue dissolved in anhydrous THF (2.0 mL) was added *N*,*N*′-carbonyldiimidazole (0.03 g, 0.21 mmol) at 0 °C; then the resulting mixture was stirred for 45 min at room temperature and concentrated. The ^{1}H NMR spectrum of the crude residue revealed a mixture of **20a** and **20b** in ca. 70:30 ratio. Chromatography on silica gel of this mixture with cyclohexane−AcOEt (2:1) afforded first **20a** (0.07 g, 63%) as a syrup and then **20b** (0.03 g, 27%) contaminated by a small amount of **20a**.

20a: $[\alpha]_D$ −43.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.82−0.92 (m, 3 H, CH_3), 1.30 (s, 20 H), 1.40−1.53 (m, 2 H), 1.54−1.95 (m, 4 H), 2.20 (dt, 2 H, $J_{4',7'}$ = 2.0, $J_{7',8'}$ = 7.0 Hz, 2 H-7′), 3.24 (ddd, 1 H, $J_{1,1'a}$ = $J_{1,2}$ = 8.0, $J_{1,1'b}$ = 2.8 Hz, H-1), 3.50−3.78 (m, 5 H), 3.68 (dd, 1 H, $J_{2,3}$ = 9.5, $J_{3,4}$ = 2.8 Hz, H-3), 4.40 (dd, 1 H, $J_{4,5}$ = 0.5 Hz, H-4), 4.47 and 4.55 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.56 and 4.84 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.63 and 4.81 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.66 and 4.78 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.72 (dt, 1 H, $J_{3',4'}$ = 6.0 Hz, H-4′), 7.20−7.40 (m, 21 H); ^{13}C NMR δ 14.1, 18.7, 22.6, 29.1, 29.2, 29.6, 31.9, 32.9, 61.2, 69.2, 73.1, 73.3, 74.2, 75.3, 75.5, 76.5, 77.0, 78.6, 80.4, 84.6, 89.3, 89.0, 128.1, 128.3, 128.4, 128.5, 137.4, 138.0, 158.1; MALDI-TOF MS 867.5 (M^+ + Na), 883.2 (M^+ + K). Anal. Calcd for $C_{54}H_{69}NO_7$: C, 76.83; H, 8.59; N, 1.65. Found: C, 76.69; H, 8.70; N, 1.62.

20b: ^{1}H NMR (DMSO-d_6, 120 °C): δ 0.82−0.92 (m, 3 H, CH_3), 1.20−1.30 (s, 20 H), 1.40−1.53 (m, 2 H), 1.54−1.95 (m, 4 H), 2.19 (dt, 2 H, $J_{4',7'}$ = 2.0, $J_{7',8'}$ = 7.0 Hz, 2 H-7′), 3.25 (ddd, 1 H, $J_{1,1'a}$ = $J_{1,2}$ = 8.0, $J_{1,1'b}$ = 2.8 Hz, H-1), 3.50−3.69 (m, 5 H), 3.68 (dd, 1 H, $J_{2,3}$ = 9.5, $J_{3,4}$ = 2.8, Hz, H-3), 4.42 (dd, 1 H, $J_{4,5}$ = 0.5 Hz, H-4), 4.48 and 4.54 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.57 and 4.84 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.64 and 4.81 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.66 and 4.78 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 5.21 (dt, 1 H, $J_{3',4'}$ = 8.0 Hz, H-4′), 7.08 (s, 1 H, N*H*), 7.20−7.40 (m, 20 H).

3′*S*-*N*-(*tert*-Butoxycarbonylamino)nonadec-5′-yn-4′-onyl 2,3,4,6-Tetra-*O*-benzyl-β-*C*-D-galactopyranoside (19). To a cold (−78 °C) solution of oxalyl chloride (0.10 g, 0.82 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was added a solution of DMSO (0.13 g, 1.63 mmol) in anhydrous CH_2Cl_2 (1.0 mL). The solution was stirred at −78 °C for 30 min, and then a solution of alcohol **18** (0.50 g, 0.54 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was added. After the reaction solution had been stirred at this temperature for 1 h, *N*,*N*′-diisopropylethylamine (0.42 g, 3.27 mmol) was added. The mixture was allowed to warm to 0 °C over 10 min and treated with cold (0 °C) aqueous HCl (1 M, 2.0 mL). The solution was extracted with CH_2Cl_2, and the combined organic phases were washed with aqueous phosphate buffer (pH 7), dried, and concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (4:1) containing Et_3N (1‰) gave the ketone **19** (0.45 g, 90%) as a syrup: $[\alpha]_D$ +8.4 (*c* 0.6, $CHCl_3$); IR (NaCl) cm^{-1} 2220, 1654; ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.82−0.94 (m, 3 H, CH_3), 1.25 (s, 20 H), 1.39 (s, 9 H), 1.40−1.60 (m, 2 H), 1.65−1.80 (m, 1 H), 1.80−1.94 (m, 2 H), 2.12−2.20 (m, 1 H, H-1′), 2.30−2.40 (m, 2 H, 2 H-7′), 3.24 (ddd, 1 H, $J_{1,1'a}$ = $J_{1,2}$ = 9.0, $J_{1,1'b}$ = 2.8 Hz, H-1), 3.50−3.64 (m, 4 H), 3.68 (dd, 1 H, $J_{2,3}$ = 9.5, $J_{3,4}$ = 2.8 Hz, H-3), 3.92−4.00 (m, 1 H, H-3′), 4.04 (dd, 1 H, $J_{4,5}$ = 0.5 Hz, H-4), 4.47 and 4.53 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.56 and 4.84 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.63 and 4.81 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.66 and 4.78 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 6.58 (s, 1 H, N*H*), 7.20−7.40 (m, 20 H); ^{13}C NMR δ 14.1, 19.0, 22.6, 27.6, 28.3, 28.9, 29.3, 29.4, 29.6, 31.9, 61.0, 62.1, 68.8, 72.2, 73.5, 74.4, 75.5, 78.7, 79.1, 79.6, 84.7, 97.8, 127.5, 127.6, 128.2, 128.4, 137.9, 138.1, 138.2, 155.4, 187.0. Anal. Calcd for $C_{58}H_{77}NO_8$: C, 76.03; H, 8.47; N, 1.53. Found: C, 76.21; H, 8.29; N, 1.58.

(3′*S*,4′*R*)-*N*-(*tert*-Butoxycarbonylamino)nonadec-5′-yn-4′-olyl 2,3,4,6-Tetra-*O*-benzyl-β-*C*-D-galactopyranoside (*anti*-18). To a cold (−78 °C) stirred solution of **19** (0.40 g, 0.44 mmol) in anhydrous THF (2.5 mL) was added L-selectride (lithium tri-*sec*-butylborohydride, 0.87 mL, 0.87 mmol, of a 1 M solution in THF). After 30 min at this temperature, the reaction was quenched with MeOH, allowed to warm to room temperature, and partitioned between Et_2O and saturated aqueous NaCl. The combined organic phases were dried and concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (3:1) containing Et_3N (1‰) gave ***anti*-18** (0.36 g, 90%, dr ≥ 95% by ^{1}H NMR analysis): $[\alpha]_D$ −13.2 (*c* 0.5, $CHCl_3$); IR cm^{-1} 2400; ^{1}H NMR δ 0.82−0.93 (m, 3 H, CH_3), 1.20−1.70 (m, 20 H), 1.43 (s, 9 H), 1.40−1.52 (m, 2 H, 2 H-8′), 1.54−1.70 (m, 3 H), 1.88−2.00 (m, 1 H, H-2′b), 2.15 (dt, 2 H, J = 1.0, 4.5, Hz, 2 H-7′), 3.06 (d, 1 H, J = 6.4 Hz, O*H*), 3.22 (ddd, 1 H, $J_{1,1'a}$ = $J_{1,2}$ = 9.0, $J_{1,1'b}$ = 2.6 Hz, H-1), 3.47−3.68 (m, 5 H), 3.68−3.80 (m, 1 H, H-3′), 3.97 (dd, 1 H, $J_{3,4}$ = 2.5, $J_{4,5}$ = 0.5 Hz, H-4), 4.41 and 4.47 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.38−4.44 (m, 1 H, H-4′), 4.63 and 4.94 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.64 and 4.94 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.68 and 4.75 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.70−4.78 (m, 1 H, N*H*), 7.20−7.40 (m, 20 H); ^{13}C NMR δ 14.1, 18.7, 22.7, 28.4, 28.9, 29.4, 29.7, 31.9, 55.8, 69.1, 73.5, 73.6, 74.5, 75.5, 77.2, 77.4, 77.7, 79.1, 79.4, 79.7, 84.8, 87.3, 127.5, 127.6, 127.8, 127.9, 128.1, 128.2, 128.4, 137.9, 138.3, 138.7, 156.9; MALDI-TOF MS: 941.3 (M^+ + Na), 957.5 (M^+ + K). Anal. Calcd for $C_{58}H_{79}NO_8$: C, 75.86; H, 8.67; N, 1.52. Found: C, 76.09; H, 8.51; N, 1.59.

(3′*S*,4′*R*)-3′-Amininononadec-5′-yn-4′-olyl 2,3,4,6-Tetra-*O*-benzyl-β-*C*-D-galactopyranoside (21). A solution of HCl in dioxane (4.8 M, 2.0 mL) and water (0.5 mL) was added at room temperature to ***anti*-18** (0.30 g, 0.33 mmol). The mixture was stirred overnight and then concentrated. The residue was dissolved in saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2, dried, and concentrated. Chromatography on silica gel of the crude residue with CH_2Cl_2/MeOH/NH_4OH (95:5:1) gave **21** (0.24 g, 90%): ^{1}H NMR δ 0.80−0.92 (m, 3 H, CH_3), 1.25 (s, 22 H), 1.40−1.50 (m, 2 H), 1.50−1.70 (m, 2 H, 2 H-1′), 2.00−2.20 (m, 2 H, 2 H-2′), 2.75 (m, 1 H, O*H*), 3.15−3.27 (m, 1 H, H-1), 3.46−3.70 (m, 6 H), 3.97 (d, 1 H, $J_{3,4}$ = 2.5, $J_{4,5}$ = 0.5, H-4), 4.38−4.44 (m, 1 H, H-4′), 4.41 and 4.48 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.62 and 4.93 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.68 and 4.75 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.68 and 4.93 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 7.20−7.40 (m, 20 H); ^{13}C NMR δ 14.1, 18.7, 22.7, 28.8, 29.3, 29.7, 30.8, 31.9, 55.0, 55.7, 65.9, 69.1, 73.7, 74.4, 75.5, 76.2, 76.6, 78.9, 79.0, 79.5, 84.9, 86.7, 127.5, 127.8, 127.9, 128.2, 128.4, 137.9, 138.4, 138.7.

(3′*S*,4′*R*)-3′-Amino-(*E*)-nonadec-5′-en-4′-olyl 2,3,4,6-Tetra-*O*-benzyl-β-*C*-D-galactopyranoside (22). To a solution of **21** (0.20 g, 0.24 mmol) in anhydrous dimethoxyetane (5.0 mL) was added $LiAlH_4$ (0.90 g, 24.4 mmol). The mixture was heated to 85 °C, stirred at this temperature for 3 h, then cooled to room temperature, and treated with aqueous KOH (4 M, 5.0 mL). The white suspension was filtered through a pad of Celite and concentrated. Chromatography on silica gel of the crude residue with CH_2Cl_2/MeOH/NH_4OH (94:5:1) gave **22** (0.13 g, 65%) as a syrup: $[\alpha]_D$ +12.4 (*c* 0.9, MeOH); ^{1}H NMR δ 0.84−0.94 (m, 3 H, CH_3), 1.28 (s, 22 H), 1.40−1.64 (m, 3 H), 1.82−2.05 (m, 3 H), 2.79 (ddd, 1 H, $J_{2'a,3'}$ = 8.3, $J_{2'b,3'}$ = 4.6, $J_{3',4'}$ = 4.1 Hz, H-3′), 3.21 (ddd, 1 H, $J_{1,1'a}$ = $J_{1,2}$ = 9.2, $J_{1,1'b}$ = 2.1 Hz, H-1), 3.44−3.72 (m, 5 H), 3.95 (dd, 1 H, $J_{3,4}$ = 2.5, $J_{4,5}$ = 0.5 Hz, H-4), 3.98 (dd, 1 H, $J_{4',5'}$ = 6.4 Hz, H-4′), 4.42 and 4.51 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.63 and 4.94 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.64 and 4.96 (2 d, 2 H, J = 10.7 Hz, PhCH_2), 4.68 and 4.76 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 5.39 (dd, 1 H, $J_{5',6'}$ = 15.1 Hz, H-5′), 5.69 (ddd, 1 H, $J_{6',7'a}$ = $J_{6',7'b}$ = 6.8 Hz, H-6′), 7.20−7.40 (m, 20 H); ^{13}C NMR δ 14.1, 22.7, 29.3, 29.4, 29.5, 29.7, 31.9, 32.4, 55.7, 69.1, 73.5, 73.7, 74.4, 75.4, 76.6, 77.4, 78.9, 79.6, 84.9, 127.5, 127.7, 127.9, 128.1, 128.2, 128.4, 134.1, 137.9, 138.4, 138.6. Anal. Calcd for $C_{53}H_{73}NO_6$: C, 77.85; H, 8.69, N, 1.71. Found: C, 77.79; H, 8.70; N, 1.70.

(3′S,4′*R*)-3′-*N*-(pentadecanoylamino)-(*E*)-nonadec-5′-en-4′-olyl 2,3,4,6-Tetra-*O*-benzyl-β-*C*-D-galactopyranoside (2b). To a solution of **22** (0.10 g, 0.12 mmol) in anhydrous THF

(5.0 mL) was added slowly aqueous AcONa (0.10 g, 12 mmol in 4 mL of H_2O) and palmitoyl chloride (0.04 mL, 0.12 mmol). The mixture was stirred for 1 h at room temperature and then diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic phases were dried and concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (3:1) containing Et_3N (1‰) gave **2b** (0.13 g, 80%): $[\alpha]_D$ −20 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 0.83−0.92 (m, 6 H, 2 C*H*$_3$), 1.25 (s, 46 H), 1.40−1.70 (m, 5 H), 1.90−2.05 (m, 3 H), 2.10 (dt, 2 H, J = 1.6, 9.1 Hz), 3.18 (ddd, 1 H, $J_{1,1'a} = J_{1,2}$ = 9.0, $J_{1,1'b}$ = 2.5 Hz, H-1), 3.44−3.60 (m, 3 H), 3.60 (dd, 1 H, $J_{2,3}$ = 8.8 Hz), 3.64 (dd, 1 H, $J_{3,4}$ = 2.3 Hz, H-3), 3.82 (d, 1 H, J = 5.1 Hz, O*H*), 3.85−3.94 (m, 1 H, H-3′), 3.96 (dd, 1 H, $J_{4,5}$ = 0.5 Hz, H-4), 4.04−4.15 (m, 1 H, H-4′), 4.42 and 4.48 (2d, 2 H, J = 11.8 Hz, PhC*H*$_2$), 4.62 and 4.94 (2 d, 2 H, J = 10.7 Hz, PhC*H*$_2$), 4.61 and 4.94 (2 d, 2 H, J = 11.8 Hz, PhC*H*$_2$), 4.69 and 4.76 (2 d, 2 H, J = 11.8 Hz, PhC*H*$_2$), 5.35 (dd, 1 H, $J_{5',4'}$ = 6.0, $J_{5',6'}$ = 15.5 Hz, H-5′), 5.67 (ddd, 1 H, $J_{6',7'a} = J_{6',7'b}$ = 6.5 Hz, H-6′), 5.78 (d, 1 H, J = 7.4 Hz, N*H*), 7.20−7.40 (m, 20 H); ^{13}C NMR δ 14.1, 22.7, 26.0, 28.5, 29.3, 29.7, 31.9, 32.4, 36.6, 55.6, 62.6, 69.1, 73.5, 73.6, 74.5, 75.9, 76.1, 76.6, 79.0, 79.5, 84.8, 127.5, 127.7, 127.8, 127.9, 128.2, 133.8, 137.7, 138.2, 175.0; MALDI-TOF MS 1082.2 (M^+ + Na), 1098.4 (M^+ + K). Anal. Calcd for $C_{69}H_{103}NO_7$: C, 78.35; H, 9.74; N, 1.32. Found C, 78.48; H, 9.62; N, 1.31.

(3′*S*,4′*R*)-4′-*O*-Acetyl-3′-*N*-(pentadecanoylamino)-(*E*)-nonadec-5′-en-4′-olyl 2,3,4,6-Tetra-*O*-acetyl-*β*-*C*-D-galactopyranoside (2a). To cold (−45 °C) stirred liquid ammonia (2.0 mL) were added a solution of **2b** (0.05 g, 0.05 mmol) in anhydrous THF (2.0 mL) and lithium (24.0 mg). The deep blue solution was stirred at −45 °C for 2 h while the blue color persisted. Ethanol was added, and the ammonia was allowed to evaporate. The mixture was concentrated, and the residue was dissolved in pyridine (2.0 mL) and Ac_2O (2.0 mL), stirred for 14 h at room temperature, and then concentrated. Chromatography on silica gel of the crude residue with cycloexane/AcOEt (2:1) containing Et_3N (1‰) gave **2a** (23.7 mg, 55%) as a yellow syrup: $[\alpha]_D$ −6.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 0.80−0.98 (m, 6 H, 2 C*H*$_3$), 1.28 (s, 46 H), 1.40−1.78 (m, 5 H), 1.98−2.20 (m, 5 H), 1.98 (s, 3 H, C*H*$_3$), 2.04 (s, 3 H, C*H*$_3$), 2.05 (s, 6 H, 2 C*H*$_3$), 2.15 (s, 3 H, C*H*$_3$), 3.42 (ddd, 1 H, $J_{1,1'a} = J_{1,2}$ = 9.0, $J_{1,1'b}$ = 2.5 Hz, H-1), 3.82−3.88 (m, 1 H, H-6a), 4.05 (dd, 1 H, $J_{5,6b}$ = 6.5, $J_{6a,6b}$ = 11.0 Hz, H-6b), 4.10−4.22 (m, 2 H, H-3′, H-5), 5.06 (dd, 1 H, $J_{2,3}$ = 9.0 Hz, H-2), 5.19 (dd, 1 H, $J_{3',4'}$ = 4.5, $J_{4',5'}$ = 7.0 Hz, H-4′), 5.27−5.31 (m, 1 H, H-4), 5.35 (dd, 1 H, $J_{5',6'}$ = 14.8, H-5′), 5.39−5.44 (m, 1 H, H-3), 5.76 (ddd, 1 H, $J_{6',7'a} = J_{6',7'b}$ = 6.5 Hz, H-6′), 6.90−6.94 (m, 1 H, N*H*); ^{13}C NMR δ 14.1, 20.6, 20.7, 20.8, 21.2, 22.7, 25.9, 27.3, 29.0, 29.4, 29.5, 29.7, 31.9, 32.4, 36.9, 50.6, 61.5, 71.3, 71.4, 72.5, 74.1, 123.9, 136.7, 170.0, 170.1, 170.2, 170.4, 173.0, 178.5; MALDI-TOF MS 931 (M^+ + Na), 947 (M^+ + K). Anal. Calcd for: $C_{51}H_{89}NO_{12}$: C, 67.45; H, 9.87; N, 1.54. Found C, 67.32; H, 9.72; N, 1.46.

Synthesis of 2a from 21. The reduction with lithium in liquid ammonia was carried out as described above starting from **21** (0.05 g, 0.06 mmol). After the mixture had been concentrated, the residue was treated with palmitoyl chloride as described for **2b**. The crude residue was dissolved in a solution of pyridine (2.0 mL) and Ac_2O (2.0 mL), stirred for 14 h at room temperature, and then concentrated. Chromatography on silica gel of the crude residue with cyclohexane/AcOEt (2:1) and Et_3N (1‰) gave **2a** contaminated by small amounts of uncharacterized byproducts (25.0 mg, 45% overall yield).

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