An Efficient and Concise Synthesis of α-Galactosylceramide

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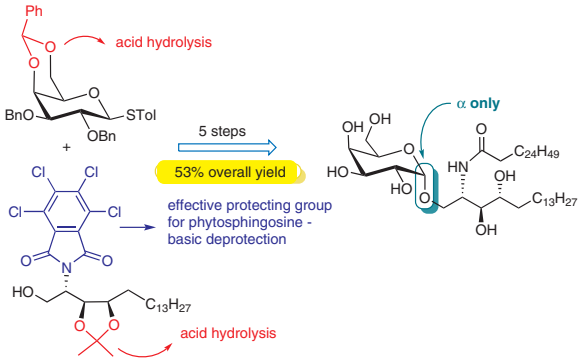

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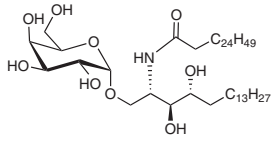
Abstract A concise and stereoselective synthesis of α-galactosylceramide (α-GalCer) is described. The key features of the synthetic strategy are the use of a phytosphingosine in which the amine is masked as a tetrachlorophthalimide and the diol as an isopropylidene acetal, and the galactosyl donor is protected as a 4,6-benzylidene to improve the α selectivity of the glycosylation reaction. The pattern of protecting groups on the donor and the acceptor have proven to give an excellent match of reactivity, allowing the glycosylation reaction to take place stereoselectively. The overall synthesis gave α-GalCer in good yields and in few steps.

Key words glycosylation, phytosphingosine, protecting groups, galactosylceramide, glycolipids, asymmetric synthesis

α-Galactosylceramide (α-GalCer) (**1**; Figure 1) is a synthetic glycolipid developed from structure–activity relationship studies performed on glycolipids isolated from the marine sponge *Agelas mauritianus*, and represents a prototype of an invariant natural killer T (iNKT) cell ligand.[1] It is able to bind to CD1d glycoprotein, associated with the membrane of antigen-presenting cells.[2] This complex is presented to the T cell receptor of iNKT cells, inducing the simultaneous release of T-helper 1 and T-helper 2 cytokines.[3] The great biological interest in α-GalCer and its derivatives has prompted the development of several synthetic approaches in which researchers tried to optimize yields, develop efficient glycosylation protocols, and reduce the overall number of steps.4

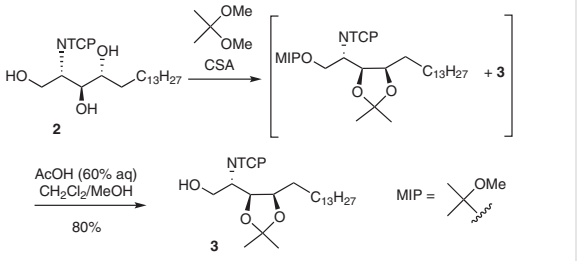
Glycolipid synthesis typically involves long procedures, low yields, and expensive reagents. The glycosylation reaction is the key step, and the choice of the acceptor and the donor is critical for the outcome of the total synthesis. In this paper, we report a convenient and concise synthesis of α-GalCer by exploiting galactosyl donor **4** ■■*now* ***4****,* *ok?*■■ and the new sphingoid acceptor **3** (Schemes 1 and 2). Galactosyl donors bearing a 4,6-*O*-benzylidene moiety are known to direct the attack of the acceptor from the α side.[5] Moreover, thioglycosides are employed as glycosyl donors as they can act at the same time as anomeric protecting groups, showing good stability toward a wide variety of reaction conditions, and are also efficient leaving groups. For these reasons, we exploited 4-methylphenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (**4**) as the donor.[6] Another significant aspect of our synthesis of α-GalCer is the choice of the sphingolipid acceptor. In fact, the use of ceramide allows rapid access to α-GalCer and its derivatives, but the nucleophilicity of the primary hydroxy group can be reduced because of a hydrogen bond with the NH of the amide, which can be the cause of fair to low yields. Our first goal was the synthesis of a new acceptor, namely a phytosphingosine derivative containing an isopropylidene protecting group for the 3,4-diol, and a tetrachlorophthalimide group to mask the amine. This is the first time that tetrachlorophthalimide has been successfully used as a protecting group in the synthesis of KRN7000-related compounds.[7] In addition, based on our previous experience, tetrachlorophthalimide-protected sphingoid derivatives are easily prepared solids that can be readily purified by crystallization and can be stored for months without noticeable decomposition. Tetrachlorophthalimide is also an orthogonal protective group with respect to acetals, being



1 α-GalCer (KRN7000)

Figure 1

resistant to acidic conditions. Accordingly, commercial phytosphingosine was converted into the tetrachlorophthalimido derivative **2** as previously described.[8] The protection of the 3,4-hydroxy groups was performed by using an excess of 2,2-dimethoxypropane under acid catalysis. Not unexpectedly,[9] the reaction gave a minor amount of the desired 3,4-acetal and a main product containing, besides the 3,4-acetonide, a mixed 2-methoxyisopropyl (MIP) acetal arising from the reaction of dimethoxypropane with the primary hydroxy group. The desired acceptor **3**[10] (Scheme 1) was subsequently obtained in 80% yield after selective deprotection of the MIP group under mild acidic conditions, by dissolving the crude mixture in 60% aqueous MeOH–CH_2Cl_2–AcOH (10:1:0.1) and warming the solution to 60 °C.[11]

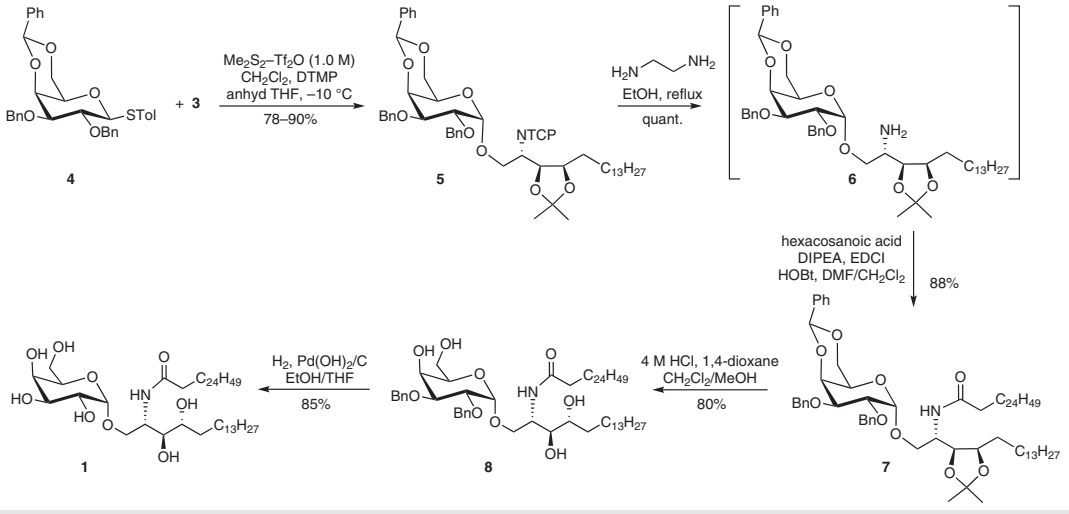


Scheme 1 Synthesis of the acceptor **3**; NTPC = tetrachlorophthalimido.

The glycosylation reaction was performed in THF with dimethyl(methylthio)sulfonium triflate (DMTST) as a promoter, according to a previously reported procedure.[7,12] The glycosylation product **5**[13] was obtained in 78% yield with complete α selectivity by using an excess of the donor. When an excess of the acceptor was used, the yield of **5** reached a satisfactory 90% yield (Scheme 2).

The tetrachlorophthalimide group was then removed by refluxing with ethane-1,2-diamine in ethanol, and the product was purified by filtration through a short pad of silica gel. The amine **6** was condensed with cerotic acid by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and hydroxybenzotriazole (HOBt) to give compound **7**[14] in 88% yield over two steps.

The final deprotection of compound **7** required the removal of the benzylidene and acetonide acetals, and the two benzyl groups. Two alternative, straightforward ways were considered: (1) simultaneous deprotection of the benzylidene and the benzyl groups by catalytic hydrogenolysis followed by acid hydrolysis of the acetonide or (2) acid removal of the acetal protecting groups and final hydrogenolysis. In following the first approach, catalytic hydrogenolysis with $Pd(OH)_2/C$ in $CHCl_3$/MeOH[15] and stirring overnight gave a mixture of products. This was quite surprising, as we have successfully used the same hydrogenolysis conditions on similar compounds in the past. On checking the pH of the reaction mixture (wet pH paper turned red), we found it to be strongly acidic, probably due to hydrogenolysis of chloroform to form HCl.[16] However, in the past, some authors have reported the same conditions for the final deprotection of α-GalCer analogues without observing the aforementioned byproducts. It is possible to hypothesize that the development of acidity is strongly dependent on the activity of the catalyst, the quality of the hydrogen (freshly prepared by treatment of $NaBH_4$ with acetic acid), and the reaction time. The acidic conditions promoted the removal of the acetonide and the migration of the acyl chain to the 4-OH, as already previously described in the literature.[17] It was also observed that the treatment of the mixture in warmed pyridine can revert the migration, giving α-GalCer as the main product, but in unsatisfactory yield. Therefore, we decided to follow the second approach.



Scheme 2 Synthesis of α-GalCer ■■*2 renumbered as **4**; OK?*■■; DTMP = 2,6-di-*tert*-butyl-4-methylpyridine

Compound **7** was dissolved in a mixture of methanol and dichloromethane and treated with 4.0 M hydrogen chloride in 1,4-dioxane.[18] After 90 minutes, triethylamine was added to quench the reaction. Purification by flash chromatography gave compound **8**[19] in 80% yield. Final hydrogenation was performed with Perlman's catalyst in 1:1 tetrahydrofuran–ethanol for three hours. Pure compound **1** was obtained by crystallization from 92:8 ethanol–water.[20] Spectroscopic data were consistent with the reported values for α-GalCer.[21]

In conclusion, a short and efficient synthesis of α-GalCer was achieved with good overall yield by exploiting a novel phytosphingosine acceptor. The synthetic approach allowed rapid access to the final glycolipid, and might be exploited to obtain other derivatives quickly and in high yields.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1293-9578.

References and Notes

(1) Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771.
(2) Kawano, T.; Cui, J.; Koezuka, Y.; Toura, I.; Kaneko, Y.; Motoki, K.; Ueno, H.; Nakagawa, R.; Sato, H.; Kondo, E.; Koseki, H.; Taniguchi, M. *Science* **1997**, *278*, 1626.
(3) Vartabedian, V. F.; Savage, P. B.; Teyton, L. *Immunol. Rev.* **2016**, *272*, 109.
(4) (a) Banchet-Cadeddu, A.; Hénon, E.; Dauchez, M.; Renault, J.-H.; Monneaux, F. A.; Haudrechy, A. *Org. Biomol. Chem.* **2011**, *9*, 3080. See also: (b) Plettenburg, O.; Bodmer-Narkevitch, V.; Wong, C.-H. *J. Org. Chem.* **2002**, *67*, 4559. (c) Schombs, M.; Park, F. E.; Du, W.; Kulkarni, S. S.; Gervay-Hague, J. *J. Org. Chem.* **2010**, *75*, 4891. (d) Boutureira, O.; Morales-Serna, J. A.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Eur. J. Org. Chem.* **2008**, 1851. (e) Figueroa-Pérez, S.; Schmidt, R. R. *Carbohydr. Res.* **2000**, *328*, 95. (f) Yen, Y.-F.; Kulkarni, S. S.; Chang, C.-W.; Luo, S.-Y. *Carbohydr. Res.* **2013**, *368*, 35; and references cited therein.
(5) (a) Yule, J. E.; Wong, T. C.; Gandhi, S. S.; Qiu, D.; Riopel, M. A.; Koganty, R. R. *Tetrahedron Lett.* **1995**, *36*, 6839. (b) Ishida, R.; Miyawaki, R.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1996**, *284*, 179. (c) Ishida, R.; Miyawaki, R.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1996**, *15*, 163.
(6) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734.
(7) Panza, L.; Compostella, F.; Imperio, D. *Carbohydr. Res.* **2019**, *472*, 50.
(8) Di Benedetto, R.; Zanetti, L.; Varese, M.; Rajabi, M.; Di Brisco, R.; Panza, L. *Org. Lett.* **2014**, *16*, 952.
(9) Barili, P. L.; Berti, G.; Catelani, G.; Colonna, F.; Marra, A. *Tetrahedron Lett.* **1986**, *27*, 2307.
(10) **(2*S*,3*S*,4*R*)-3,4-*O*-Isopropylidene-2-(tetrachlorophthalimido)octadecan-1-ol** (**3**)
Camphorsulfonic acid (0.3 g, 1.29 mmol) was added to a mixture of compound **2** (3.0 g, 5.14 mmol) in 2,2-dimethoxypropane (60 mL), and the mixture was stirred at r.t. for 30 min. The mixture was diluted with EtOAc(100 mL) and washed with aq $NaHCO_3$ (2 × 100 mL) and brine, then dried ($MgSO_4$) and concentrated under vacuum. The crude product was redissolved in 10:1 CH_2Cl_2–MeOH (66 mL) and 60% aq AcOH (0.6 mL) was added. The mixture was warmed at 60 °C for 90 min then diluted with EtOAc (100 mL), washed with aq $NaHCO_3$ (2 × 100 mL) and brine, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by dry column vacuum chromatography[22] (cyclohexane–EtOAc, 10:0 to 8:2) to give a yellow solid; yield: 2.57 g (80%); mp 86–88 °C, $[\alpha]_D^{20}$ –5.7 (*c* 1.0 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.96 (dd, *J* = 10.0, 5.4 Hz, 1 H), 4.48 (ddd, *J* = 10.0, 8.6, 5.1 Hz, 1 H), 4.18–3.75 (m, 3 H), 2.05 (br s, 1 H), 1.67–1.42 (m, 5 H), 1.37 (s, 3 H), 1.35–1.06 (m, 24 H), 0.89 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 140.5, 129.9, 127.1, 108.5, 77.6, 74.1, 61.4, 52.9, 31.9, 29.7, 29.6, 29.54, 29.5, 29.42, 29.36, 29.0, 28.2, 26.2, 25.8, 22.7, 14.1. HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{29}H_{40}Cl_4NO_5$: 624.16311; found: 624.16376.
(11) Thimon, C.; Panza, L.; Morin, C. *Synlett* **2003**, 1399.
(12) Tatai, J.; Fügedi, P. *Org. Lett.* **2007**, *9*, 4647.
(13) **(2*S*,3*S*,4*R*)-3,4-*O*-Isopropylidene-2-(tetrachlorophthalimido)octadecyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside** (**5**)
Triflic anhydride (1.7 mL, 10 mmol) was added to a solution of dimethyl disulfide (1 mL, 11.3 mmol) in anhyd CH_2Cl_2 (7.5 mL) at −10 °C, and the mixture was stirred for 30 min to give a 1.0 M solution of Me_2S_2–Tf_2O.
Compound **3** (1.19 g, 2.15 mmol), compound **4** (0.89 g, 1.44 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (0.59 g, 2.88 mmol) were dissolved in anhyd THF (13 mL) under argon, and 4 Å molecular sieves were added. The mixture was stirred at r.t. for 1 h, then cooled to −10 °C in a salt–ice bath before adding the 1.0 M Me_2S_2–Tf_2O (2.9 mL) and stirring for 30 min. The reaction was quenched with Et_3N (0.7 mL) and the mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (2 × 40 mL) and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography [silica gel, cyclohexane–EtOAc (9:1)] to give a white solid; yield: 1.19 g (78%; on changing the ratio of donor **2** to acceptor **3** to 1:1.5, the yield increased to 90%); mp 87–89 °C, $[\alpha]_D^{20}$ +15.9 (*c* 1.0 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.46 (m, 2 H), 7.45–7.26 (m, 8 H), 7.23–7.14 (m, 3 H), 6.98 (dd, *J* = 6.6, 3.0 Hz, 2 H), 5.47 (s, 1 H), 4.98 (dd, *J* = 10.3, 5.3 Hz, 1 H), 4.90 (d, *J* = 3.3 Hz, 1 H), 4.78–4.56 (m, 3 H), 4.36 (dd, *J* = 12.5 Hz, 2 H), 4.29–3.88 (m, 7 H), 3.83 (dd, *J* = 10.1, 3.3 Hz, 1 H), 3.69 (s, 1 H), 1.60 (m, 2 H), 1.51 (s, 3 H), 1.39 (s, 3 H), 1.35–0.95 (m, 24 H), 0.91 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.1, 138.8, 138.2, 137.8, 129.4, 128.8, 128.3, 128.08, 128.06, 127.7, 127.6, 127.3, 127.1, 126.3, 126.1, 108.6, 101.0, 99.1, 77.6, 76.2, 75.9, 74.9, 73.5, 72.6, 69.4, 66.4, 63.1, 51.4, 31.9, 29.7, 29.6, 29.52, 29.47, 29.4, 29.0, 28.4, 26.2, 25.9, 22.7, 14.1. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{56}H_{67}Cl_4NNaO_{10}$: 1078.33873; found: 1078.33862.

(14) **(2*S*,3*S*,4*R*)-2-(Hexacosanoylamino)-3,4-*O*-isopropylideneoctadecyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside** (**7**)
Compound **5** (1.0 g, 0.95 mmol) was dissolved in 1:1 EtOH–THF (10 mL) and ethane-1,2-diamine (0.32 mL) was added. The mixture was warmed at 60 °C for 3 h, and then the solvent was removed under vacuum. The crude product was purified on a short pad of silica, eluting with cyclohexane–EtOAc (7:3 then 5:5). Amine **6** was obtained in quantitative yield and directly used for the next step.
Amine **6** (0.74 g, 0.95 mmol) was dissolved in CH_2Cl_2 (22 mL), and the solution was added to a solution previously prepared by dissolving hexacosanoic acid (0.45 g, 1.1 mmol), DIPEA (0.37 g, 2.8 mmol), EDCI (0.36 g, 1.89 mmol), and HOBt (0.26 g, 1.89 mmol) in DMF (11 mL). The resulting solution was stirred overnight at 40 °C and then allowed to cool to r.t. The solution was diluted with Et_2O and washed with 1 N HCl, sat. aq $NaHCO_3$, H_2O, and brine, then dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by crystallization from EtOAc and collected by filtration to give a white solid; yield: 0.97 g (88%); mp 110–112 °C, $[\alpha]_D^{20}$ +73.8 (*c* 1.0 $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 7.6, 1.9 Hz, 2 H), 7.48–7.26 (m, 13 H), 5.81 (d, *J* = 9.0 Hz, 1 H), 5.52 (s, 1 H), 5.18 (d, *J* = 3.5 Hz, 1 H), 4.91 (d, *J* = 11.2 Hz, 1 H), 4.80 (s, 2 H), 4.69 (d, *J* = 11.2 Hz, 1 H), 4.30–4.26 (m, 2 H), 4.15–3.93 (m, 6 H), 3.88 (dd, *J* = 11.3, 3.1 Hz, 1 H), 3.77–3.62 (m, 2 H), 2.03 (dt, *J* = 12.0, 7.3 Hz, 2 H), 1.98–1.45 (m, 5 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.37–1.28 (m, 68 H), 0.91 (t, *J* = 6.8 Hz, 6 H). ■■*1 extra H?*■■ ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 138.6, 138.4, 137.8, 128.9, 128.43, 128.35, 128.14, 128.09, 127.9, 127.8, 127.7, 127.6, 126.3, 107.9, 101.1, 99.1, 77.7, 76.1, 75.9, 75.8, 74.3, 74.0, 71.5, 69.5, 67.8, 62.8, 48.8, 36.9, 31.9, 29.8, 29.72, 29.68, 29.62, 29.5, 29.4, 28.8, 28.0, 26.6, 25.9, 25.8, 22.7, 14.1. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{74}H_{120}NO_9$: 1166.89631; found: 1166.89575.

(15) For examples, see: (a) Tashiro, T.; Hongo, N.; Nakagawa, R.; Seino, K.; Watarai, H.; Ishii, Y.; Taniguchi, M.; Mori, K. *Bioorg. Med. Chem.* **2008**, *16*, 8896. (b) Park, J.-J.; Lee, J.-H.; Ghosh, S. C.; Bricard, G.; Venkataswamy, M. M.; Porcelli, S. A.; Chung, S.-K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3906. (c) Cheng, J. M. H.; Chee, S. H.; Knight, D. A.; Acha-Orbea, H.; Hermans, I. F.; Timmer, M. S. M.; Stocker, B. L. *Carbohydr. Res.* **2011**, *346*, 914.

(16) Xu, L.; Yao, X.; Khan, A.; Mavrikakis, M. *ChemCatChem* **2016**, *8*, 1739.

(17) Anderson, R. J.; Compton, B. J.; Tang, C.; Authier-Hall, A.; Hayman, C. M.; Swinerd, G. W.; Kowalczyk, R.; Harris, P.; Brimble, M. A.; Larsen, D. S.; Gasser, O.; Weinkove, R.; Hermans, I. F.; Painter, G. F. *Chem. Sci.* **2015**, *6*, 5120.

(18) Michieletti, M.; Bracci, A.; Compostella, F.; De Libero, G.; Mori, L.; Fallarini, S.; Lombardi, G.; Panza, L. *J. Org. Chem.* **2008**, *73*, 9192.

(19) **(2*S*,3*S*,4*R*)-2-Hexacosanoylamino-3,4-dihydroxyoctadecyl 2,3-Di-*O*-benzyl-α-D-galactopyranoside** (**8**)
To a solution of **7** (0.95 g, 0.81 mmol) in CH_2Cl_2 (228 mL) and MeOH (45 mL) was added 4 M HCl in 1,4-dioxane (4.5 mL) at 0 °C, and the mixture was stirred at r.t. for 90 min. Et_3N (5 mL) was slowly added and then the mixture was washed with H_2O (2 × 100 mL) and brine, dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, PE–*i*-PrOH (9:1)] to give a white solid; yield: 0.68 g (80%); mp 76–78 °C, $[\alpha]_D^{20}$ +49.9 (*c* 1.0 $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 10 H), 6.40 (d, *J* = 8.3 Hz, 1 H), 4.93 (d, *J* = 3.6 Hz, 1 H), 4.87 (d, *J* = 11.7 Hz, 1 H), 4.78 (d, *J* = 11.5 Hz, 1 H), 4.74 (s, 1 H), 4.70 (d, *J* = 11.7 Hz, 1 H), 4.28 (dd, *J* = 8.1, 3.5 Hz, 1 H), 4.12 (d, *J* = 2.6 Hz, 1 H), 3.98–3.72 (m, 7 H), 3.51 (t, *J* = 5.2 Hz, 2 H), 2.62–2.10 (br m, 4 H), 2.19 (t, *J* = 7.9 Hz, 2 H), 1.63 (d, *J* = 7.4 Hz, 3 H), 1.54–1.09 (m, 72 H), 0.90 (t, *J* = 6.8 Hz, 6 H). ■■*3 extra H?*■■ ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 137.7, 137.6, 128.62, 128.57, 128.13, 128.11, 128.06, 127.8, 98.7, 77.9, 76.2, 75.2, 74.2, 73.2, 72.4, 69.9, 68.4, 62.8, 49.6, 36.81, 31.9, 29.7, 29.6, 29.44, 29.38, 29.34, 25.8, 22.7, 14.1. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{64}H_{112}NO_9$: 1038.83371; found: 1038.83401.

(20) **(2*S*,3*S*,4*R*)-2-Hexacosanoylamino-3,4-dihydroxyoctadecyl-α-D-galactopyranoside (1)**
A mixture of compound **8** (430 mg, 0.41 mmol) and Pearlman's catalyst (86 mg) in EtOH (15 mL) and THF (15 mL) was stirred under H_2 for 3 h. The catalyst was removed by filtration through a Celite pad, and the product was recovered by washing with warm EtOH. Evaporation of the solvent and crystallization from EtOH–H_2O (92:8) gave a white solid; yield: 301 mg (85%). Spectroscopic data were consistent with the reported values for α-GalCer (see ref. 21).

(21) Luo, S.-Y.; Kulkarni, S. S.; Chou, C.-H.; Liao, W.-M.; Hung, S.-C. *J. Org. Chem.* **2006**, *71*, 1226.

(22) Pedersen, D. S.; Rosenbohm, C. *Synthesis* **2001**, 2431.

