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Synthesis of Sphingadienine-type Glucocerebrosides[1]

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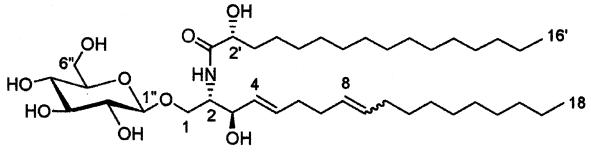
Abstract—Sphinga-4,8-dienine derivatives were synthesized from a vinyl-epoxide **5** via three routes. First, reaction of **5** with 2-dodecenyl cyanocuprate afforded a 1:1 mixture of (4*E*,8*E*)- and (4*E*,8*Z*)-sphingadienine derivatives in high yield. Second, the (4*E*,8*E*)-isomer was selectively synthesized via allylic bromide-allylic sulfone coupling followed by desulfonylation. Third, the (4*E*,8*Z*)-isomer was selectively synthesized via S_N2'-type addition of di(cyanomethyl)copper-lithium followed by Wittig olefination. These synthetic intermediates were converted to sphingadienine-type glucocerebrosides **1a** and **1b** which have calcium ionophoretic activity.

Introduction

Sphingolipids, e.g. ceramides, sphingomyelin, cerebrosides and gangliosides, are important constituents of cellular membranes. The principal component of sphingolipids is the long-chain base, sphingosine.[2] In nature, the most widely occurring of sphingoid bases is D-*erythro*-sphingosine [4(*E*)-sphingenine], which has one (*E*)-double bond between C-4 and C-5. Sphingadienines, which have two double bonds in the hydrocarbon chain, are minor sphingoid bases obtained from fungi,[3] plants,[4] marine organisms[5] and mammalian tissues.[6] In recent years, it has been reported that simple mono-glucocerebrosides containing sphinga-4,8-dienine in the hydrophobic moiety exhibit significant activities. In 1983, Yamazaki et al. reported that glucocerebrosides from *Tetragonia tetragonides* showed anti-ulcerogenic activity.[7] In 1990, Kitagawa et al. reported[8] that soya-cerebrosides from soybean, the seeds of *Glycine max* Merrill, showed ionophoretic activity for Ca^{2+} ion. Also Ina et al. reported[9] that cerebrosides from the bark of *Prunus jamasakura* showed repellent activity against the Blue Mussel, *Mytilus edulis*. The major constituents of all these cerebrosides were determined to be (2*S*,3*R*,4*E*,8*E*, 2′*R*)-1-*O*-β-D-glucopyranosyl-2-(2′-hydroxypalmitoyl)-amino-4,8-octadecadien-1,3-diol (**1a**) and its (8*Z*)-isomer (**1b**). For the ionophoretic property, the (8*Z*)-isomer showed higher Ca^{2+} ion binding activity than the (8*E*)-isomer, whereas usual (4*E*)-sphingenine-type cerebroside showed little activity.[8] Several syntheses[10] of **1a** and/or **1b** have been reported. The scarcity in nature as well as the interesting properties, especially the ionophoretic activity, of **1** prompted us to investigate their synthesis.



Glucocerebroside **1a** (2*S*, 3*R*, 4*E*, 8*E*, 2′*R*)
Glucocerebroside **1b** (2*S*, 3*R*, 4*E*, 8*Z*, 2′*R*)

In this paper, we report a regio- and stereocontrolled synthesis of glucocerebrosides **1a** and **1b**, employing a vinyl-epoxide derived from D-glucosamine as a key intermediate of the sphingadienine moiety.

Results and Discussion

Stereocontrolled syntheses of sphingadienines

Cross-coupling reaction with allylic cuprates. Our retrosynthetic analysis of **1** is shown in Fig. 1. Glucocerebrosides **1** consist of three segments, that is, sphinga-4,8-dienine, D-glucose, and (2*R*)-hydroxypalmitic acid. The glucose residue and the optically active fatty acid can be introduced by using a suitably protected glycosyl donor **3** and a recently reported acyl donor **4**, respectively. Thus the analysis is focused on the synthetic strategy for the sphingadienine moiety. We already reported[11] a stereocontrolled synthesis of D-*erythro*-C_{18}-sphingosine,[12] utilizing S_N2'-type reaction[13] of dodecylmagnesium bromide with a vinyl-epoxide **5**, which was prepared from *N*-benzoyl-D-glucosamine **6** in six steps,[14] in the presence of a catalytic amount of copper(I) cyanide (CuCN). According to this approach, sphinga-4,8-dienine derivatives would be obtained by employing 2-dodecenylmagnesium halide instead of *n*-$C_{12}H_{25}MgBr$.

Keywords: glycolipids; dienes; vinyl-epoxide; coupling reactions.
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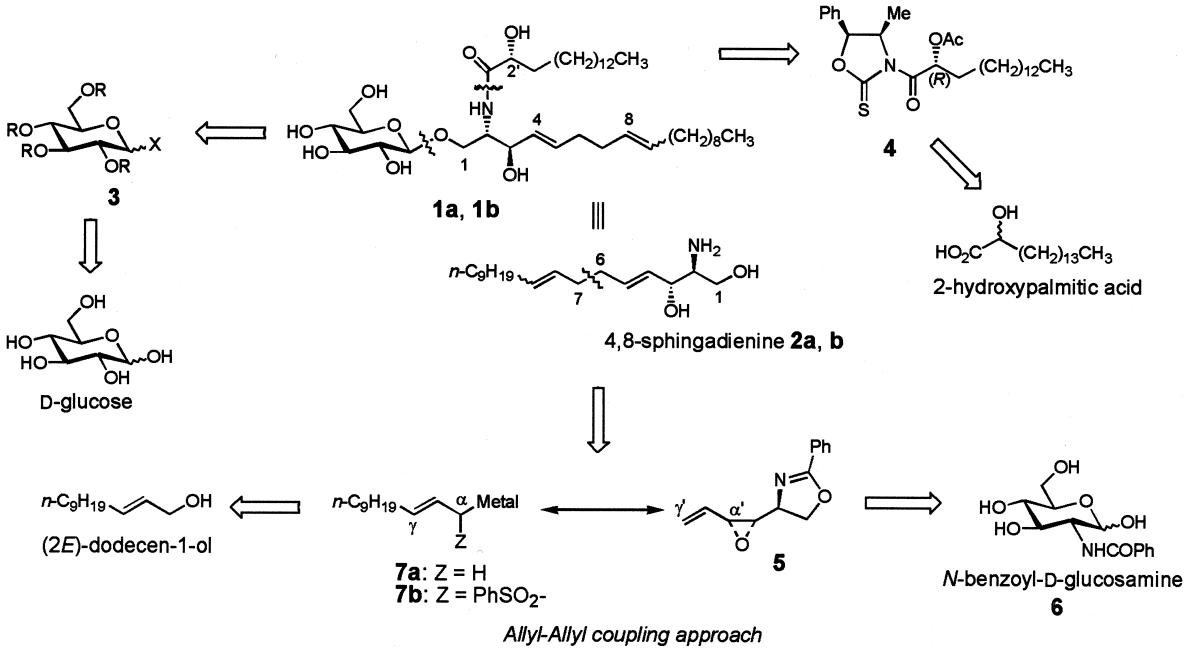
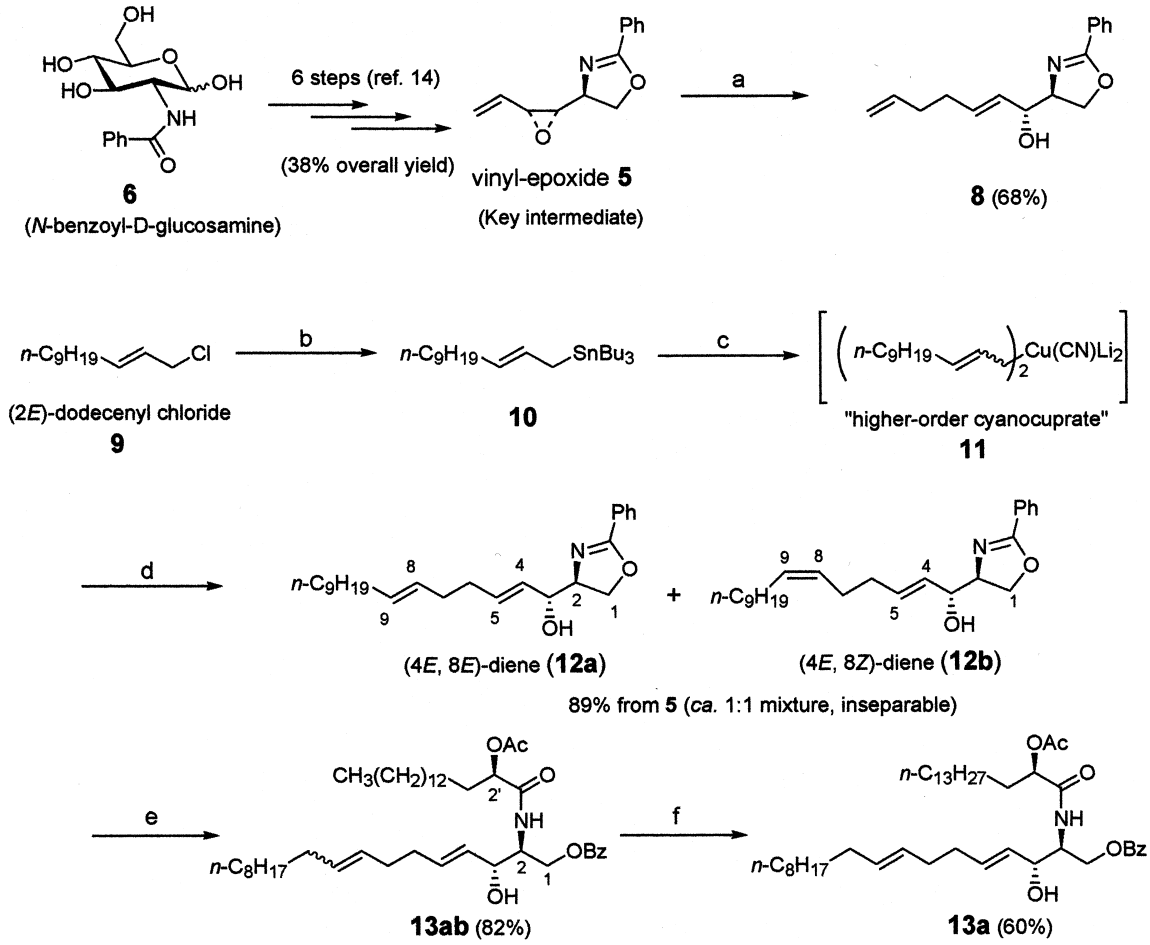


Figure 1. Retrosynthetic analysis of glucocerebrosides **1a**,**b**.



Scheme 1. Reagents and conditions: (a) CH_2=$CHCH_2MgBr$ (2 equiv.), CuCN (10 mol%), THF, −70 to −20°C; (b) *n*-Bu_3SnLi (1.0 equiv.), THF, −70 to −20°C; (c) MeLi (1.0 equiv.), THF, −70 to −10°C, then CuCN (0.5 equiv), LiCl (1.0 equiv.), THF −70°C; (d) vinyl-epoxide **5** (0.25 equiv. to **10**), THF, −70 to −20°C, 2 h; (e) 2*M*-HCl, THF room temperature 15 h; then **4** (1.5 equiv.), Et_3N, DMF, 60°C, 6 h; (f) 1-methyltetrazol-5-yl disulfide (0.5 equiv.), AIBN, toluene, 100°C, 4 h, then recrystallization from hexane.

Thus installation of the 1,5-diene part in the sphingadienine would be achieved by using 2-dodecenyl metal derivatives **7a** as allylic nucleophiles[15] and the vinyl-epoxide **5** as an allylic electrophile. However, regiocontrol of the reaction is a serious problem associated with this allyl–allyl cross-coupling approach to 1,5-dienes. Control of the olefin geometry is also a problem when γ-substituted allylic metals are used. For example, 2-butenylmagnesium bromide is known to isomerize rapidly between the (*Z*)- and (*E*)-isomers even at −80°C.[16] However, this isomerization is favorable for our case since both (*E*)- and (*Z*)-isomers can be formed from an (*E*)-allylic halide.

There have been several reports on the allyl–allyl cross-coupling reactions. Yamamoto et al. reported[17a] that γ-substituted allylic Grignard reagents reacted regioselectively with allylic 1-diphenylphosphates to give γ-α′ coupling products bearing one terminal olefin. In contrast, they also reported[17b] that, in the presence of CuCN, similar coupling reactions afforded mixtures of regio- and geometrical-isomers, in which α-γ′ coupling products predominated. Normant et al. reported[18] that the reaction of γ-substituted allylic Grignard reagents with vinyl-epoxides in the presence of CuBr occurred regioselectively to afford 2,6-dien-1-ols bearing two internal olefins in high yields. In general, γ-substituted allylic cuprates tend to react at the less-substituted terminus to give the coupling products with predominantly internal olefin.[19,20]

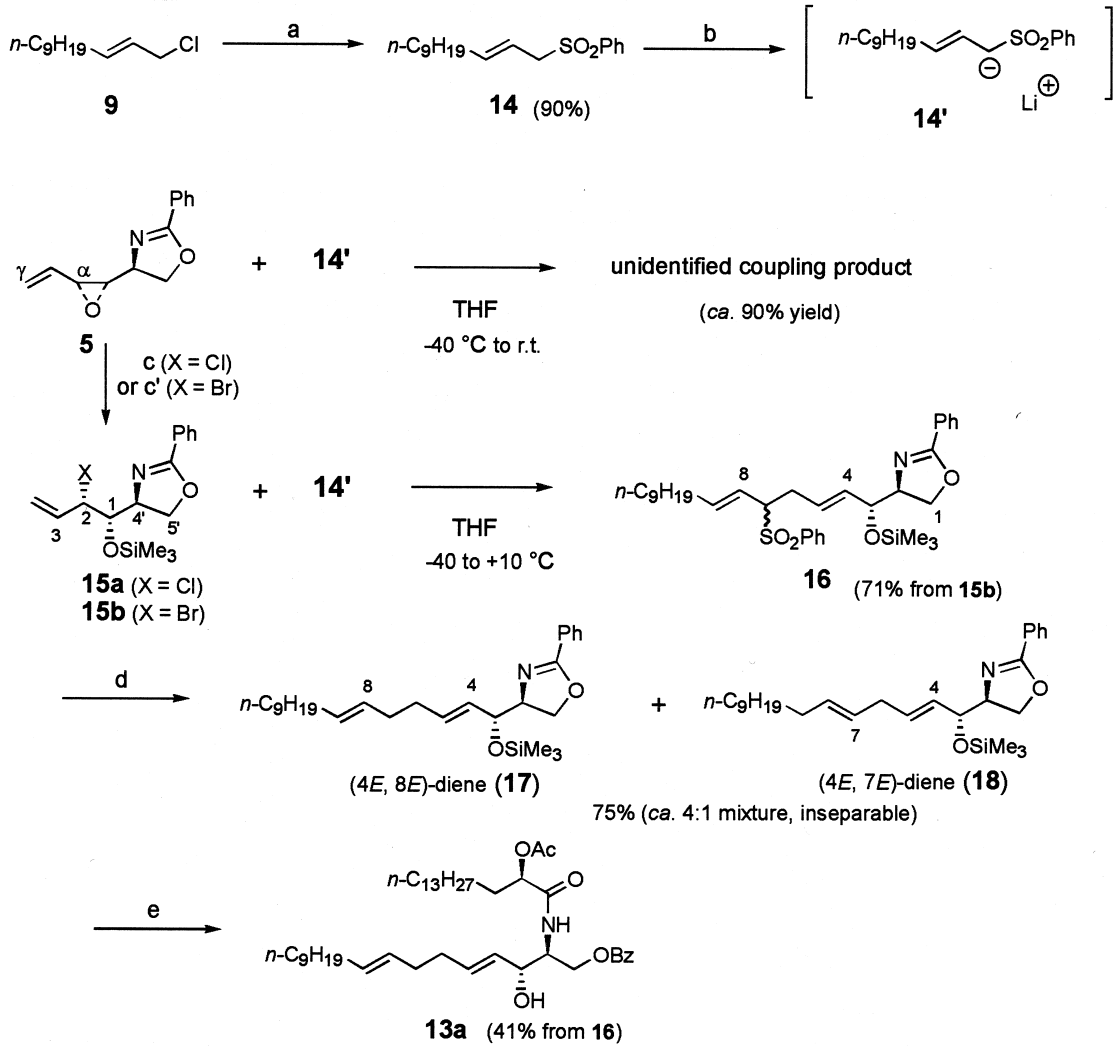
Encouraged by these precedents, we investigated the reaction of the vinyl-epoxide **5** with allylic cuprates. (Scheme 1) At first, as a model experiment, allylmagnesium bromide was employed in the presence of CuCN (10 mol%). This reaction provided the desired S_N2'-type reaction product **8** having an (*E*)-olefin in 68% yield. Next we tried to prepare 2-dodecenyl metal derivatives (**7a** in Fig. 1) from 2(*E*)-dodecenyl chloride **9**, which was readily prepared from commercially available 2(*E*)-dodecen-1-ol[21] with LiCl, methanesulfonyl chloride, and 2,6-lutidine.[22] In our hands, however, attempts to prepare 2-dodecenylmagnesium chloride using activated Mg,[23] to avoid homo-coupling, were unsuccessful. We then turned our attention to allylic higher-order cyanocuprates developed by Lipshutz.[24] The required 2-dodecenyllithium could be formed via tin–lithium exchange reaction. Thus 2-dodecenyl chloride **9** was treated with tributyltinlithium to give 1-tributylstannyl-2-dodecene **10**. Treatment of **10** with methyllithium (1 equiv.) in THF gave 2-dodecenyllithium, which was treated in situ with CuCN (0.5 equiv.) and LiCl to generate the higher-order cyanocuprate **11**. Reaction of **11** with the vinyl-epoxide (0.25 equiv. to **10**) was rapid at −70°C, affording the cross-coupled product in high yield based on **5**. Its ^{1}H NMR spectrum showed the presence of four internal olefinic protons at δ 5.3–5.9 ppm and the absence of terminal olefin, indicating that the reaction took place at the desired position. The large coupling constant (15.5 Hz) between the protons at lower field indicated the (*E*)-geometry of the olefin adjacent to hydroxy group. However, the geometry of the C_8–C_9 olefin (sphingosine numbering) could not be determined by ^{1}H NMR. Its ^{13}C NMR spectrum showed 12 sp^2 carbon signals at δ 127–133 ppm and relatively small peaks at δ 26.8, 27.2, 32.1 and 32.6 ppm. The small peaks around δ 27 ppm and those around δ 32 ppm are assigned to methylene carbons adjacent to (*Z*)-olefinic carbons and those to (*E*)-olefinic carbons, respectively.[7,8,25] Therefore, the product consists of (4*E*,8*E*)-diene **12a** and (4*E*,8*Z*)-diene **12b** in ca. 1:1 ratio. This result was consistent with that reported by Normant et al.[18] mentioned above. Unfortunately, separation of the isomers was found to be difficult not only at this stage but also at later stages of the synthesis.[26]

For the synthesis of (4*E*,8*E*)-diene-type ceramide from the mixture, olefin-isomerization was then examined. Acid catalyzed ring opening of the oxazoline in **12** gave 1-*O*-benzoyl-sphingadienine hydrochloride, which upon treatment with (2*R*)-acetoxypalmitoyl imide **4** (Fig. 1) as previously reported[1] afforded the amide **13**. Treatment of **13** with 1-methyltetrazol-5-yl disulfide in the presence of 2,2′-azobis(isobutyronitrile) (AIBN)[27] at 100°C gave an equilibrium mixture of (4*E*,8*E*)- and (4*E*,8*Z*)-dienes in a ratio of 5:1 as determined by NMR. Recrystallization of the major product from hexane afforded the pure (4*E*,8*E*)-diene **13a** in ca. 60% yield from **13**. The physical data of **13a** were identical with those reported.[10b]

This cross-coupling approach appeared to be attractive since both (4*E*,8*E*)- and (4*E*,8*Z*)-sphingadienine derivatives were obtained from the common precursor in one step for carbon chain elongation. However, the difficulty in separating the isomers and the toxicity of organotin compounds and CuCN led us to search for an alternative route.

Selective synthesis of (4*E*,8*E*)-sphingadienine. For the synthesis of the (4*E*,8*E*)-diene, our attention was focused on allylic sulfones as stabilized allylic nucleophiles (**7b** in Fig. 1). Grieco et al.[28] reported the preparation of geometrically pure 1,5-dienes via coupling of allylic aromatic sulfones with allylic halides followed by reductive desulfonylation with lithium in ethylamine. Later a regioselective desulfonylation under milder reaction conditions was developed by using lithium triethylborohydride with a palladium catalyst.[29a] The latter method has been applied to the syntheses of natural products.[30] Thus we tried the coupling reaction of **5** with 2-dodecenyl phenyl sulfone **14**, which was readily prepared from **9** and sodium benzenesulfinate. (Scheme 2) Treatment of **14** with *n*-butyllithium gave the yellow-colored anion **14′**, which was treated with **5** to give a product. ^{1}H NMR indicated that the major product resulted from equimolar coupling, but it was neither the expected S_N2' product nor S_N2 reaction product. In the presence of CuCN, the coupling reaction did not take place.

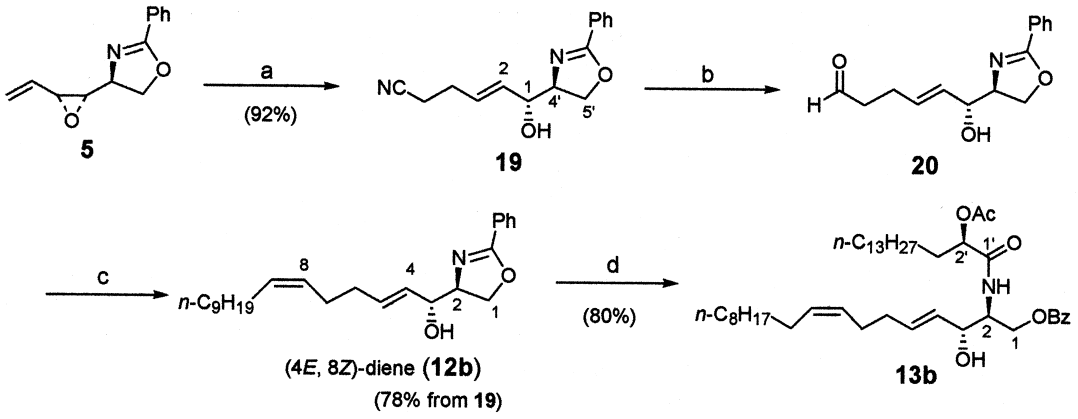
A recent paper reported[31] that lithiated methyl (phenylsulfonyl)acetate reacted predominantly with a primary bromide in the presence of vinyl-epoxide moiety. This and our results led us to examine the conversion of the vinyl-epoxide moiety in **5** to allylic halide, which would be more reactive toward sulfone anion, by opening the epoxy-ring with a hydrogen halide (HX) equivalent. Although we could not predict the regioselectivity (S_N2 or S_N2') of the epoxy-ring opening with HX equivalent, we anticipated that, regardless of the halogen position, the bulky sulfone reagent **14′** would attack at the less-substituted site to give the coupling product with internal diene. We employed



Scheme 2. Reagents and conditions: (a) $PhSO_2Na$ (2 equiv.), DMF, 50°C, 5 h; (b) BuLi (1.0 equiv.), THF, −40°C; (c) Me_3SiCl (4 equiv.), CH_3CN, 0°C to room temperature, then Et_3N (4 equiv.); (c′) Me_3SiCl (3.6 equiv.), LiBr (4 equiv.), CH_3CN, 0–10°C, 3 h, then Et_3N (4 equiv.), 5–10°C; (d) $LiBEt_3H$ (3 equiv.), $Pd(OAc)_2$ (10 mol%), dppp (10 mol%), THF, 0–5°C, 2 h; (e) 2*M*-HCl, THF, room temperature, 15 h, then **4** (1.5 equiv.), Et_3N, DMF, 60°C, 5 h, then recrystallization from hexane.

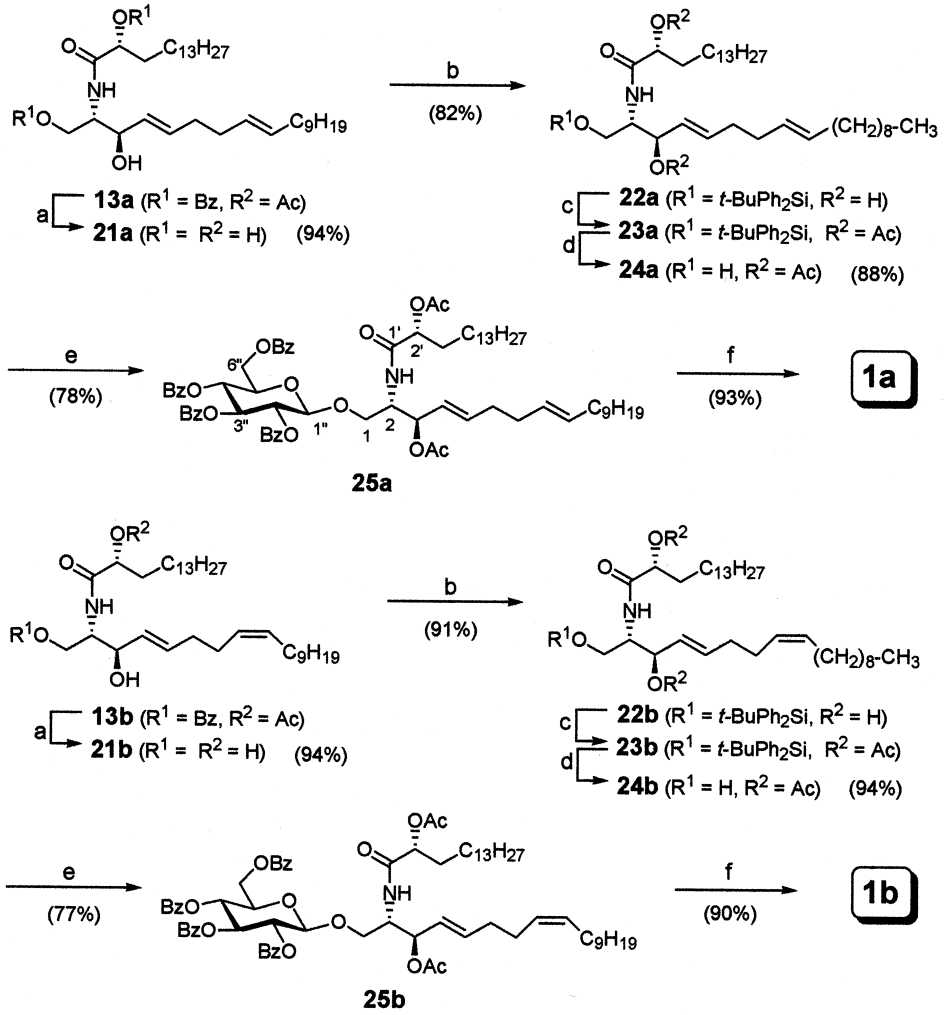
trimethylsilyl halide (TMSX) as a HX equivalent since the reaction would give *O*-TMS protected vicinal halohydrin,[32] which should *not* revert to the epoxide under basic reaction conditions. Treatment of **5** with TMSCl and LiCl in acetonitrile gave allylic chloride **15a** in 70% yield. Its ^1H NMR spectrum showed the presence of terminal olefin, indicating that the chloride was introduced at the α position of the epoxide regioselectively. Similarly, **5** was treated with premixed TMSCl and LiBr to give the allylic bromide **15b**, which was not contaminated with the chloride as determined by NMR. Treatment of the chloride **15a** with the lithiated 2-dodecenyl phenyl sulfone **14′** at 50°C gave the desired S_N2' reaction product with (*E*,*E*)-diene **16**, but the yield was only 35%. In contrast, reaction of the bromide **15b** with **14′** proceeded smoothly at 0–10°C to afford **16** in 71% yield as a 1:1 diastereomeric mixture. Desulfonylation of **16** was achieved with $LiBEt_3H$ in the presence of palladium acetate[29b] and 1,3-bis(diphenylphosphino)-propane (dppp) to give the product in 75% yield. Its ^1H and ^{13}C NMR spectra indicated that the product was an inseparable 4:1 mixture of the desired (4*E*,8*E*)-diene **17** and regioisomeric (4*E*,7*E*)-diene **18**[33] resulting from S_N2' reduction. Alternatively, in view of the coordination effect of the hydroxy group, we examined a desulfonylation reaction after desilylation of **16** with Bu_4NF. However, the ratio of the regioisomers was similar. Separation of the isomers was achieved in a similar manner as mentioned above. Thus ring opening of the oxazoline followed by *N*-acylation with **4** gave the 1-*O*-benzoyl-ceramide, from which the pure (4*E*,8*E*)-ceramide **13a** was obtained by recrystallization in 41% overall yield from **16**.

Selective synthesis of (4*E*,8*Z*)-sphingadienine. Next we investigated a selective synthesis of the (8*Z*)-olefin. We adopted a two-stage chain-elongation strategy, i.e. addition of an acetaldehyde equivalent to **5** and subsequent Wittig olefination. (Scheme 3) Thus **5** was treated with di(cyanomethyl)copper-lithium[34] prepared from lithiated acetonitrile and CuI to give the S_N2'-type product **19** having (*E*)-olefin in high yield. The nitrile was reduced by diisobutylaluminum hydride (DIBAL-H) at −70 to −50°C to give the aldehyde **20**. At higher temperatures, the C=N bond of



Scheme 3. Reagents and conditions: (a) $LiCH_2CN$ (4 equiv.), CuI (2 equiv.), THF, −70 to −10°C, 5 h; (b) *i*-Bu_2AlH (2.4 equiv.), toluene, −70 to −50°C; (c) $Ph_3P{=}CH{-}(CH_2)_8CH_3$ (2.8 equiv.), THF −70–0°C; (d) 2*M*-HCl, THF, room temperature, 15 h then **4** (1.5 equiv.), Et_3N. DMF., 60°C, 6 h.

the oxazoline should be reduced. Without purification, the aldehyde **20** was subjected to Wittig olefination with decylidene triphenylphosphorane to afford the (4*E*,8*Z*)-sphingadienine derivative **12b** in 78% yield. When potassium *t*-butoxide was used as a base in the olefination, no (8*E*)-isomer was detected by ^{13}C NMR. Ring opening of the oxazoline in **12** followed by *N*-acylation with the imide **4** gave the 1-*O*-benzoyl-ceramide **13b** in 80% yield. The physical data of **13b** were identical with those reported.[10b]



Scheme 4. Reagents and conditions: (a) NaOMe, MeOH–CH_2Cl_2, 0–5°C, 1 h; (b) *t*-$BuPh_2SiCl$ (1.5 equiv.), imidazole (5 equiv.), DMF, CH_2Cl_2, 0–5°C, 0.5 h; (c) Ao_2O (4 equiv.), pyridine, DMAP (cat.), THF, 0–10°C; (d) Bu_4NF (2 equiv.), AcOH, THF, room temperature, 3 h; (e) 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (1.8 equiv.), AgOTf (1.8 equiv.), M.S. 4A, CH_2Cl_2, −20–0°C, 2 h; (f) NaOMe (1 equiv.), MeOH–THF, 0–10°C, 2 h.

Since the (8*Z*)-isomer **12b** has been efficiently synthesized, the (8*E*)-isomer can be obtained by the olefin inversion reaction as shown in Scheme 1. However, the reaction usually gives an equilibrium mixture of (*E*)- and (*Z*)-olefins and isolation of the pure (*E*)-isomer is sometimes tedious. The (8*E*)-olefin would be selectively obtained from **20** by Julia olefination.[35] However, Julia olefin synthesis usually requires 3 steps from aldehydes ((1) addition of sulfone reagent; (2) activation of the resultant alcohol; (3) reductive elimination to olefin). In addition, our substrate has an allylic alcohol and an oxazoline, both of which may be incompatible with the reaction conditions. Thus we did not examine this approach to the (8*E*)-isomer.

Improved synthesis of glucocerebrosides

Since Mori et al. already reported[10b] the synthesis of the glucocerebrosides from the protected sphingadienine derivatives **13a,b**, a formal synthesis of **1a**,**b** has been finished. However, we found the first step, protection of the secondary hydroxy group of **13** with *t*-butyldiphenylsilyl (TBDPS) chloride, to be somewhat capricious and poorly reproducible. An alternative route was explored via usual protecting group manipulations.[36] (Scheme 4) Deacylation of **13a** with NaOMe in methanol–CH_2Cl_2 gave the unprotected ceramide **21a**. Selective protection of the primary hydroxy group with TBDPS-Cl gave the 1-*O*-TBDPS ether **22a** in 82% yield. Acetylation of the secondary hydroxy groups followed by desilylation afforded the protected ceramide **24a**. The ceramide **24a** was treated with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide [Fig. 1, **3** (R=benzoyl, X=Br)] in the presence of silver trifluoromethanesulfonate (AgOTf) at −20–0°C to afford the desired β-glucoside **25a** in 78% yield. This glycosylation method[37] seems to be more efficient than those used in the previous syntheses[10a,b,e,f] since the glycosyl donor (perbenzoylated glucosyl bromide) is readily available[38] and rather stable, and the reaction products were free from glycosyl orthoester derivative[39] and 1-*O*-benzoylated **24a**.[40] Finally **25a** was deacylated with NaOMe in methanol–THF to afford the glycolipid **1a**. In a similar manner, the (4*E*,8*Z*)-glucocerebroside **1b** was synthesized from **13b**. The physical data of **1a** and **1b** were in good agreement with those reported.[10] Thus this route provided **1** in 6 steps from **13** with better overall yields (49–56%) than the previous one (14–37% yields).[10b]

Conclusion

We have achieved stereoselective syntheses of sphinga-4,8-dienines by using the vinyl-epoxide **5** as a key chiral building block. The protected (4*E*,8*E*)-ceramide **13a** was synthesized from **5** via 2-dodecenyl cuprate coupling followed by olefin-isomerization in 43% overall yield, or via dodecenyl sulfone coupling in 26% overall yield. The (4*E*,8*Z*)-ceramide **13b** was also synthesized via two-stage chain-elongation including Wittig olefination in 57% overall yield from **5**. Despite some technical difficulties, the first cross-coupling approach with dodecenyl cuprate seems to be still attractive and promising from a viewpoint of synthetic chemistry. These ceramides **13a** and **13b** were efficiently converted to sphingadienine-type glucocerebrosides **1a** and **1b**, respectively.

Experimental

Air- and moisture-sensitive reactions were carried out under argon or nitrogen atmosphere. Melting points were determined with a Yanaco melting point apparatus MP-500D and are uncorrected. Optical rotations were measured with a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz on a JEOL JNM-GSX-270 spectrometer for solutions in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) was used as internal standard (δ_H=0) for ^{1}H NMR and $CDCl_3$ served as internal standard (δ_C=77.0) for ^{13}C NMR. When pyridine-d_5 was used, pyridine-d_5 served as internal standard (δ_H=7.19, δ_C=123.5). Infrared (IR) spectra were measured with a JASCO FT-IR 620 spectrophotometer. Elemental analyses were performed by the analytical center in this Institute (NIMC). High-resolution mass spectra (HRMS) and FAB mass spectra (FAB-MS) were obtained on a Hitachi M-80B and a JEOL DX-303 mass spectrometers, respectively. Thin layer chromatography (TLC) was performed on Merck precoated silica gel 60F_{254} plates. Column chromatography was performed on silica gel (Wako gel C-200 or C-300). Organic solutions after extractive work-up were dried over Na_2SO_4, filtered through a cotton plug, and concentrated under reduced pressure.

(1*R*,2*E*,4′*S*)-1-(2′-Phenyl-4′,5′-dihydrooxazol-4′-yl)-hepta-2,6-dien-1-ol (8). To a stirred suspension of the vinyl-epoxide **5** (108 mg, 0.50 mmol) and CuCN (5 mg, 50 μmol) in THF (5 ml) at −70°C was added dropwise a 1.0 M solution of allylmagnesium bromide in Et_2O (1.0 ml, 1.0 mmol), and the mixture was allowed to warm to −20°C. The reaction was quenched by addition of saturated aq. NH_4Cl (2 ml), and the mixture was diluted with AcOEt (15 ml) and H_2O (5 ml). The layers were separated and the aqueous phase was extracted with AcOEt (2×15 ml). The combined organic layers were successively washed with H_2O and brine (10 ml each), dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane–AcOEt (5:2) to afford the diene **8** (87 mg, 68% yield) as a colorless solid: mp 80–82°C; R_f 0.30 (hexane–AcOEt, 2:1); $[\alpha]_D^{25}$ −5.1° (*c* 0.55, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 2.17 (4H, t-like, *J*=3.0 Hz, 4-H_2, 5-H_2), 4.10 (1H, br, OH), 4.37 (3H, m, 4′-H and 5′-H_2), 4.63 (1H, br d, *J*=5.6 Hz, 1-H), 4.98 (1H, dt, *J*=1.0, 10.2 Hz, 7-H_{cis}), 5.03 (1H, dt, *J*=1.0, 17.5 Hz, 7-H_{trans}), 5.47 (1H, dd, *J*=5.5, 15.5 Hz, 2-H), 5.74–5.92 (2H, m, 3-H, 6-H), 7.29 (2H, m, Ph), 7.41 (1H, m, Ph), 7.75 (2H, m, Ph); δ_C (67.8 MHz, $CDCl_3$) 31.7, 33.2, 67.4, 71.1, 71.4, 114.8, 127.0, 128.1 (2C), 128.2 (2C), 128.6, 131.3, 132.1, 138.0, 165.5; ν_{max} (KBr) 3162 (broad), 2914, 2841, 1649, 1450, 1365, 1273, 1099, 971, 910, 693 cm^{-1}; Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.55; H, 7.50; N, 5.39.

1-Tributylstannyl-2-dodecene (10). To a stirred solution of diisopropylamine (0.30 ml, 2.1 mmol) in THF (10 ml) under argon at −30°C was added a 1.5 M solution of

n-butyllithium in hexane (1.4 ml, 2.1 mmol), and the solution was stirred for 20 min. To this solution was added dropwise tributyltin hydride (0.6 ml, 2.0 mmol), and the mixture was stirred for 20 min at −30°C before being cooled to −70°C. To this solution was added a solution of 2(*E*)-dodecenyl chloride (405 mg, 2.0 mmol) in THF (4 ml), and the mixture was allowed to warm to −20°C. The solution was diluted with hexane (20 ml) and aq. NH_4Cl (20 ml), and the layers were separated. The aqueous phase was extracted with hexane (2×20 ml) and the combined organic layers were successively washed with H_2O and brine, and then dried. Removal of the solvent gave a colorless oil, which was passed through a short pad of silica gel eluting with hexane to give the allylic stannane **10** (940 mg, 103%) as a colorless oil: δ_H 0.77–0.95 (6H, m), 0.88 (3H, t, *J*=6.8 Hz, 12-CH_3), 0.89 (9H, t, *J*=7.2 Hz), 1.26 (14H, s), 1.23–1.37 (6H, m), 1.41–1.54 (6H, m), 1.68 (2H, d, *J*=8.2 Hz, 1-H_2), 1.94 (2H, q, *J*=6.9 Hz, 4-H_2), 5.21 (1H, dt, *J*=6.9, 14.8 Hz, 4-H), 5.51 (1H, dt, *J*=8.2, 15.2 Hz, 2-H); ν_{max} (neat) 2956, 2922, 2853, 1463, 1376, 1071, 959, 873, 717, 686 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{50}Sn$ (M^+): 456.2935. Found: 456.2913. Although this oil contains small amounts of **9** and Bu_3SnH, it was used in the next step without further purification.

1-*O*,2-*N*-Protected (4*E*,8*E*)-sphingadienine (12a) and (4*E*,8*Z*)-sphingadienine (12b). To a stirred solution of the stannane **10** (400 mg, 0.86 mmol) in THF (4 ml) was added dropwise a 1.0 M solution of methyllithium in Et_2O (0.8 ml, 0.8 mmol) over 5 min at −70°C. The resulting pale yellow solution was allowed to warm to −10°C, and was then cooled to −70°C. To this solution was added a solution of CuCN (36 mg, 0.40 mmol) and LiCl (34 mg, 0.8 mmol) in THF (1 ml), and the resulting orange-brown solution was stirred for 20 min at −70°C. To this solution was added a solution of vinyl-epoxide **5** (43 mg, 0.20 mmol) in THF (1 ml), and the mixture was allowed to warm to −20°C. The mixture was treated with saturated aq. NH_4Cl (2 ml), followed by AcOEt (15 ml) and H_2O (5 ml). The layers were separated and the aqueous phase was extracted with AcOEt (2×15 ml). The organic layer was successively washed with H_2O and brine, dried, and concentrated. The residue was chromatographed on a column with hexane–AcOEt (4:1→5:2) as eluent to afford 1:1 mixture of the (4*E*,8*E*)- and (4*E*,8*Z*)-dienes **12ab** (68 mg, 89% yield) as a colorless solid: R_f 0.28 (hexane–AcOEt, 3:1); δ_H (sphingosine numbering) 0.88 (3H, t, *J*=6.6 Hz, 18-CH_3), 1.26 (14H, s-like, 11–17-CH_2), 2.00 (2H, m, 10-H_2) 2.12 (4H, m, 6-H_2, 7-H_2), 4.02 (1H, br s, OH), 4.37 (3H, m, 1-H_2 and 2-H), 4.63 (1H, br d, *J*=5.0 Hz, 3-H), 5.35–5.51 (3H, m, 4-H, 8-H, 9-H), 5.85 (1H, br d, *J*=15.5 Hz, 5-H), 7.29 (2H, m, Ph), 7.41 (1H, m, Ph), 7.76 (2H, m, Ph); δ_C 14.1, 22.6, 26.8 (**b**), 27.2 (**b**), 29.1, 29.3, 29.47, 29.54, 29.6, 31.8, 32.1 (**a**), 32.5, 32.6 (**a**), 67.4, 71.2, 71.5, 127.0, 128.1 (2C), 128.2 (2C), 128.3, 128.4, 128.6, 129.1, 130.5, 131.0, 131.2, 132.4, 132.5, 165.5; ν_{max} (KBr) 3190 (broad), 2922, 2851, 1648, 1468, 1450, 1364, 1274, 1098, 969, 692 cm^{-1}; HRMS Calcd for $C_{25}H_{37}NO_2$ (M^+): 383.2824. Found: 383.2824.

(2*S*,3*R*,4*E*,8*EZ*,2′*R*)-2-(2′-Acetoxyhexadecanoyl)amino-1-*O*-benzoyl-4,8-octadecadiene-1,3-diol (13ab). To a stirred solution of **12ab** (77 mg, 0. 20 mmol) in THF (2.7 ml) was added a 2.0 M aq. HCl (0.3 ml), and the mixture was stirred for 16 h at room temperature. To this solution were added $CHCl_3$–MeOH (8:1) (10 ml) and H_2O (10 ml). The layers were separated and the aqueous phase was extracted with $CHCl_3$–MeOH (8:1) (2×10 ml). The combined organic extracts were dried and concentrated under reduced pressure to give crude 1-*O*-benzoyl-4,8-sphingadienine hydrochloride (82 mg) as a colorless foam. This foam and (*R*)-acetoxy-palmitoyl imide **4** (150 mg, 0.30 mmol) were dissolved in *N*,*N*-dimethylformamide (2 ml). To this solution was added triethylamine (40 μl, 0.29 mmol), and the mixture was stirred at 60°C for 6 h. The reaction mixture was diluted with AcOEt and H_2O (10 ml), and extracted with AcOEt (3×10 ml). The combined organic layers were dried and concentrated to give a yellow oil, which was purified by chromatography with hexane–AcOEt (3:1) to give **13ab** (115 mg, 82%) as a colorless solid: R_f 0.27 (hexane–AcOEt, 3:1); δ_H 0.88 (6H, t, *J*=6.6 Hz), 1.25 (38H, s-like), 1.79 (2H, m), 1.97 (2H, m), 2.09 (4H, m), 2.12 (3H, s), 2.86 (1H, br s), 4.30 (1H, m), 4.38 (2H, m), 4.65 (1H, dd, *J*=8.6, 12.5 Hz), 5.08 (1H, dd, *J*=5.1, 7.1 Hz), 5.38 (2H, m), 5.54 (0.5H, dd, *J*=6.4, 15.3 Hz), 5.56 (0.5H, dd, *J*=6.4, 15.3 Hz), 5.81 (1H, dt-like, *J*=6.5, 15.5 Hz), 6.64 (1H, d, *J*=7.9 Hz), 7.45 (2H, m), 7.58 (1H, m), 8.00 (2H, m); δ_C 14.1, 20.8, 22.7, 24.8, 26.6, 27.3, 29.2, 29.3, 29.4, 29.5, 29.68, 29.70, 31.9, 31.98, 32.02, 32.3, 32.6, 53.7, 63.0, 73.1, 74.1, 128.2, 128.3, 128.3, 128.4, 129.5, 128.9, 129.4, 129.7, 130.8, 131.3, 133.4, 134.0, 134.1, 167.1, 169.8, 170.9.

(2*S*,3*R*,4*E*,8*E*,2′*R*)-2-(2′-Acetoxyhexadecanoyl)amino-1-*O*-benzoyl-4,8-octadecadiene-1,3-diol (13a). A mixture of **13ab** (70 mg, 0.10 mmol), 1-methylterazol-5-yl disulfide (12 mg, 0.05 mmol), 2,2′-azobis(isobutyronitrile) (8 mg, 50 μmol) in toluene (4 ml) under argon was heated at 100°C for 4 h. Removal of the solvent gave a pale-yellow solid, which was purified by preparative TLC eluting with hexane–AcOEt to give the ceramide **13a** (63 mg, 90%) as a colorless solid. Recrystallization from hexane gave pure **13a** (42 mg, 60% from **13ab**) as a colorless solid: mp 75–77°C; $([\alpha]_D^{24}$ +9.5° (*c* 1.0, $CHCl_3$) {lit.[10b] mp 77.0–78.0°C; $([\alpha]_D^{21}$ +9.0° (*c* 0.66, $CHCl_3$)}; δ_H 0.88 (6H, t, *J*=6.6 Hz, 18- and 16′-CH_3), 1.25 (38H, s-like, 19×CH_2), 1.78 (2H, m, 3′-H_2), 1.96 (2H, q, *J*=6.6 Hz, 10-H_2), 2.08 (4H, m, 6-H_2, 7-H_2), 2.11 (3H, s, CH_3CO), 2.80 (1H, d, *J*=5.1 Hz, OH), 4.28 (1H, m, 3-H), 4.36 (1H, m, 2-H), 4.37 (1H, dd, *J*=3.9, 12.5 Hz, 1-Ha), 4.64 (1H, dd, *J*=8.5, 12.7 Hz, 1-Hb), 5.07 (1H, dd, *J*=5.1, 7.1 Hz, 2′-H), 5.38 (2H, m, 8-H, 9-H), 5.54 (1H, dd, *J*=6.3, 15.6 Hz, 4-H), 5.80 (1H, dt, *J*=6.6, 15.4 Hz, 5-H), 6.63 (1H, d, *J*=7.6 Hz, NH), 7.44 (2H, m, Ph), 7.58 (1H, m, Ph), 8.00 (2H, m, Ph); δ_C 14.1, 20.8, 22.7, 24.8, 29.2, 29.32, 29.35, 29.36, 29.51, 29.55, 29.58, 29.59, 29.64, 29.68, 31.9, 31.96, 32.00, 32.3, 32.6, 53.7, 63.0, 73.1, 74.1, 128.2, 128.5, 128.9, 129.4, 129.7, 131.3, 133.4, 134.1, 167.1, 169.7, 170.8; ν_{max} (KBr) 3287 (broad), 2919, 2850, 1745, 1727, 1655, 1550, 1468, 1452, 1381, 1278, 1232, 1029, 964, 705 cm^{-1}; Anal. Calcd for $C_{43}H_{71}NO_6$: C, 73.99; H, 10.25; N, 2.01. Found: C, 73.88; H, 10.43; N, 1.98.

2-Dodecenyl phenyl sulfone (14). To a stirred solution of **9** (507 mg, 2.5 mmol) in DMF (6 ml) was added sodium phenylsulfinate dihydrate (1.00 g, 5.0 mmol) at room temp., and the resulting suspension was stirred at 50°C for

5 h. The mixture was diluted with H_2O and extracted with AcOEt. The combined extracts were successively washed with H_2O and brine, dried and concentrated in vacuo. The residue was purified by chromatography eluting with hexane–AcOEt (9:1→7:1) to give the allylic sulfone **14** (693 mg, 90%) as a colorless oil: R_f 0.33 (hexane–AcOEt, 6:1); δ_H 0.88 (3H, t, J=6.6 Hz), 1.25 (14H, br s), 1.98 (2H, q, J=6.5 Hz), 3.75 (2H, d, J=6.9 Hz), 5.38 (1H, dt, J=6.9, 15.5 Hz, 4-H), 5.50 (1H, dt, J=6.2, 15.5 Hz, 1-Ha), 7.54 (2H, m), 7.64 (1H, m), 7.85 (2H, m); δ_C 14.1, 22.6, 28.6, 29.0, 29.3, 29.4, 29.5, 31.8, 32.5, 60.1, 115.8, 128.5, 128.9, 133.5, 138.3, 141.9; ν_{max} (neat) 2956, 2925, 2854, 1466, 1447, 1320, 1308, 1146, 1087, 971, 733, 689 cm^{-1}; HRMS Calcd for $C_{18}H_{29}O_2S$ $(M+H)^+$: 309.1888. Found: 309.1871.

(4*S*,1′*S*,2′*S*)-2-Phenyl-4-(2′-bromo-1′-trimethylsilyloxy-3′-butenyl)-4,5-dihydrooxazole (15b). To a solution of LiBr (175 mg, 2.0 mmol) in acetonitrile (6 ml) under nitrogen was added chlorotrimethylsilane (0.22 ml, 1.8 mmol), and the mixture was stirred for 30 min at room temperature before being cooled by an ice-water bath. To this solution was added vinyl-epoxide **5** (112 mg, 0.52 mmol), and the mixture was stirred for 3 h at 5–10°C. To this mixture was added triethylamine (0.3 ml, 2.0 mmol), and the stirring was continued for 1 h at 5–10°C. The mixture was diluted with AcOEt (15 ml) and aq. $NaHCO_3$ (10 ml). The layers were separated and the aqueous phase was extracted with AcOEt (2×15 ml). The combined organic extracts were dried and concentrated to give an orange oil, which was purified by chromatography eluting with hexane–AcOEt (5:1) to give the allylic bromide **15b** (136 mg, 71%; 89% yield based on recovered **5**: 23 mg, 20.5%) as a colorless solid: mp 70–71°C; $[\alpha]_D^{23}$ −15.2° (*c* 1.28, $CHCl_3$); R_f 0.42 (hexane–AcOEt, 6:1); δ_H 0.07 (9H, s), 4.23 (1H, dd, J=2.1, 5.7 Hz, 1′-H), 4.35 (1H, m), 4.48 (1H, dd, J=5.7, 9.7 Hz, 2′-H), 4.50–4.58 (2H, m), 5.15 (1H, dd, J=0.7, 10.0 Hz, 4′-H_{cis}), 5.27 (1H, dt, J=0.9, 16.8 Hz, 4′-H_{trans}), 6.01 (1H, dt, J=9.9, 16.8 Hz, 3′-H), 7.40 (2H, m, Ph), 7.47 (1H, m, Ph), 7.93 (2H, m, Ph); δ_C 0.6, 58.4, 67.2, 69.6, 77.2, 118.1, 127.6, 128.2, 128.3, 131.3, 135.9, 164.6; ν_{max} (KBr) 2961, 2895, 1649, 1463, 1362, 1249, 1024, 938, 879, 840, 697 cm^{-1}; HRMS Calcd for $C_{16}H_{23}NO_2SiBr$ $(M+H)^+$: 368.0681. Found: 368.0591.

(4*S*,1′*R*,2′*E*,5′*RS*,6′*E*)-2-Phenyl-4-(5′-phenylsulfonyl-1′-trimethylsilyloxyhexadeca-2′,6′-dienyl)-4,5-dihydrooxazole (16). To a stirred solution of 2-dodecenyl phenyl sulfone **14** (200 mg, 0.65 mmol) in THF (5 ml) under argon was added a 1.5 M solution of *n*-butyllithium in hexane (0.4 ml, 0.65 mmol) at −70°C, and the resulting orange solution was allowed to warm to −40°C. To this solution was added a solution of the bromide **15b** (108 mg, 0.29 mmol) in THF (2 ml), and the mixture was allowed to warm to +10°C. The mixture was treated with saturated aq. NH_4Cl (2 ml), and diluted with AcOEt (15 ml) and H_2O (5 ml). The layers were separated and the aqueous phase was extracted with AcOEt (2×15 ml). The organic layer was successively washed with H_2O and brine, dried and concentrated. The residue was chromatographed on a column with hexane–AcOEt (5:1→3:1) as eluent to afford (*E*,*E*)-diene **16** diastereomeric mixture; 125 mg, 71% yield) as a colorless oil: R_f 0.41 and 0.36 (hexane–AcOEt, 2:1); δ_H −0.02 (9H, s), 0.87 (3H, t, J=6.5 Hz), 1.15–1.30 (14H, br s), 1.93 (2H, q, J=6.3 Hz), 2.43 (1H, m), 2.90 (1H, m), 3.49 (1H, ddd, J=3.2, 9.0, 11.0 Hz), 4.20–4.40 (4H, m), 5.20 (0.5H, dd, J=9.0, 15.4 Hz), 5.21 (0.5H, dd, J=9.0, 15.4 Hz), 5.36 (0.5H, dt, J=6.6, 15.4 Hz), 5.37 (0.5H, dt, J=6.6, 15.4 Hz), 5.59 (2H, m), 7.39 (2H, m), 7.47 (1H, m), 7.52 (2H, m), 7.63 (1H, m), 7.82 (2H, m), 7.91 (2H, m); δ_C 0.21, 0.22, 14.1, 22.7, 28.70, 28.74, 29.09, 29.12, 29.3, 29.4, 29.5, 30.17, 30.20, 31.9, 32.5, 32.6, 67.7, 67.8, 68.86, 68.93, 71.4, 71.5, 73.3, 73.4, 121.25, 121.31, 125.8, 125.9, 127.8, 128.2, 128.3, 128.8, 129.2, 131.2, 133.5, 133.9, 137.4, 141.01, 141.05, 164.57, 164.60; HRMS Calcd for $C_{34}H_{50}NO_4SSi$ $(M+H)^+$: 596.3229. Found: 596.3127.

***N*,*O*,*O*-Protected (4*E*,8*E*)-sphingadienine (17).** A mixture of **16** (84 mg, 0.18 mmol), $Pd(OAc)_2$ (3 mg, 13 μmol), and 1,3-bis(diphenylphosphino)propane (6 mg, 14 μmol) in THF (4 ml) was stirred at room temperature for 30 min. To this mixture was added a 1.0 M solution of lithium triethylborohydride in THF (0.4 ml, 0.4 mmol) at 0°C, and the resulting orange-brown solution was stirred for 1 h. The mixture was treated with acetone (50 μl), and diluted with AcOEt (10 ml) and H_2O (10 ml), and the layers were separated. The organic layer was washed with brine (10 ml) and the combined aqueous layers were extracted with AcOEt (2×10 ml). The combined organic extracts were dried, concentrated and purified by chromatography eluting with hexane–AcOEt (6:1) to give a 4:1 mixture of **17** and **18** (48 mg, 75%; **17**: 60% yield) as a colorless oil: R_f 0.43 (hexane–AcOEt, 6:1); $[\alpha]_D^{23}$ +0.16° (*c* 2.4, $CHCl_3$); **17**: δ_H (sphingosine numbering) 0.03 (9H, s), 0.88 (3H, t, J=6.5 Hz, 18-CH_3), 1.26 (14H, s, 11–17-CH_2), 1.92-2.16 (6H, m, 6-, 7-, 10-CH_2), 4.28 (2H, m, 2-H, 3-H), 4.36-4.44 (2H, m, 1-H_2), 5.40 (2H, m, 8-H, 9-H), 5.47 (1H, dd,J=5.0, 15.5 Hz, 4-H), 5.72 (1H, dt, J=6.3, 15.5 Hz, 5-H), 7.40 (2H, m, Ph), 7.47 (1H, m, Ph), 7.94 (2H, m, Ph); δ_C 0.3, 14.1, 22.7, 29.2, 29.3, 29.5, 29.6, 31.9, 32.3, 32.4, 32.6, 67.9, 71.7, 73.8, 127.9, 128.2 (4C), 129.2, 130.2, 131.07, 131.10, 131.4, 164.4; ν_{max} (KBr) 2925, 2854, 1651, 1468, 1451, 1358, 1251, 1088, 1026, 968, 842, 694 cm^{-1}; HRMS Calcd for $C_{28}H_{45}NO_2Si$ $(M+H)^+$: 455.3219. Found: 455.3163.

(2*S*,3*R*,4*E*,8*E*,2′*R*)-2-(2′-Acetoxyhexadecanoyl)amino-1-*O*-benzoyl-4,8-octadecadiene-1,3-diol (13a). In the same manner as described for the synthesis of **13ab** from **12ab**, a 4:1 mixture of **17** and **18** (52 mg, 0.11 mmol) gave the 2′-*O*-acetyl-1-*O*-benzoyl-ceramide (69 mg, 86%) as a colorless solid. Recrystallization from hexane afforded pure **13a** (44 mg, 41% from **16**).

(1*R*,2*E*,4′*S*)-5-Cyano-1-(2′-phenyl-4′,5′-dihydrooxazol-4′-yl)-2-penten-1-ol (19). To a stirred solution of diisopropylamine (0.56 ml, 4.0 mmol) in THF (8 ml) under argon was added a 1.5 M solution of butyllithium in hexane (2.6 ml, 3.9 mmol) at −40°C, and the solution was stirred for 20 min before being cooled to −70°C. To this solution was added a solution of CH_3CN (165 mg, 4.0 mmol) in THF (1 ml), and the mixture was allowed to warm. At −40°C, CuI (381 mg, 2.0 mmol) was added in one portion, and the resulting yellowish-brown suspension was stirred for 10 min at −70°C. To the mixture was added a solution of vinyl-epoxide **5** (198 mg, 0.92 mmol) in THF (4.0 ml), and

the mixture was allowed to warm to −10°C. The mixture was treated with saturated aq. NH_4Cl (2 ml), and diluted with AcOEt (15 ml) and H_2O (5 ml). The layers were separated and the aqueous phase was extracted with AcOEt (2×15 ml). The organic layer was successively washed with H_2O and brine (10 ml each), dried and concentrated. The residue was purified by chromatography eluting with hexane–AcOEt (1:3) to give the nitrile **19** (218 mg, 92%) as a colorless solid: mp 121–122°C; $[\alpha]_D^{25}$ −1.58° (*c* 1.0, $CHCl_3$); R_f 0.30 (hexane–AcOEt, 1:2); δ_H 2.43 (4H, s, 4-H_2, 5-H_2), 4.38 (3H, m, 4′-H and 5′-H_2), 4.67 (1H, br d, *J*=4.3 Hz, 1-H), 5.64 (1H, dd, *J*=4.6, 15.5 Hz, 2-H), 5.89 (1H, ddt, *J*=1.7, 6.6, 15.5 Hz, 3-H), 7.30 (2H, m, Ph), 7.42 (1H, m, Ph), 7.76 (2H, m, Ph); δ_C 17.4, 28.1, 67.4, 70.7, 70.9, 126.9, 127.6, 128.1, 128.2, 131.4, 132.0, 165.9; ν_{max} (KBr) 3171 (broad), 2251 (CN), 1646, 1366, 1273, 1124, 1101, 967, 696 cm^{-1}; Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.37; H, 6.26; N, 11.01.

(1*R*,2*E*,4′*S*)-5-Formyl-1-(2′-phenyl-4′,5′-dihydrooxazol-4′-yl)-2-penten-1-ol (20). To a stirred suspension of the nitrile **19** (128 mg, 0.50 mmol) in toluene (5 ml) was added a 1.5 M solution of diisobutylaluminum hydride in toluene (0.8 ml, 1.2 mmol) at −70°C over a period of 5 min, and the mixture was stirred for 50 min at between −70 and −50°C. The mixture was treated with acetone (50 μl) and diluted with AcOEt (10 ml) and 5% aq. tartaric acid (10 ml). The layers were separated and the organic layer was washed with brine. The combined aqueous layers were neutralized with aq. $NaHCO_3$ and extracted with AcOEt (2×10 ml). The combined organic layers were dried and concentrated to give crude aldehyde **20** (118 mg, 91%) as a colorless solid: R_f 0.30 (hexane–AcOEt, 1:2); δ_H 2.42 (2H, m), 2.55 (2H, m), 2.63 (1H, br, OH), 4.37 (3H, m), 4.55 (1H, d, *J*=5.2 Hz), 5.53 (1H, dd, *J*=5.3, 15.5 Hz), 5.85 (1H, ddt, *J*=1.5, 6.4, 15.5 Hz), 7.34 (2H, m), 7.47 (1H, m), 7.80 (2H, m), 9.77 (1H, t, *J*=1.4 Hz, CHO); δ_C 24.8, 43.0, 67.3, 71.0, 71.2, 126.9, 128.1, 128.2, 129.6, 130.3, 131.3, 165.7, 201.7; ν_{max} (KBr) 3189 (broad), 2907, 1724 (CHO), 1647, 1450, 1364, 1273, 1098, 967, 696 cm^{-1}. This solid was used in the next step without further purification.

1-*O*,2-*N*-Protected (4*E*,8*Z*)-sphingadienine (12b). To a stirred solution of decyltriphenylphosphonium bromide (550 mg, 1.1 mmol) in THF (7.5 ml) was added potassium *t*-butoxide (112 mg, 1.0 mmol) in three portions at −40°C. The resulting red-orange solution was allowed to warm to −20°C, and was then cooled to −70°C. To this solution was added a solution of the aldehyde **20** (105 mg, 0.40 mmol) in THF (1.5 ml) and the mixture was allowed to warm to 0°C. The mixture was treated with saturated aq. NH_4Cl (2 ml) and diluted with AcOEt (15 ml) and H_2O (10 ml). The layers were separated and the aqueous phase was extracted with AcOEt (2×15 ml). The organic layer was successively washed with H_2O and brine, dried and concentrated. The residue was chromatographed on a column with hexane–AcOEt (5:2) as eluent to afford (*E*,*Z*)-diene **12b** (120 mg, 78%) as a colorless solid: mp 57–59°C; $[\alpha]_D^{25}$ −3.7° (*c* 2.4, $CHCl_3$) {lit.[10b] mp 58.0–58.5°C; $[\alpha]_D^{23}$ −4.23° (*c* 0.39, $CHCl_3$)}; δ_H (sphingosine numbering) 0.88 (3H, t, *J*=6.6 Hz, 18-CH_3), 1.26 (14H, s-like, 11–17-CH_2), 2.01 (2H, q, *J*=6.5 Hz, 10-H_2), 2.13 (4H, m, 6-H_2, 7-H_2), 4.38 (3H, m, 1-H_2 and 2-H), 4.56 (1H, br d, *J*=5.3 Hz, 3-H), 5.36 (2H, m, 8-H, 9-H), 5.47 (1H, dd, *J*=5.6, 15.5 Hz, 4-H), 5.84 (1H, m, 5-H), 7.36 (2H, m, Ph), 7.46 (1H, m, Ph), 7.86 (2H, m, Ph); δ_C 14.1, 22.6, 26.8, 27.3, 29.3, 29.5, 29.6, 29.7, 31.9, 32.5, 67.4, 71.2, 71.4, 127.0, 128.1 (2C), 128.2 (2C), 128.5, 128.6, 130.5, 131.2, 132.4, 165.6; ν_{max} (KBr) 3175 (broad), 2919, 2850, 1651, 1469, 1449, 1360, 1270, 1107, 1093, 971, 690 cm^{-1}; Anal. Calcd for $C_{25}H_{37}NO_2$: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.16; H, 9.81; N, 3.56.

(2*S*,3*R*,4*E*,8*Z*,2′*R*)-2-(2′-Acetoxyhexadecanoyl)amino-1-*O*-benzoyl-4,8-octadecadiene-1,3-diol (13b). To a stirred solution of **12b** (135 mg, 0.35 mmol) in THF (4.5 ml) was added a 2.0 M aq. HCl (0.5 ml) and the mixture was stirred for 16 h at room temperature. To this solution were added $CHCl_3$–MeOH (8:1) (10 ml) and H_2O (10 ml). The layers were separated and the aqueous phase was extracted with $CHCl_3$–MeOH (8:1) (2×10 ml). The combined organic extracts were dried and concentrated in vacuo to give crude 1-*O*-benzoyl-sphingadienine hydrochloride (145 mg) as a colorless foam. This foam (145 mg) and (*R*)-acetoxypalmitoyl imide **4** (260 mg, 0.53 mmol) were dissolved in *N*,*N*-dimethylformamide (3 ml). To this solution was added triethylamine (70 μl, 0.50 mmol), and the mixture was stirred at 60°C for 6 h. The reaction mixture was diluted with AcOEt and H_2O (10 ml), and extracted with AcOEt (3×10 ml). The combined organic layers were dried and concentrated to give a yellow oil, which was purified by chromatography with hexane–AcOEt (3:1) to give **13b** (198 mg, 80%) as a colorless solid: mp 60–62°C; $[\alpha]_D^{23}$ +5.0° (*c* 2.7, $CHCl_3$) {lit.[10b] mp 58.5–59.5°C; $[\alpha]_D^{23}$ +6.17° (*c* 0.55, $CHCl_3$)}; δ_H 0.88 (6H, t, *J*=6.6 Hz, 18- and 16′-CH_3), 1.25 (38H, s-like, 19×CH_2), 1.79 (2H, m, 3′-H_2), 2.01 (2H, 10-H_2), 2.12 (7H, m, CH_3CO, 6-H_2, 7-H_2), 2.90 (1H, br s, OH), 4.31 (1H, m, 3-H), 4.38 (1H, m, 2-H), 4.38 (1H, dd, *J*=3.6, 12.5 Hz, 1-Ha), 4.65 (1H, dd, *J*=8.6, 12.5 Hz, 1-Hb), 5.08 (1H, dd, *J*=5.1, 7.1 Hz, 2′-H), 5.37 (2H, m, 8-H, 9-H), 5.56 (1H, dd, *J*=6.4, 15.3 Hz, 4-H), 5.81 (1H, br d, *J*=15.5 Hz, 5-H), 6.65 (1H, d, *J*=7.6 Hz, NH), 7.44 (2H, m, Ph), 7.58 (1H, m, Ph), 8.00 (2H, m, Ph); δ_C 14.1, 20.8, 22.4, 24.7, 26.6, 27.3, 29.2, 29.3, 29.56, 29.64, 31.86, 31.92, 32.3, 53.7, 62.9, 73.0, 74.0, 128.3, 128.36, 128.44, 129.4, 129.6, 130.7, 133.4, 134.0, 167.0, 169.7, 170.8; ν_{max} (KBr) 3174 (broad), 3106, 2921, 2852, 1751, 1727, 1661, 1573, 1468, 1452, 1375, 1274, 1229, 1099, 1071, 706 cm^{-1}; Anal. Calcd for $C_{43}H_{71}NO_6$: C, 73.99; H, 10.25; N, 2.01. Found: C, 74.27; H, 10.29; N, 1.94.

(2*S*,3*R*,4*E*,8*E*,2′*R*)-2-(2′-Hydroxyhexadecanoyl)amino-4,8-octadecadiene-1,3-diol (21a). To an ice-cooled solution of **13a** (108 mg, 0.15 mmol) in CH_2Cl_2 (2 ml) and MeOH (1 ml) was added a 1.0 M solution of NaOMe in MeOH (0.1 ml, 0.1 mmol), and the mixture was stirred for 1 h at this temperature. Acetic acid (10 mg) was added and the solvent was removed. Residual white solid was washed successively with MeOH, H_2O, and haxane–AcOEt (2:1) to give **21a** (60 mg) as a colorless solid. The filtrate was extracted with AcOEt as usual to give a pale-yellow solid, which was purified by chromatography eluting with CH_2Cl_2–MeOH (15:1→10:1) to give the additional **21a** (20 mg; total 80 mg, 94%) as white granules: mp 97–100°C;$[\alpha]_D^{23}$ +5.6° (*c* 1.0, $CHCl_3$) {lit.[10b] mp 104–105°C; $[\alpha]_D^{23}$ +7.84° (*c* 0.25, $CHCl_3$)}; δ_H ($CDCl_3$–CD_3OD) 0.88 (6H, t, *J*=6.6 Hz, 18- and 16′-CH_3), 1.26 (38H, s-like,

19×CH_2), 1.54 (1H, m, 3′-Ha), 1.77 (1H, m, 3′-Hb), 1.96 (2H, m, 10-H_2), 2.08 (4H, m, 6-H_2, 7-H_2), 3.69 (1H, dd, *J*=3.3, 11.2 Hz, 1-Ha), 3.80 (1H, dd, *J*=4.6, 11.5 Hz, 1-Hb), 3.85 (1H, m, 2-H), 4.04 (1H, dd, *J*=3.5, 8.0 Hz, 2-H), 4.14 (1H, t, *J*=5.8 Hz, 3-H), 5.40 (2H, m, 8-H, 9-H), 5.48 (1H, dd, *J*=6.4, 15.4 Hz, 4-H), 5.76 (1H, dt, *J*=6.3, 15.2 Hz, 5-H); ν_{max} (KBr) 3359, 3278, 2919, 2849, 1631, 1535, 1468, 1433, 1315, 1080, 963, 721 cm^{-1}; Anal. Calcd for $C_{34}H_{65}NO_4$: C, 74.00; H, 11.87; N, 2.54. Found: C, 73.98; H, 11.85; N, 2.42.

(2*S*,3*R*,4*E*,8*E*,2′*R*)-1-(*t*-Butyldiphenylsilyl)oxy-2-(2′-hydroxyhexadecanoyl)amino-4,8-octadecadien-3-ol (22a). To an ice-cooled solution of **21a** (72 mg, 0.13 mmol) and imidazole (45 mg, 0.65 mmol) in CH_2Cl_2 (2 ml) and DMF (1 ml) was added *t*-butyldiphenylchlorosilane (55 mg, 0.20 mmol), and the mixture was stirred for 30 min at this temperature. The reaction was quenched with MeOH (50 μl) and the mixture was diluted with AcOEt and H_2O, and the layers were separated. The organic layer was washed with brine and the combined aqueous layers were extracted with AcOEt. The combined organic extracts were dried and concentrated to give a residue, which was purified by chromatography eluting with hexane–AcOEt (3:1) to afford the ceramide **22a** (84 mg, 82%) as a waxy solid: R_f 0.35 (hexane–AcOEt, 3:1); $[\alpha]_D^{25}$ +10.0° (*c* 1.7, $CHCl_3$); δ_H 0.88 (6H, t, *J*=6.6 Hz), 1.07 (9H, s, *t*-Bu), 1.26 (38H, s-like), 1.60 (1H, m), 1.78 (1H, m), 1.95 (2H, q, *J*=6.2 Hz), 2.06 (4H, m), 2.35 (1H, br, OH), 3.44 (1H, br d, *J*=8.1 Hz, OH), 3.75 (1H, dd, *J*=4.9, 11.5 Hz), 3.97 (2H, m), 4.05 (1H, m), 4.21 (1H, m), 5.39 (2H, m), 5.48 (1H, dd, *J*=6.2, 15.5 Hz), 5.77 (1H, dt, *J*=6.4, 15.6 Hz), 7.09 (1H, d, *J*=7.8 Hz), 7.40 (6H, m, Ph), 7.63 (4H, m, Ph); δ_C 14.1, 19.1, 22.7, 25.1, 26.82, 26.84, 29.2, 29.3, 29.4, 29.5, 29.60, 29.65, 29.69, 31.90, 31.91, 32.2, 32.4, 32.6, 35.1, 54.0, 63.7, 72.3, 73.9, 127.9, 129.1, 129.2, 130.1, 131.1, 132.46, 132.51, 133.0, 135.5, 135.6, 173.9; FAB-MS (positive) *m*/*z* (relative intensity %) 790 (M^++H, 22), 772 (M−OH, 49), 732 (M−C_4H_9, 10), 712 (M−C_6H_5, 14).

(2*S*,3*R*,4*E*,8*E*,2′*R*)-3-Acetoxy-2-(2′-acetoxyhexadecanoyl)amino-4,8-octadecadien-1-ol (24a). To an ice-cooled solution of **22a** (75 mg, 0.095 mmol) and 4-(dimethylamino)pyridine (2 mg) in CH_2Cl_2 (2 ml) were added pyridine (0.2 ml) and acetic anhydride (0.15 ml) and the mixture was stirred at 5–10°C for 2 h. The mixture was treated with MeOH (0.1 ml), and then diluted with AcOEt and H_2O. After extractive work-up, the organic layer was dried and concentrated to give crude diacetate **23a** (90 mg), which was used in the next step without further purification: δ_H 0.88 (6H, t, *J*=6.6 Hz), 1.07 (9H, s), 1.26 (38H, s-like), 1.80 (2H, m), 1.94 (2H, m), 1.96 (3H, s), 2.00 (3H, s), 2.05 (4H, m), 3.63 (1H, dd, *J*=3.9, 10.5 Hz), 3.78 (1H, dd, *J*=2.2, 10.5 Hz), 4.25 (1H, m), 5.23 (1H, dd, *J*=4.9, 6.8 Hz), 5.32–5.48 (4H, m), 5.83 (1H, br d, *J*=15 Hz), 6.57 (1H, d, *J*=8.3 Hz), 7.39 (6H, m), 7.59 (4H, m). To a solution of the crude diacetate **23a** in THF (2 ml) were added acetic acid (12 μl, 0.2 mmol) and a 1.0 M solution of tetrabutylammonium fluoride in THF (0.2 ml, 0.2 mmol), and the mixture was stirred at room temperature for 3 h. The mixture was diluted with AcOEt and H_2O and the layers were separated. The organic layer was washed with brine and the combined aqueous layers were extracted with AcOEt. The combined organic extracts were dried and concentrated to give a residue, which was purified by chromatography eluting with hexane–AcOEt (3:1→3:2) to give **24a** (53 mg, 88%) as a colorless solid: mp 69–71°C; R_f 0.27 (hexane–AcOEt, 3:2); $[\alpha]_D^{26}$ −1.6° (*c* 2.6, $CHCl_3$); δ_H 0.88 (3H, t, *J*=6.6 Hz, 18- and 16′-CH_3), 1.25 (38H, s-like, 19×CH_2), 1.81 (2H, m, 3′-H_2), 1.96 (2H, q, *J*=6.3 Hz, 10-H_2), 2.09 (3H, s, CH_3CO), 2.09 (4H, m, 6-H_2, 7-H_2), 2.15 (3H, s, CH_3CO), 2.75 (1H, br, OH), 3.64 (2H, m, 1-H_2), 4.09 (1H, m, 2-H), 5.14 (1H, dd, *J*=4.9, 7.1 Hz, 2′-H), 5.32 (1H, t, *J*=7.2 Hz, 3-H), 5.39 (2H, m, 8-H, 9-H), 5.49 (1H, dd, *J*=7.4, 15.3 Hz, 4-H), 5.81 (1H, dt, *J*=6.0, 15.4 Hz, 5-H), 6.65 (1H, d, *J*=8.5 Hz, NH); δ_C 14.1, 20.9, 21.1, 22.6, 24.8, 29.19, 29.27, 29.32, 29.41, 29.50, 29.57, 29.63, 29.66, 31.8, 31.9, 32.3, 32.6, 53.1, 61.3, 73.9, 74.2, 124.8, 128.7, 131.4, 136.5, 169.8, 170.1, 171.0; ν_{max} (KBr) 3320 (broad), 2955, 2921, 2851, 1733, 1659, 1543, 1469, 1374, 1227, 1028, 968 cm^{-1}; Anal. Calcd for $C_{38}H_{69}NO_6$: C, 71.77; H, 10.94; N, 2.20. Found: C, 72.14; H, 10.97; N, 2.08.

(2*S*,3*R*,4*E*,8*E*,2′*R*)-2-(2′-Acetoxyhexadecanoyl)amino-3-*O*-acetyl-1-*O*-(2″,3″,4″,6″-tetra-*O*-benzoyl-β-D-glucopyranosyl)-4,8-octadecadien-1,3-diol (25a). A solution of **24a** (42 mg, 0.66 mmol), 2,3,4,6-tetra-*O*-benzoyl-α-D-glucosyl bromide (80 mg, 0.12 mmol), oven-dried molecular sieves 4A (50 mg) in dichloromethane (2.5 ml) was stirred under argon at room temperature for 30 min before being cooled to −20°C. To this suspension was added AgOTf (31 mg, 0.12 mmol) in toluene (0.5 ml), and the mixture was stirred at −20–0°C for 2 h. The resulting suspension was diluted with AcOEt (10 ml), and the insoluble material was filtered off and washed thoroughly with AcOEt (15 ml). The filtrate was washed with aq. $NaHCO_3$, H_2O and brine (10 ml each). The combined aqueous layers were extracted with AcOEt (2×20 ml), and the organic extracts were dried and concentrated. The residue was purified by chromatography eluting with hexane–AcOEt (3:1→5:2) to afford the glycoside **25a** (63 mg, 78%) as a colorless solid: R_f 0.30 (hexane–AcOEt, 5:2); $[\alpha]_D^{26}$ +8.8° (*c* 1.2, $CHCl_3$); δ_H 0.88 (6H, t, *J*=6.6 Hz, 18- and 16′-CH_3), 1.25 (38H, s-like, 19×CH_2), 1.66 (2H, m, 3′-H_2), 1.93 (2H, m, 10-H_2), 1.95 (3H, s, CH_3CO), 1.96 (3H, s, CH_3CO), 1.99 (4H, m, 6-H_2, 7-H_2), 3.64 (1H, dd, *J*=4.4, 10.0 Hz, 1-Ha), 4.04 (1H, dd, *J*=3.7, 10.2 Hz, 1-Hb), 4.17 (1H, m, 5″-H), 4.31 (1H, m, 2-H), 4.49 (1H, dd, *J*=5.0, 12.1 Hz, 6″-Ha), 4.65 (1H, dd, *J*=3.2, 12.2 Hz, 6″-Hb), 4.85 (1H, d, *J*=7.8 Hz, 1″-H), 4.95 (1H, dd, *J*=5.4, 6.3 Hz, 2′-H), 5.28–5.43 (4H, m, 3-, 4-, 8- and 9-H), 5.48 (1H, dd, *J*=7.8, 9.8 Hz, 2″-H), 5.67 (1H, t, *J*=9.6 Hz, 4″-H), 5.73 (1H, m, 5-H), 5.89 (1H, t, *J*=9.6 Hz, 3″-H), 6.31 (1H, d, *J*=9.0 Hz, NH), 7.22–7.58 (12H, m), 7.80 (2H, m), 7.90 (2H, m), 7.93 (2H, m), 8.02 (2H, m); δ_C 14.1, 20.7, 21.0, 22.7, 24.6, 29.2, 29.3, 29.45, 29.53, 29.60, 29.63, 29.7, 31.7, 31.9, 32.3, 32.6, 50.6, 63.0, 67.4, 69.5, 72.0, 72.4, 72.8, 73.1, 73.9, 100.8, 124.6, 128.3, 128.4, 128.7, 128.9, 129.0, 129.5, 129.8, 131.1, 133.1, 133.2, 133.4, 136.5, 165.0, 165.1, 165.7, 166.1, 169.56, 169.58, 169.7; ν_{max} (KBr) 2925, 2853, 1732, 1690, 1519, 1452, 1371, 1265, 1094, 1069, 1027, 710 cm^{-1}; FAB-MS (positive) *m*/*z* (%) 1214 (M^++H, 3), 1154 (M−CH_3CO_2, 26), 579 (18).

(2*S*,3*R*,4*E*,8*E*,2′*R*)-1-*O*-(β-D-Glucopyranosyl)-2-(2′-hydroxyhexadecanoyl)amino-4,8-octadecadiene-1,3-diol (1a). To a stirred solution of **25a** (55 mg, 45 μmol) in MeOH (1 ml) and THF (1 ml) was added 1.0 M solution of NaOMe in MeOH (50 μl, 50 μmol), and the mixture was stirred for 2 h at 5–10°C. Acetic acid (10 mg) was added and the solvent was removed. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2–MeOH (9:1→7:1) to afford the cerebroside **1a** (30 mg, 93%) as a colorless solid: mp 180°C (125°C- liquid crystal-like) {lit.[10a] 184–186°C; lit.[10b] 184–185°C; lit.[10c] 184°C}; R_f 0.33 (CH_2Cl_2–MeOH, 7:1); $[\alpha]_D^{24}$ +4.0° (*c* 0.95, $CHCl_3$–MeOH, 1:1) {lit.[7] $[\alpha]_D^{15.5}$ +5.4° (*c* 0.648, $CHCl_3$–MeOH, 2:3); lit.[10b] $[\alpha]_D^{24}$ +10.5° (*c* 0.30, $CHCl_3$–MeOH, 2:3); lit.[10c] $[\alpha]_D^{20}$ +5.4° (*c* 0.4, MeOH)}; δ_H (pyridine-d_5) 0.85 (6H, t, *J*=6.3 Hz, 18- and 16′-CH_3), 1.24 (38H, s-like, 19×CH_2), 1.74 (2H, br, 3′-H_2), 2.00 (2H, m, 10-H_2), 2.13 (4H, m, 6-H_2, 7-H_2), 3.89 (1H, m, 5″-H), 4.01 (1H, m, 2″-H), 4.20 (3H, m, 1-Ha, 3″-H, 4″-H), 4.33 (1H, dd, *J*=5.0, 11.8 Hz, 6″-Ha), 4.49 (1H, br d, *J*=11.5 Hz, 6″-Hb), 4.57 (1H, m, 2′-H), 4.69 (1H, dd, *J*=5.4, 10.7 Hz, 1-Hb), 4.76 (m, 2H, 2-H, 3-H), 4.91 (1H, d, *J*=7.5 Hz, 1″-H), 5.48 (2H, m, 8-H, 9-H), 5.95 (2H, m, 4-H, 5-H), 8.33 (1H, d, *J*=8.3 Hz, NH); δ_C (pyridine-d_5) 14.1, 22.8, 25.7, 29.4, 29.5, 29.67, 29.73, 29.8, 29.9, 32.0, 32.6, 32.8, 35.4, 54.2, 62.3, 69.7, 71.2, 72.0, 72.2, 74.8, 78.0, 78.2, 105.2, 129.8, 131.0, 131.6, 132.2, 175.7; ν_{max} (KBr) 3370 (broad), 2956, 2920, 2850, 1645, 1537, 1469, 1082, 1046, 963 cm^{-1}; FAB-MS (positive) *m*/*z* (%) 714 (M^++H, 19), 697 (M−OH+H, 20), 534 (22).

(2*S*,3*R*,4*E*,8*Z*,2′*R*)-2-(2′-Hydroxyhexadecanoyl)amino-4,8-octadecadiene-1,3-diol (21b). In a similar manner as described for the synthesis of **21a**, **13b** (160 mg, 0.23 mmol) in CH_2Cl_2 (2 ml) and MeOH (1 ml) was treated with a 1.0 M solution of NaOMe in MeOH (0.1 ml, 0.1 mmol) at 0°C, and the mixture was stirred for 1 h. Acetic acid was added and the solvent was removed. The residue was purified by chromatography eluting with CH_2Cl_2–MeOH (20:1→15:1) to give **21b** as a colorless solid (120 mg, 94%); mp 72–75°C; $[\alpha]_D^{24}$ +6.1° (*c* 2.4, $CHCl_3$) {lit.[10b] mp 78.0–79.5°C; $[\alpha]_D^{22}$ +6.29° (*c* 0.18, $CHCl_3$)}; δ_H 0.88 (6H, t, *J*=6.7 Hz), 1.25 (38H, s-like), 1.60 (1H, m), 1.78 (1H, m), 2.01 (2H, q, *J*=6.6 Hz), 2.12 (4H, m), 3.75 (1H, dd, *J*=3.3, 11.2 Hz), 3.80–3.96 (2H, m), 4.10 (1H, dd, *J*=3.8, 8.0 Hz), 4.25 (1H, m), 5.36 (2H, m), 5.56 (1H, dd, *J*=6.2, 15.5 Hz), 5.79 (1H, br d, *J*=15.0 Hz), 6.65 (1H, d, *J*=7.6 Hz); δ_C 14.1, 22.7, 25.3, 26.7, 27.3, 29.3, 29.4, 29.5, 29.6, 29.67, 29.69, 29.73, 29.74, 31.88, 31.90, 32.4, 34.5, 54.6, 61.6, 72.4, 73.5, 128.4, 128.8, 130.7, 133.7, 176.1; ν_{max} 3465, 3351, 3271, 2917, 2849, 1618, 1556, 1469, 1377, 1319, 1070, 965, 718 cm^{-1}; Anal. Calcd for $C_{34}H_{65}NO_4$: C, 74.00; H, 11.87; N, 2.54. Found: C, 74.10; H, 11.91; N, 2.45.

(2*S*,3*R*,4*E*,8*Z*,2′*R*)-1-(*t*-Butyldiphenylsilyl)oxy-2-(2′-hydroxyhexadecanoyl)amino-4,8-octadecadien-3-ol (22b). In the same manner as described for the synthesis of **22a**, **21b** (111 mg, 0.20 mmol) gave 1-*O*-TBDPS ceramide **22b** (144 mg, 91%) as a waxy solid: R_f 0.35 (hexane–AcOEt, 3:1); $[\alpha]_D^{25}$ +10.5° (*c* 2.0, $CHCl_3$); δ_H 0.88 (6H, t, *J*=6.6 Hz, 18- and 16′-CH_3), 1.07 (9H, s, *t*-Bu), 1.26 (38H, s-like, 19×CH_2), 1.60 (1H, m, 3′-Ha), 1.78 (1H, m, 3′-Hb), 2.00 (2H, q, *J*=6.2 Hz, 10-H_2), 2.09 (4H, m, 6-H_2, 7-H_2), 2.33 (1H, br d, *J*=4.6 Hz, OH), 3.40 (1H, br d, *J*=7.3 Hz, OH), 3.75 (1H, dd, *J*=4.9, 11.5 Hz, 1-Ha), 3.97 (2H, m, 1-Ha, 2-H), 4.05 (1H, m, 2′-H), 4.21 (1H, m, 3-H), 5.34 (2H, m, 8-H, 9-H), 5.49 (1H, dd, *J*=6.1, 15.4 Hz, 4-H), 5.77 (1H, br d, *J*=15.4 Hz, 5-H), 7.08 (1H, d, *J*=7.6 Hz, NH), 7.40 (6H, m, Ph), 7.63 (4H, m, Ph); δ_C 14.1, 19.1, 22.7, 25.1, 26.8, 26.9, 27.3, 29.3, 29.5, 29.6, 29.7, 31.9, 32.4, 35.1, 54.1, 63.6, 72.3, 73.9, 127.9, 128.6, 129.3, 130.0, 130.7, 132.48, 132.52, 133.0, 135.5, 135.6, 173.9; Anal. Calcd for $C_{50}H_{83}NO_4Si$: C, 75.99; H, 10.59; N, 1.77. Found: C, 76.10; H, 10.71; N, 1.74.

(2*S*,3*R*,4*E*,8*Z*,2′*R*)-3-Acetoxy-2-(2′-acetoxyhexadecanoyl)-amino-4,8-octadecadien-1-ol (24b). In the same manner as described for the synthesis of **22a**, **22b** (120 mg, 0.15 mmol) gave crude full-protected ceramide **23b** (140 mg) as a colorless oil: R_f 0.46 (hexane–AcOEt, 5:1); δ_H 0.88 (6H, t, *J*=6.6 Hz), 1.07 (9H, s), 1.26 (38H, s-like), 1.77 (2H, m), 1.96 (3H, s), 2.00 (3H, s), 2.00 (2H, q, *J*=6.2 Hz), 2.08 (4H, m), 3.64 (1H, dd, *J*=3.8, 10.4 Hz), 3.77 (1H, dd, *J*=2.2, 10.5 Hz), 4.25 (1H, m), 5.23 (1H, dd, *J*=4.9, 6.8 Hz), 5.27–5.50 (4H, m), 5.84 (1H, br d, *J*=15 Hz), 6.57 (1H, d, *J*=9.5 Hz), 7.40 (6H, m), 7.59 (4H, m). In the same manner as described for the synthesis of **24a**, the crude **23b** (140 mg) gave the di-*O*-acetyl-ceramide **24b** (91 mg, 94% from **22b**) as a colorless solid: mp 70–72°C; R_f 0.34 (hexane–AcOEt, 1:1); $[\alpha]_D^{26}$ −0.6° (*c* 1.2, $CHCl_3$); δ_H 0.88 (6H, t, *J*=6.6 Hz), 1.25 (38H, s-like), 1.78 (2H, m), 2.00 (2H, q, *J*=6.3 Hz), 2.10 (3H, s), 2.11 (4H, m), 2.16 (3H, s), 2.72 (1H, br), 3.65 (2H, m), 4.10 (1H, m), 5.14 (1H, dd, *J*=4.8, 7.2 Hz), 5.26–5.45 (3H, m), 5.51 (1H, dd, *J*=7.3, 15.1 Hz), 5.81 (1H, dt, *J*=5.9, 15.4 Hz), 6.66 (1H, d, *J*=8.5 Hz); δ_C 14.1, 20.9, 21.1, 22.6, 24.8, 26.4, 27.3, 29.26, 29.32, 29.4, 29.56, 29.58, 29.63, 29.66, 31.8, 31.9, 32.3, 53.2, 61.4, 74.0, 74.1, 124.9, 128.2, 130.9, 136.4, 169.8, 170.2, 171.0; ν_{max} (KBr) 3275 (broad), 2955, 2921, 2852, 1747, 1667, 1567, 1468, 1372, 1245, 1229, 1073, 979 cm^{-1}; HRMS Calcd for $C_{38}H_{69}NO_6$ (M^+): 635.5125. Found: 635.5132.

(2*S*,3*R*,4*E*,8*Z*,2′*R*)-2-(2′-Acetoxyhexadecanoyl)amino-3-*O*-acetyl-1-*O*-(2″,3″,4″,6″-tetra-*O*-benzoyl-β-D-gluco-pyranosyl)-4,8-octadecadien-1,3-diol (25b). In the same manner as described for the synthesis of **25a**, **24b** (62 mg, 0.097 mmol) afforded the glucoside **25b** (91 mg, 77, 88% yield based on recovered **24b**: 8 mg, 13%) as a colorless oil: R_f 0.30 (hexane–AcOEt, 5:2); $[\alpha]_D^{26}$ +13.1° (*c* 1.2, $CHCl_3$); δ_H 0.88 (6H, t, *J*=6.8 Hz, 18- and 16′-CH_3), 1.25 (38H, s-like, 19×CH_2), 1.65 (2H, m, 3′-H_2), 1.93 (2H, m, 10-H_2), 1.95 (3H, s, CH_3CO), 1.97 (3H, s, CH_3CO), 2.01 (4H, m, 6-H_2, 7-H_2), 3.65 (1H, dd, *J*=4.2, 10.3 Hz, 1-Ha), 4.04 (1H, dd, *J*=3.7, 10.3 Hz, 1-Hb), 4.17 (1H, m, 5″-H), 4.31 (1H, m, 2-H), 4.50 (1H, dd, *J*=4.8, 12.1 Hz, 6″-Ha), 4.65 (1H, dd, *J*=2.6, 12.0 Hz, 6″-Hb), 4.85 (1H, d, *J*=7.8 Hz, 1″-H), 4.94 (1H, dd, *J*=5.4, 6.3 Hz, 2′-H), 5.22–5.45 (4H, m, 3-, 4-, 8- and 9-H), 5.48 (1H, dd, *J*=7.8, 9.8 Hz, 2″-H), 5.67 (1H, t, *J*=9.6 Hz, 4″-H), 5.74 (1H, m, 5-H), 5.89 (1H, t, *J*=9.6 Hz, 3″-H), 6.31 (1H, d, *J*=9.0 Hz, NH), 7.20–7.60 (12H, m), 7.80 (2H, m), 7.90 (2H, m), 7.93 (2H, m), 8.02 (2H, m); δ_C 14.1, 20.6, 21.0, 22.7, 24.6, 26.5, 27.3, 29.3, 29.5, 29.60, 29.64, 29.7, 31.7, 31.9, 32.3, 50.5, 63.0, 67.4, 69.5, 72.0, 72.4, 72.8, 73.1,

74.0, 100.8, 124.8, 128.3, 128.4, 128.7, 129.0, 129.5, 129.7, 130.7, 133.1, 133.2, 133.4, 136.4, 165.0, 165.1, 165.7, 166.1, 169.6, 169.7; ν_{max} (KBr) 2925, 2854, 1731, 1691, 1518, 1452, 1371, 1265, 1094, 1069, 1027, 710 cm^{-1}; FAB-MS (positive) *m*/*z* (%) 1237 (M^++Na, 69), 1155 (93), 579 (100).

(2*S*,3*R*,4*E*,8*Z*,2′*R*)-1-*O*-(β-D-Glucopyranosyl)-2-(2′-hydroxyhexadecanoyl)amino-4,8-octadecadiene-1,3-diol (1b). In the same manner as described for the synthesis of **1a**, **25b** (72 mg, 59 μmol) afforded the cerebroside **1b** (38 mg, 90%) as a colorless solid: mp 173°C (115°C- liquid crystal-like) {lit.[10a] 183°C; lit.[10b] 192–194°C; lit.[10d] 183°C}; R_f 0.33 (CH_2Cl_2–MeOH, 7:1); $[\alpha]_D^{26}$ +4.4° (*c* 1.30, $CHCl_3$–MeOH, 1:1) {lit.[10a] $[\alpha]_D^{20}$ +4.6° (*c* 1.76, $CHCl_3$–MeOH, 1:1); lit.[10b] $[\alpha]_D^{24}$ +13.4° (*c* 0.43, $CHCl_3$–MeOH, 2:3); lit.[10d] $[\alpha]_D^{20}$ +4° (*c* 0.2, MeOH); lit.[10f] $[\alpha]_D^{24}$ +5.6° (*c* 0.1, MeOH)}; δ_H (pyridine-d_5) 0.85 (6H, t, *J*=6.3 Hz, 18- and 16′-CH_3), 1.25 (38H, s-like, 19×CH_2), 1.75 (2H, br, 3′-H_2), 2.03 (2H, q, *J*=5.7 Hz, 10-H_2), 2.17 (4H, m, 6-H_2, 7-H_2), 3.89 (1H, m, *J*=2.6, 4.6, 9.9 Hz, 5″-H), 4.01 (1H, m, 2″-H), 4.19 (2H, m, 3″-H, 4″-H), 4.23 (1H, dd, *J*=2.4, 10.3 Hz, 1-Ha), 4.33 (1H, dd, *J*=5.0, 11.8 Hz, 6″-Ha), 4.49 (1H, br d, *J*=12.4 Hz, 6″-Hb), 4.57 (1H, m, 2′-H), 4.69 (1H, dd, *J*=5.4, 10.7 Hz, 1-Hb), 4.76 (m, 2H, 2- and 3-H), 4.90 (1H, d, *J*=7.8 Hz, 1″-H), 5.47 (2H, m, 8-H, 9-H), 5.90 (1H, br d, *J*=15.4 Hz, 5-H), 6.00 (1H, dd, *J*=5.1, 15.4 Hz, 4-H), 8.34 (1H, d, *J*=8.1 Hz, NH); δ_C ($CDCl_3$–CD_3OD) 13.7, 22.4, 25.0, 26.4, 27.0, 29.1, 29.3, 29.4, 29.5, 31.6, 32.2, 34.2, 52.8, 60.9, 68.3, 69.4, 71.6, 71.8, 73.1, 75.9, 102.7, 128.3, 128.9, 130.4, 133.6, 175.8; ν_{max} (KBr) 3365 (broad), 2957, 2920, 2850, 1644, 1536, 1469, 1082, 960 cm^{-1}; Anal. Calcd for $C_{40}H_{75}NO_9H_2O$: C, 65.63; H, 10.60; N, 1.91. Found: C, 65.85; H, 10.44; N, 1.88.

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37. (a) Garreg, P. J.; Norberg, T. *Acta Chem. Scand. Ser. B* **1979**, *33*, 116. (b) Reimer, K. B.; Meldal, M.; Kusumoto, S.; Fukase, K.; Bock, K. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 925.
38. This compound can be purchased from Aldrich Chemical Co.
39. Formation of the orthoester often complicates the reaction

and lowers the yield of the desired glycoside, see: (a) Kunz, H; Harreus, A. *Liebigs Ann. Chem.* **1982**, 41. (b) Sato, S.; Nunomura, S.; Nakano, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 4097.

40. When *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl) trichloroacetimidate was used as donor, 1-*O*-acetylated ceramides were formed in 10–20% yields; See Ref. 10e and Sugiyama, S.; Honda, M.; Komori, T. *Liebigs Ann. Chem.* **1990**, 1063.