Synthesis of Ceramide Analogues Having the C(4)−C(5) Bond of the Long-Chain Base as Part of an Aromatic or Heteroaromatic System

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Two efficient and stereoselective methods are described for the preparation of aryl and heteroaryl ceramide analogues **2** and **3**. The first route involves the addition of an aryllithium or a heteroaryllithium reagent (**7a** or **25a**, respectively) to the L-serine-derived aldehyde **4**, followed by hydrolysis of the oxazolidine, liberation of the amino group, and *N*-acylation. The second route, which was used to prepare arylceramide analogue **2** in eight steps and 28% overall yield starting with 3-bromobenzaldehyde, utilizes a Heck reaction to afford (*E*)-α,*β*-unsaturated ester **16**, then osmium-catalyzed asymmetric dihydroxylation for the introduction of the desired chirality at C-2 and C-3. Regioselective α-azidation of α-*O*-nosyl-*β*-hydroxyester **18** with sodium azide, followed by $LiAlH_4$ reduction of the azido and ester groups and *N*-acylation, complete the synthesis of arylceramide analogue **2**.

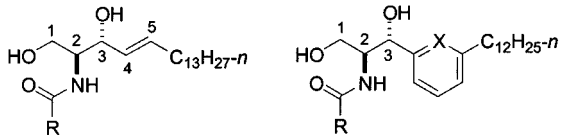
Introduction

Ceramide (*N*-acylsphingosine, **1**) is a long-chain aliphatic 2-amido-1,3-diol with a C(4),C(5)-trans double bond; the predominant long-chain base found in mammalian cells has 18 carbons (Chart 1).[1] Ceramide is an important signaling molecule that has been implicated in a myriad of physiological events, including the regulation of cell growth and differentiation, inflammation, and apotosis.[2] The mechanisms by which ceramide regulates cellular functions involve its ability to stimulate kinases and protein phosphatases.[2]

Ceramide is one of the major lipid components of human skin. It comprises about 35% of the total lipids in human stratum corneum (the apical skin layer).[3] Its role in normal skin tissue function includes maintenance of the permeability barrier and water-binding properties of the outer layer.[4]

Ceramides are the minimally required sphingolipids for activation of membrane fusion of Semliki Forest virus (SFV).[5] The C(4)−C(5) trans double bond in the sphingoid base of naturally occurring **1** may be crucial for ceramide's capacity to modulate various fundamental biological functions.[6] Indeed, it was shown very recently that an unnatural ceramide analogue having a trans C(5)−C(6) double bond is unable to support fusion of SFV.[7] To obtain more information about viral fusion at the molecular level, we set out to prepare a series of new ceramide analogues in which unsaturated functional groups are incorporated. In the present study, the C(4)−C(5) double bond of the long-chain base was incorporated into an aromatic ring such as benzene and pyridine (Chart 1, compounds **2** and **3**). These analogues will allow us to test whether a C(4)−C(5)-double bond that is part of an aromatic or heteroaromatic system can substitute for the aliphatic double bond in the long-chain base of **1** in the activation of fusion of SFV with target membranes.

Chart 1



1 **2** X = CH, R = *n*-$C_{15}H_{31}$ **3** X = N, R = *n*-C_3H_7

Results and Discussion

Synthesis of Arylceramide Analogue 2. The development of new methods for the synthesis of sphingosine and its stereoisomers has been an active field of research.[8] In 1988, Garner and co-workers used L-serine aldehyde **4** ("Garner aldehyde," which is prepared from L-(*N*-Boc) serine methyl ester) for the synthesis of

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(1) Karlsson, K.-A. *Chem. Phys. Lipids* **1970**, *5*, 6−43.

(2) (a) Hannun, Y. A. *Science* **1996**, *274*, 1855−1859. (b) Ariga, T.; Jarvis, W. D.; Yu, R. K. *J. Lipid Res.* **1998**, *39*, 1−16. (c) Mathias, S.; Peña, L. A.; Kolesnick, R. N. *Biochem. J.* **1998**, *335*, 465−480. (d) Perry, D. K.; Hannun, Y. A. *Biochim. Biophys. Acta* **1998**, *1436*, 233−243.

(3) (a) Lampe, M. A.; Burlingame, A. L.; Whitney, J.; Williams, M. L.; Brown, B. E.; Roitman, E.; Elias, P. M. *J. Lipid Res.* **1983**, *24*, 120−130. (b) Downing, D. T. *J. Lipid Res.* **1992**, *33*, 301−313. (c) Wertz, P. W.; Kremer, M.; Squier, C. A. *J. Invest. Dermatol.* **1992**, *98*, 375−378. (d) Gildenast, T.; Lasch, J. *Biochim. Biophys. Acta* **1997**, *1346*, 69−74.

(4) (a) Scheuplein, R. J.; Blank, I. H. *Physiol. Rev.* **1971**, *51*, 702−747. (b) Long, S. A.; Wertz, P. W.; Strauss, J. S.; Downing, D. T. *Arch. Dermatol. Res.* **1985**, *277*, 284−287.

(5) (a) Nieva, J. L.; Bron, R.; Corver, J.; Wilschut, J. *EMBO J.* **1994**, *13*, 2797−2804. (b) Wilschut, J.; Nieva, J. L.; Bron, R.; Moesby, L.; Reddy, K. C.; Bittman, R. *Mol. Membr. Biol.* **1995**, *12*, 143−149.

(6) Corver, J.; Moesby, L.; Erukulla, R. K.; Reddy, K. C.; Bittman, R.; Wilschut, J. *J. Virol.* **1995**, *69*, 3220−3223.

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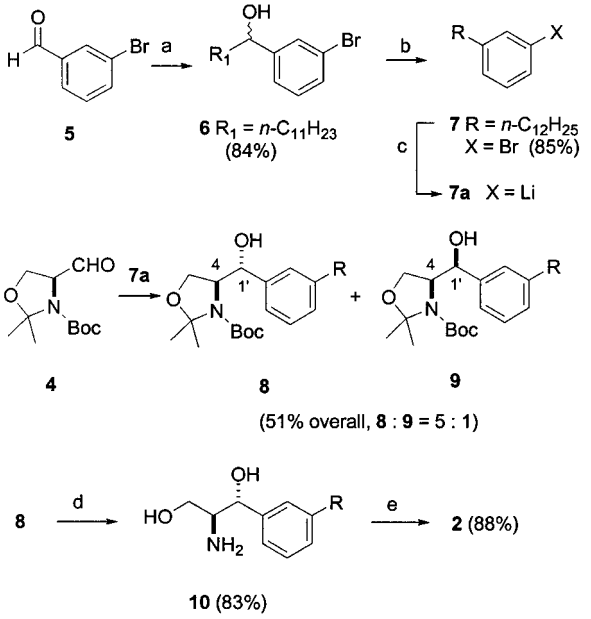
Scheme 1. Synthesis of Ceramide Analogue 2[a]



[a] Reagents and conditions: (a) n-$C_{11}H_{23}MgBr$, THF, 0 °C; (b) Me_3SiCl, NaI, MeCN, hexane, rt; (c) n-BuLi, THF, −42 °C; (d) 1 M HCl, THF, 70 °C; (e) p-$O_2NC_6H_4CO_2C_{15}H_{31}$-$n$, THF, rt.

sphingosine.[9a] One of the routes used in the present work started with Garner aldehyde **4** as the chiral synthon to prepare the target compounds **2** and **3**. In this route, the stereochemistry at C-2 of the target ceramide analogue is introduced from the L-serine-derived aldehyde **4**. Our approach to **2**, which represents an analogue of natural ceramide (**1**) in which the aliphatic trans double bond is incorporated into a benzene ring, is shown in Scheme 1. Reaction of 3-bromobenzaldehyde **5** with undecylmagnesium bromide in THF at 0 °C gave benzylic alcohol **6**, which was reduced by using chlorotrimethylsilane in the presence of sodium iodide in acetonitrile-hexane to yield aryl bromide **7**.[10] The latter was lithiated (n-BuLi, THF, −42 °C) and reacted with aldehyde **4** to give a mixture of *erythro*-**8** and *threo*-**9** in 51% overall yield. The ratio of **8**:**9** was found to be 5:1 by high-temperature ^1H NMR spectroscopy.[11] Addition of 2 equiv of HMPA[12] did not improve the diastereoselectivity significantly. After diastereomers **8** and **9** were separated chromatographically,[13] acid hydrolysis of **8** (1 M HCl in THF, 70 °C) provided D-*erythro*-sphingosine **10**. Ceramide analogue **2** was obtained by N-acylation of sphingosine **10** with p-nitrophenyl palmitate.

Scheme 2. Oxidation and Diastereoselective Reduction

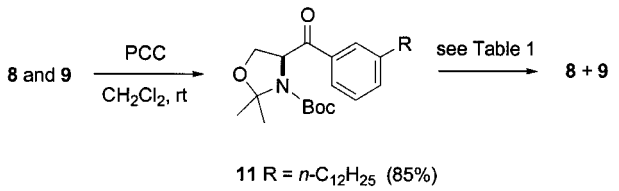


Table 1. Diastereoselective Reduction of 11

11 —(See Scheme 2)→ 8 + 9

reducing agent	solvent	T (°C)	time (h)	overall yield (%)	ratio (**8**:**9**)
DIBAL	THF	0	0.5	94	26:1
$NaBH_4$	MeOH	0 to rt	2	90	1.0:3.2
$LiBH_4$	MeOH	0 to rt	2	93	1.0:2.9
Red-Al	toluene	0	2	92	1.0:2.3

Diastereoselective Reduction of L-(*N*-Boc)-oxazolidine Ketone 11. Scheme 2 outlines an improved chirospecific route to **2**. For induction of stereochemistry at C-3 of the target ceramide analogue, ketone **11** was prepared by PCC oxidation of a mixture of **8** and **9**, and several reducing agents were screened for attempted diastereoselective reduction. As shown in Table 1, high erythro selectivity was observed with DIBAL, which gave *erythro*-**8**/*threo*-**9** in a ratio of 26:1. However, the undesired threo diastereomer was formed as the major product with the other reducing agents we used. $LiBH_4$ and $NaBH_4$ gave a ∼3:1 ratio of threo/erythro isomers; Red-Al also resulted in threo selectivity (**9**:**8**, 2.3:1.0 ratio), in agreement with previous studies on the reduction of a ketone linked to an *N*-Boc-protected oxazolidine.[8e,15]

Stereochemistry at C(3) of Ceramide Analogue 2. To establish the configurations of **8** and **9**, we converted **8** to the corresponding acetonide **13** in two steps (Scheme 3).[14,16] First, the oxazolidine group was removed by treatment with an acidic resin (Amberlyst 15) in methanol, forming **12**; then, acetalization (2,2-dimethoxypropane, PPTS, CH_2Cl_2) afforded **13**. Since the protons on C(4) and C(5) occupy the axial position in the chair conformation of **13**, erythro derivative **13** is expected to have a larger coupling constant ($J_{4,5}$ ∼10 Hz) than threo derivative **15** ($J_{4,5}$ ∼1−3 Hz).[14] The configurations of **13** and **15** were confirmed by their coupling constants ($J_{4,5}$ = 9.3 Hz in **13** and $J_{4,5}$ = 1.3 Hz in **15**).

Conversion of 3-Bromobenzaldehyde (5) to 2. Scheme 4 outlines our second route to arylceramide

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(9) (a) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395−4398. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364. (c) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18−27.

(10) (a) For dehydroxylation with Me_3SiCl−NaI-MeCN, see: Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1987**, *28*, 3817−3818, and references therein. (b) Selective dehydroxylation of **6** was also attempted with: (i) palladium-catalyzed hydrogenolysis (H_2/10% Pd/C in EtOH); (ii) Wolff−Kishner reduction of the corresponding ketone of **6**. However, with H_2/10% Pd/C, both the hydroxyl group and the bromine in **6** were removed. The reproducibility of the Wolff−Kishner reaction was poor, with a maximum yield of 56%.

(11) The ratio of **8**:**9** was determined by 400-MHz ^1H NMR (C_6D_6 at 60 °C): C(1′)−H; δ 5.10 (br s) for **8**, δ 4.92 (d, J = 7.8 Hz) for **9**.

(12) Herold[14] found that the reaction of 1-pentadecyllithium with aldehyde **4** at −78 °C produced high erythro stereoselectivity when HMPA was used as the cosolvent. HMPA competes effectively with the *N*-Boc group for coordination to the metal ion; a nonchelated Felkin-Ahn model can rationalize attack of the alkynyl anion at the less-hindered *re* face of aldehyde **4**, leading to D-erythro product.[8d] However, we noted only a slight effect on the diastereoselectivity when HMPA was added as a cosolvent (ratio of **8**:**9**, 5.7:1.0).

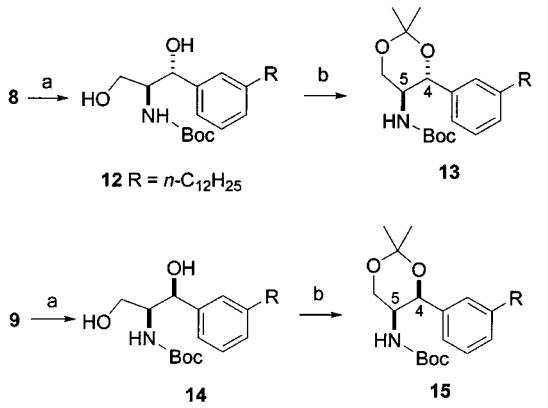
(13) TLC analysis (Merck silica gel 60F-254, developed with 1:4 EtOAc/hexane) showed the formation of **8** (R_f 0.54) and **9** (R_f 0.48).

(14) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354−362.

(15) Nishida, A.; Sorimachi, H.; Iwaida, M.; Matsumizu, M.; Kawate, T.; Nakagawa, M. *Synlett* **1998**, *4*, 389−390.

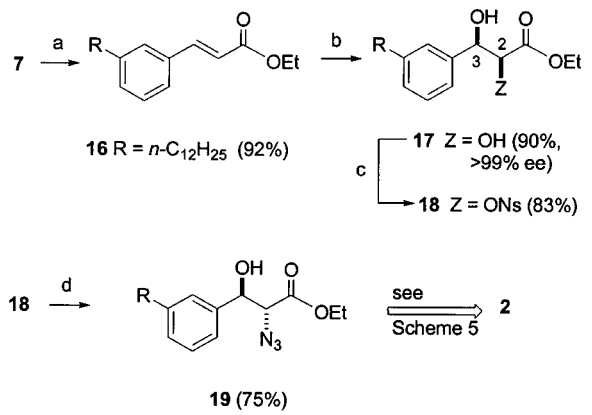
(16) Van Overmeire, I.; Boldin, S. A.; Dumont, F.; Van Calenbergh, S.; Slegers, G.; De Keukeleire, D.; Futerman, A. H.; Herdewijn, P. *J. Med. Chem.* **1999**, *42*, 2697−2705.

Scheme 3. Synthesis of Acetonides 13 and 15[a]



[a] Reagents and conditions: (a) Amberlyst 15, MeOH, rt; (b) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt.

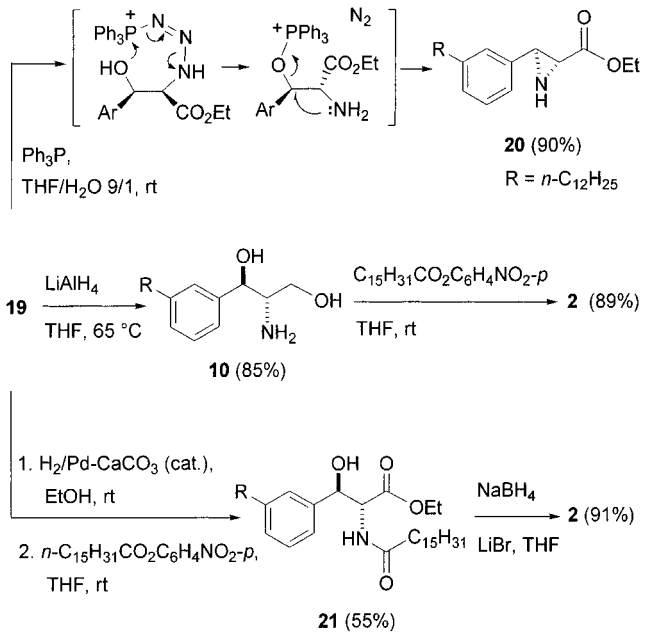
Scheme 4. Preparation of α-Azido Ester 19[a]



[a] Reagents and conditions: (a) $CH_2{=}CHCO_2Et$, $(Ph_3P)_4Pd(0)$, Et_3N, DMF, 120 °C; (b) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O 1/1, rt; (c) *p*-$O_2NC_6H_4SO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; (d) NaN_3, DMF, 55 °C.

analogue **2**, i.e., via a Heck reaction[17] to provide the desired α,*β*-unsaturated ester **16**. Reaction of *m*-bromododecylbenzene **7** with ethyl acrylate in the presence of a catalytic amount of tetrakis(triphenylphosphine)Pd(0) at 120 °C afforded cinnamate derivative **16** in high yield (92%). Sharpless asymmetric dihydroxylation[18] of **16** provided diol ester **17** in 90% yield and >99% ee.[19] Regioselective α-azidation of diol ester **17** was achieved via nosylate intermediate **18**. The selectivity of the mononosylation reaction at C-2 of diol **17** may arise because of intramolecular hydrogen bonding between the C-3 hydroxy group and the carbonyl group[20a] or the difference in acidity of the two hydroxy groups.[20b] The desired 3-hydroxy-2-nosylate **18** was obtained in 83% yield, together with a small amount of α,*β*-unsaturated byproduct (generated when the α,*β*-dinosylate intermediate undergoes elimination).[20b] No *β*-mononosylate was detected by TLC and NMR. Nucleophilic substitution of nosylate **18** with NaN_3 in DMF at 55 °C furnished the desired azido ester **19** in 75% yield.[21]

Scheme 5. Syntheses of Aryl-Substituted Ceramide Analogue 2 and the Corresponding Sphingosine Analogue 10



Synthesis of Heteroarylceramide Analogue 3. Compound **3** represents an analogue of natural ceramide in which the trans double bond is incorporated into a

(17) For reviews of the Heck reaction, see: (a) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371−7393. (b) Heck, R. F. In *Palladium Reagents in Organic Synthesis;* Academic: New York, 1985. (c) de Meijere, A.; Meger, F. E. *Angew. Chem., Intl. Ed. Engl.* **1994**, *33*, 2379−2411. (d) Bräse, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; pp 99−166. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

(18) For an optimized reaction procedure of an asymmetric dihydroxylation reaction, see: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771.

(19) The enantiomeric excess (ee) was determined by ^1H NMR analysis of the corresponding bis-Mosher esters derived from diol (−)-**17** and its enantiomer (+)-**17**.

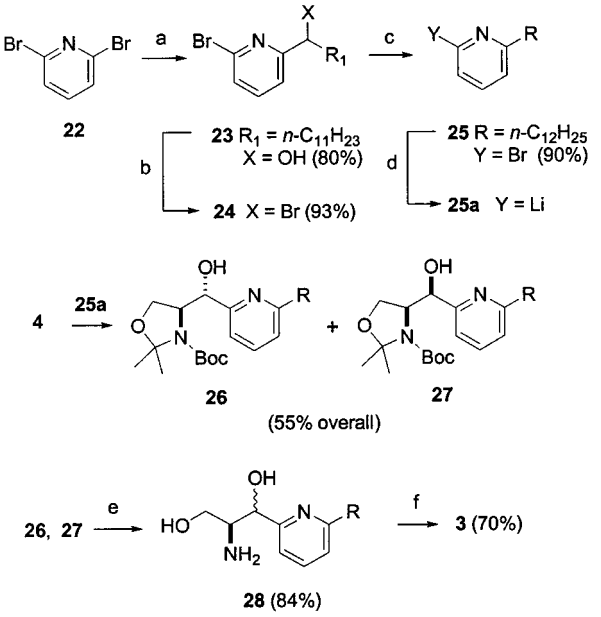
(20) (a) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957−1959. (b) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869−2875.

(21) It has been reported that such a substitution reaction is stereospecific in DMF but not in DMSO.[20b]

(22) For a review about the Staudinger reaction, see: Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437−472.

(23) For a review of the Mitsunobu reaction, see: Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.

Scheme 6. Synthesis of Ceramide Analogue 3[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C, (ii) n-$C_{11}H_{23}CHO$, −78 °C to rt; (b) NBS, Ph_3P, CH_2Cl_2, 0 °C to rt; (c) $NaBH_4$, DMSO, rt; (d) *n*-BuLi, THF, −78 °C; (e) 1 M HCl, THF, 70 °C; (f) p-$O_2NC_6H_4CO_2C_3H_7$-*n*, THF, rt.

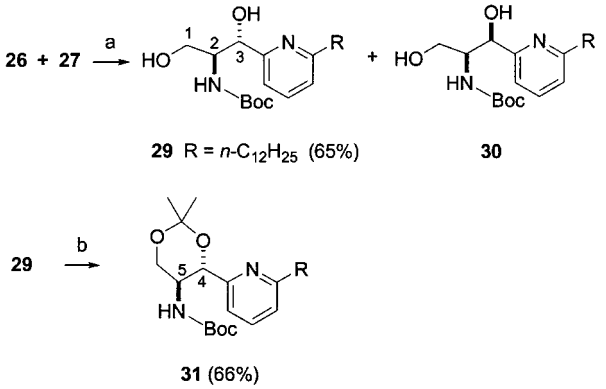
pyridine ring. The synthesis of **3** (Scheme 6) started with commercially available 2,6-dibromopyridine **22**, which was lithiated at −78 °C and reacted with dodecanal to give alcohol **23** in 80% yield. The alcohol was converted to bromide **24** in 93% yield by Mitsunobu reaction. Reduction of the benzylic bromide with sodium borohydride in DMSO provided **25** in 90% yield. Lithiation of **25** followed by reaction with Garner aldehyde **4** gave a mixture of *erythro*-**26** and *threo*-**27**; the ratio of **26**:**27** was estimated to be ∼5:1 by ^{1}H NMR spectroscopy. Diastereoisomers **26** and **27** could not be separated by column chromatography. Hydrolysis of **26** and **27** (1 M HCl, THF, 70 °C, 5 h) resulted in the formation of diastereomeric sphingoid alcohol **28**. Since chromatographic separation of the diastereoisomers at this stage was still difficult, sphingosine analogue **28** was *N*-acylated with *p*-nitrophenyl butyrate. Fortunately, the ceramide diastereoisomers were separated by column chromatography, and the desired D-erythro stereoisomer **3** was obtained in 70% yield.[24]

To establish the configuration at C(3) in **29**, a mixture of **26** and **27** was converted to **29** and **30** (Scheme 7). Careful separation of the diastereomers by column chromatography gave **29** in 65% yield. Conversion of **29** to the corresponding acetonide **31** and NMR analysis ($J_{4,5}$ = 9.6 Hz) confirmed the absolute configuration of **29**.

Experimental Section[25]

Reagents. $LiAlH_4$, $NaBH_4$, Lindlar catalyst, AD-mix-α/β, and *p*-nitrophenyl butyrate were purchased from Sigma-Aldrich. Sodium azide and 2,6-dibromopyridine were purchased from Lancaster and Acros, respectively. Garner aldehyde **4** was prepared from *N*-Boc-L-serine methyl ester as described previously.[9b,c] Mosher esters were prepared as described previously.[26] *p*-Nitrophenyl palmitate was prepared by the reaction of palmitic acid with *p*-nitrophenol in CH_2Cl_2 in the presence of DCC and DMAP. Tetrakis(triphenylphosphine)Pd(0) was prepared according to a reported procedure.[27] NMR spectra were recorded in $CDCl_3$ unless otherwise noted.

Scheme 7. Synthesis of Acetonide 31[a]



[a] Reagents and conditions: (a) Amberlyst 15, MeOH, rt; (b) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt.

1-(3′-Bromophenyl)-1-dodecanol (6). A suspension of 0.48 g (20 mmol) of magnesium powder in 15 mL of dry THF was treated dropwise with a solution of 5.0 g (21 mmol) of 1-bromoundecane in 20 mL of dry THF under argon atmosphere at room temperature. The reaction mixture was stirred until almost all of the magnesium metal reacted (∼3 h). After the reaction mixture was chilled to 0 °C, a solution of 1.9 g (10 mmol) of 3-bromobenzaldehyde in 20 mL of THF was added dropwise over 10 min. The reaction mixture was stirred at 0 °C for 3 h, and then poured into 20 mL of ice-cold 1 M HCl solution. The product was extracted with Et_2O (3 × 40 mL). The combined organic phase was washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (hexane/EtOAc 4:1) gave 2.84 g (84%) of the desired alcohol **6** as a low-melting white solid: IR 3601, 3456 cm^{-1}; ^{1}H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.12−1.50 (m, 18H), 1.55−1.90 (m, 2H), 2.30 (s, 1H), 4.56 (t, 1H, J = 5.9 Hz), 7.05−7.24 (m, 2H), 7.30−7.40 (m, 1H), 7.45 (s, 1H); ^{13}C NMR δ 14.08, 22.64, 25.63, 29.30, 29.42, 29.48, 29.54, 29.57, 29.59, 31.87, 39.06, 73.89, 122.47, 124.46, 128.94, 129.90, 130.36, 147.24.

1-Bromo-3-dodecylbenzene (7). To a mixture of Me_3SiCl (1.3 g, 12 mmol), NaI (1.8 g, 12 mmol), and MeCN (0.59 g, 12 mmol) was added a solution of 0.68 g (2.0 mmol) of benzylic alcohol **6** in 2 mL of hexane at room temperature. The reaction mixture was stirred at this temperature under nitrogen until the disappearance of alcohol **6** was noticed by TLC (∼48 h). The reaction mixture was then diluted with 20 mL of water, extracted with hexane (3 × 30 mL), and dried (Na_2SO_4). Concentration gave a liquid residue that was purified by flash chromatography (hexane), giving 0.55 g (85%) of product **7** as a colorless oil: ^{1}H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.10−1.40 (m, 18H), 1.50−1.60 (m, 2H), 2.54 (t, 2H, J = 7.8 Hz), 7.06−7.14 (m, 2H), 7.23−7.31 (m, 2H); ^{13}C NMR δ 14.13, 22.69, 29.21, 29.35, 29.45, 29.55, 29.64, 29.66, 31.26, 31.92, 35.63, 122.29, 127.06, 128.65, 129.75, 131.42, 145.29.

***N*-*tert*-Butoxycarbonyl (4*S*)-4-[1′-(3″-Dodecylphenyl)-hydroxymethyl]-2,2-dimethyl-1,3-oxazolidine (8, 9).** To a solution of 0.39 g (1.2 mmol) of **7** in 10 mL of dry THF at −42 °C was added 0.5 mL (1.25 mmol) of *n*-BuLi (a 2.5 M solution in hexane) dropwise under argon atmosphere. After the mixture was stirred for 1 h, a solution of 0.23 g (1.0 mmol) of aldehyde **4** in 5 mL of dry THF was added dropwise over a 5-min period. The mixture was stirred at −42 °C for 3 h. The reaction was quenched by addition of aqueous saturated $NaHCO_3$ solution (5 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 15 mL).

(24) The ratio of **3** to its threo diastereoisomer was ∼5: 1.

(25) General experimental details have been described; see ref 7.

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The combined organic phase was washed twice with brine, dried ($MgSO_4$), and evaporated. Column chromatography (hexane/EtOAc 4:1) gave 242 mg (51%) of a mixture of **8** and **9**.[11] Pure **8** and **9** were obtained by chromatography (hexane/EtOAc 4:1) by gravity on multiple columns.[13] **8**: $[\alpha]^{25}_D$ −11.3° (*c* 10.9, $CHCl_3$); IR 3613, 3366, 1690 1390, 1167 cm^{-1}; ^1H NMR (C_6D_6, 60 °C) δ 0.88 (t, 3H, J = 6.7 Hz), 1.10−1.80 (m, 35H), 2.55 (t, 2H, J = 7.7 Hz), 3.52 (t, 1H, J = 8.9 Hz), 3.97 (d, 1H, J = 8.9 Hz), 4.11 (br s, 1H), 5.10 (br s, 1H), 6.99 (d, 1H, J = 7.2 Hz), 7.15 (t, 1H, J = 7.7 Hz), 7.23 (d, 1H, J = 7.5 Hz), 7.31 (s, 1H). **9**: ^1H NMR (C_6D_6, 60 °C) δ 0.90 (t, 3H, J = 5.5 Hz), 1.10−1.80 (m, 35H), 2.53 (t, 2H, J = 7.7 Hz), 3.46 (t, 1H, J = 7.8 Hz), 3.74 (d, 1H, J = 8.9 Hz), 4.19 (br s, 1H), 4.92 (d, 1H, J = 7.8 Hz), 7.02 (d, 1H, J = 7.3 Hz), 7.15 (1H, overlap with C_6H_6 peak), 7.22 (d, 1H, J = 7.5 Hz), 7.30 (s, 1H).

(2*S*,3*R*)-3-(3′-Dodecylphenyl)-2-aminopropane-1,3-diol [(−)-10]. Method A (Scheme 1). A solution of 48 mg (1.0 mmol) of **8** in 3 mL of 1 M HCl and 3 mL of THF was heated at 70 °C with stirring for 5 h under argon. The reaction mixture was cooled to room temperature, and neutralized with 1 M NaOH (3 mL). The product was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine and dried (Na_2SO_4). Flash chromatography ($CHCl_3$/MeOH/concd NH_4OH 130:25:4) gave 28 mg (83%) of sphingosine analogue **10** as a white solid: mp 55.2−56.2 °C. **Method B (Scheme 5).** To an ice-cooled suspension of 57 mg (1.5 mmol) of $LiAlH_4$ in 15 mL of dry THF under nitrogen was injected a solution of 101 mg (0.25 mmol) of azido ester **19** in 4 mL of THF. The reaction mixture was stirred at room temperature for 2 h and then at 65 °C until the full consumption of the azido ester was noticed by TLC (∼2 h). After being chilled to 0 °C, the reaction mixture was filtered through a pad of silica gel in a sintered glass funnel to remove the salt and the excess $LiAlH_4$.[28] The pad was washed with $CHCl_3$/MeOH/concd NH_4OH 130:25:4 to collect the product. After concentration, the residue was purified by flash chromatography ($CHCl_3$/MeOH/concd NH_4OH 130:25:4). A solution of the product in $CHCl_3$ was passed through a Cameo filter (Fisher Scientific) to remove the dissolved silica gel. Concentration gave 71 mg (85%) of **10** as a white solid: mp 55.0−56.0 °C; $[\alpha]^{25}_D$ −22.0° (*c* 3.4, $CHCl_3$); IR 3609, 3383, 1604, 1462, 1233, 1035, 893 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.10−1.32 (m, 18H), 1.56 (m, 2H), 2.56 (t, 2H, J = 7.9 Hz), 2.79 (br s, 4H), 2.98 (dt, 1H, J = 6.1, 5.1 Hz), 3.62 (m, 2H), 4.58 (d, 1H, J = 6.1 Hz), 7.08 (m, 3H), 7.21 (t, 1H, J = 7.5 Hz); ^{13}C NMR δ 14.07, 22.65, 29.32, 29.42, 29.48, 29.59, 29.62, 29.65, 31.52, 31.88, 35.97, 57.22, 63.50, 76.45, 123.66, 126.37, 127.88, 128.38, 141.51, 143.32.

(2*S*,3*R*)-3-(3′-Dodecylphenyl)-2-palmitoylamidopropane-1,3-diol [(−)-2]. To a solution of 30 mg (0.09 mmol) of **10** in 3 mL of dry THF was added 68 mg (0.18 mmol) of *p*-nitrophenyl palmitate at room temperature. The mixture was stirred for 48 h and then concentrated under reduced pressure. Purification by flash chromatography ($CHCl_3$/MeOH 9:1) afforded 45 mg (88%) of **2** as a white solid: mp 92.1−92.8 °C; $[\alpha]^{25}_D$ −5.4° (*c* 1.7, $CHCl_3$); IR 3599, 3429, 1655, 1500 cm^{-1}; ^1H NMR δ 0.86 (t, 6H, J = 7.0 Hz), 1.23 (m, 42H), 1.58 (m, 4H), 2.19 (t, 2H, J = 7.8 Hz), 2.57 (t, 2H, J = 7.9 Hz), 2.77 (br s, 1H), 3.57 (dd, 1H, J = 11.5, 3.5 Hz), 3.79 (dd, 1H, J = 11.5, 3.3 Hz), 4.04 (m, 1H), 4.99 (d, 1H, J = 3.6 Hz), 6.32 (d, 1H, J = 7.8 Hz), 7.08 (d, 1H, J = 7.4 Hz), 7.17 (s, 1H), 7.17 (d, 1H, J = 6.6 Hz), 7.24 (t, 1H, J = 7.5 Hz); ^{13}C NMR δ 14.09, 22.67, 25.71, 29.28, 29.35, 29.37, 29.43, 29.51, 29.61, 29.64, 29.67, 29.69, 31.60, 31.91, 36.01, 36.82, 55.46, 61.74, 76.05, 122.99, 125.83, 127.93, 128.46, 140.79, 143.42, 173.98; HR-MS (DCI, MH^+) *m/z* calcd for $C_{37}H_{68}NO_3$ 574.5199, found 574.5187.

***N*-*tert*-Butoxycarbonyl (4*S*)-4-(3′-Dodecylbenzoyl)-2,2-dimethyl-1,3-oxazolidine [(−)-11].** To a mixture of 0.48 g (1.0 mmol) of **8** and **9** in 15 mL of CH_2Cl_2 was added 0.43 g (2.0 mmol) of PCC. The reaction mixture was stirred at room temperature for 5 h. The mixture was filtered through a pad of silica gel, which was washed with CH_2Cl_2, and the solvent was evaporated. Flash chromatography (hexane/EtOAc 9:1) of the residue afforded 0.41 g (85%) of ketone **11** as a white solid: mp 60.0−61.0 °C; $[\alpha]^{25}_D$ −42.0° (*c* 3.1, $CHCl_3$); IR 1702, 1390, 1243, 1173 cm^{-1}; ^1H NMR[29] (C_6D_6) δ 0.90 (t, 3H, J = 6.5 Hz), 1.10−1.50 (m, 29H), 1.55 and 1.72 (two sets of s, 3H), 1.92 and 2.04 (two sets of s, 3H), 2.36 (m, 2H), 3.66 (two sets of m, 2H), 5.08 (dd, 0.67H, J = 7.6, 3.7 Hz), 5.32 (dd, 0.33H, J = 7.3, 3.0 Hz), 7.06 (m, 2H), 7.50 (d, 0.67H, J = 7.3 Hz), 7.55 (d, 0.33H, J = 7.5 Hz), 7.81 (s, 1H); ^{13}C NMR (C_6D_6) δ 14.34, 23.08, 25.04, 25.21, 25.89, 26.32, 28.29, 28.35, 29.56, 29.62, 29.79, 29.85, 30.00, 30.08, 30.10, 31.62, 31.68, 32.30, 36.01, 62.07, 62.39, 65.75, 66.11, 79.63, 79.99, 94.51, 95.48, 125.86, 126.10, 128.68, 128.83, 133.21, 133.46, 135.91, 135.96, 143.70, 143.92, 151.47, 152.00, 195.15, 195.61.

DIBALH Reduction of Ketone 11. To a solution of 0.10 g (0.21 mmol) of ketone **11** in dry THF (10 mL) was added, dropwise, ∼0.60 mL (∼0.90 mmol) of DIBALH (a 1.5 M solution in toluene) at 0 °C under argon atmosphere. The rate of addition was very slow to maintain the low temperature. The reaction mixture was stirred for 0.5 h at 0 °C until TLC analysis showed the reaction to be complete. The reaction was quenched by slow addition of 0.5 mL of MeOH followed by 5.0 mL of cold 5% aqueous potassium sodium tartrate solution. The product was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (hexane/EtOAc 4:1) gave 94 mg (94%) of **8** and **9** in a ratio of 26:1.

(2*S*,3*R*)-3-(3′-Dodecylphenyl)-2-*tert*-butoxycarbonylaminopropane-1,3-diol [(−)-12]. To a solution of 0.10 g (0.21 mmol) of **8** in 5 mL of MeOH was added 0.15 g of Amberlyst 15, and the heterogeneous mixture was stirred at room temperature for 48 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated. Flash chromatography ($CHCl_3$/MeOH 9:1) of the residue afforded 73 mg (80%) of **12** as a white solid: mp 76.5−77.5 °C; $[\alpha]^{25}_D$ −5.8° (*c* 5.5, $CHCl_3$); IR 3612, 3436, 1699, 1496 cm^{-1}; ^1H NMR (C_6D_6) δ 0.86 (t, 3H, J = 8.0 Hz), 1.10−1.50 (m, 29H), 1.59 (s, 2H), 2.54 (t, 2H, J = 8.0 Hz), 3.58 (d, 1H, J = 6.6 Hz), 3.63 (s, 1H), 3.82 (d, 1H, J = 10.3 Hz), 3.98 (d, 1H, J = 3.4 Hz), 4.20 (d, 1H, J = 4.4 Hz), 5.03 (t, 1H, J = 4.7 Hz), 5.58 (d, 1H, J = 8.3 Hz), 7.01 (d, 1H, J = 7.3 Hz), 7.15−7.40 (m, 3H); ^{13}C NMR (C_6D_6) δ 14.36, 23.07, 28.45, 29.81, 29.89, 30.02, 30.12, 30.16, 32.09, 32.32, 36.44, 57.32, 62.03, 75.82, 79.38, 124.00, 126.68, 127.89, 128.12, 128.53, 142.01, 143.09, 156.48.

(4*R*,5*S*)-5-*tert*-Butoxycarbonylamino-4-(3′-dodecylphenyl)-2,2-dimethyl-1,3-dioxane [(+)-13]. To a solution of 43 mg (0.10 mmol) of **12** and 100 mg (1.0 mmol) of 2,2-dimethoxypropane in dry 5 mL of CH_2Cl_2 was added 25 mg (0.10 mmol) of PPTS. The mixture was stirred for ∼48 h at room temperature, concentrated under reduced pressure, and purified by flash chromatography (hexane/EtOAc 4:1), yielding 32 mg (67%) of **13** as a white solid: mp 68.2−69.6 °C; $[\alpha]^{25}_D$ +10.9° (*c* 7.9, $CHCl_3$); IR 3436, 1701, 1496, 1366, 1243, 1161 cm^{-1}; ^1H NMR (C_6D_6) δ 0.88 (m, 3H), 1.10−1.0 (m, 37H), 2.53 (t, 2H, J = 7.6 Hz), 3.60 (br s, 1H), 3.70−4.00 (m, 2H), 4.90 (d, 1H, $J_{4,5}$ = 9.3 Hz), 7.10−7.50 (m, 4H); ^{13}C NMR (C_6D_6) δ14.34, 19.45, 23.09, 28.28, 29.37, 29.80, 29.98, 30.06, 30.09, 30.13, 32.05, 32.30, 36.42, 51.48, 63.09, 74.68, 78.82, 99.00, 125.26, 127.89, 128.30, 139.94, 142.91, 154.86.

Ethyl *m*-Dodecylcinnamate (16). A solution of 1.0 g (3.1 mmol) of bromide **7**, 0.60 g (6.0 mmol) of ethyl acrylate, 0.60 g (6.0 mmol) of Et_3N, and 30 mg (26 μmol) of $(Ph_3P)_4Pd(0)$ in 10 mL of DMF was stirred at 120 °C under argon atmosphere for 6 h. After the reaction mixture was allowed to cool to room temperature, 15 mL of aqueous 1 M HCl solution was added, and stirring was continued for 5 min. The product was extracted with Et_2O (3 × 30 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (hexane/EtOAc 9:1) yielded 0.98 g

(28) For a note about this workup method, see: He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7618−7626.

(29) The oxazolidine system undergoes a dynamic equilibrium at ambient temperature.[9b,c]

(92%) of cinnamate derivative **16** as a colorless oil: IR 1704, 1637 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, $J = 7.0$ Hz), 1.10−1.40 (m, 21H), 1.50−1.70 (m, 2H), 2.59 (t, 2H, $J = 7.8$ Hz), 4.25 (q, 2H, $J = 7.1$ Hz), 6.41 (d, 1H, $J = 16.0$ Hz), 7.17 (d, 1H, $J = 7.4$ Hz), 7.26 (t, 1H, $J = 7.5$ Hz), 7.30 (s, 1H), 7.32 (d, 1H, $J = 7.4$ Hz), 7.65 (d, 1H, $J = 16.0$ Hz); ^{13}C NMR δ 14.14, 14.33, 22.71, 29.29, 29.37, 29.51, 29.59, 29.67, 31.40, 31.93, 35.65, 35.81, 60.44, 117.94, 125.44, 127.51, 128.12, 128.75, 128.88, 130.48, 134.38, 143.60, 144.91, 167.10; HR-MS (DEI, M^+) *m/z* calcd for $C_{23}H_{36}O_2$ 344.2715, found 344.2709.

Ethyl (2*S*,3*R*)-3-(3′-Dodecylphenyl)-2,3-dihydroxypropionate [(−)-17]. After a solution of 1.4 g of AD-mix-β and 95 mg (1.0 mmol) of $MeSO_2NH_2$ in 30 mL of *t*-BuOH/H_2O 1/1 was stirred vigorously at room temperature for 30 min, 0.35 g (1.0 mmol) of α,β-unsaturated ester **16** was added. The reaction mixture was stirred vigorously until the disappearance of the α,β-unsaturated ester was noted. Sodium sulfite (1.50 g, 1.46 mmol) was added to quench the reaction. Stirring was continued for another 30 min. The product was extracted with EtOAc (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a yellow solid residue, which was dissolved in minimum volume of EtOAc and passed through a pad of silica gel in a sintered glass funnel to remove the ligand. The pad was washed with hexane/EtOAc 2:1 to collect the product. Concentration of the filtrate provided an almost pure product, which was purified by column chromatography (hexane/EtOAc 2:1), giving 0.34 g (90%) of diol **17** as a white solid: mp 49.0−49.5 °C. Compound (−)-**17** was formed in >99% ee, as estimated by ^1H NMR analysis of the Mosher esters[26] derived from both enantiomers; (+)-**17** was prepared by reaction of **16** with AD-mix-α: $[\alpha]^{25}_D$ −4.4° (*c* 2.3, $CHCl_3$); IR 3549, 1725 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, $J = 7.0$ Hz), 1.16−1.31 (m, 21H), 1.58 (m, 2H), 2.58 (t, 2H, $J = 8.0$ Hz), 2.83 (br s, 2H), 4.21 (dq, 2H, $J = 7.3, 1.3$ Hz), 4.31 (d, 1H, $J = 3.1$ Hz), 4.94 (d, 1H, $J = 3.1$ Hz), 7.10 (d, 1H, $J = 7.4$ Hz), 7.18 (m, 2H), 7.23 (m, 1H); ^{13}C NMR δ 14.02, 14.09, 22.65, 29.32, 29.37, 29.48, 29.57, 29.61, 29.64, 31.50, 31.88, 35.97, 62.06, 74.62, 74.74, 123.46, 126.26, 128.07, 128.26, 139.79, 143.13, 172.76; HR-MS [DCI, MNH_4+] *m/z* calcd for $C_{23}H_{42}NO_4$ 396.3114, found 396.3120.

Ethyl (2*S*,3*R*)-3-(3′-Dodecylphenyl)-2-nosyloxy-3-hydroxypropionate [(−)-18]. To an ice-cooled solution of 0.38 g (1.0 mmol) of diol ester **17** in 25 mL of CH_2Cl_2 was added 0.51 g (5.0 mmol) of Et_3N, followed by 0.26 g (1.2 mmol) of 4-nitrobenzenesulfonyl chloride. The yellow solution was stirred at 0 °C under argon until the full consumption of diol ester **17** was observed (TLC). Methanol (0.5 mL) was added to quench the reaction. After the solvents were removed under reduced pressure, the yellow residue was purified by column chromatography (hexane/EtOAc 3:1), giving 0.47 g (83%) of α-nosylate ester **18** as a pale yellow oil: $[\alpha]^{25}_D$ −37.8° (*c* 1.93, $CHCl_3$); IR 3606, 1745, 1536 cm^{-1}; ^1H NMR δ 0.85 (t, 3H, $J =$ 7.5 Hz), 1.17 (t, 3H, $J = 7.2$ Hz), 1.24 (m, 19H), 1.49 (m, 2H), 2.45 (t, 2H, $J = 8.0$ Hz), 4.16 (t, 2H, $J = 7.2$ Hz), 4.98 (d, 1H, $J = 3.8$ Hz), 5.16 (d, 1H, $J = 3.8$ Hz), 6.95−7.20 (m, 5H), 7.76 (d, 2H, $J = 7.0$ Hz), 8.15 (d, 2H, $J = 7.0$ Hz); ^{13}C NMR δ 13.74, 14.02, 22.58, 29.24, 29.28, 29.37, 29.49, 29.53, 29.56, 31.42, 31.80, 35.70, 62.41, 73.34, 82.51, 123.27, 123.95, 125.93, 128.36, 128.38, 128.87, 137.37, 141.21, 143.31, 150.32, 166.50; HR-MS (DCI, MNH_4^+) calcd for *m/z* $C_{29}H_{45}N_2O_8S$ 581.2897, found 581.2872.

Ethyl (2*R*,3*R*)-3-(3′-Dodecylphenyl)-2-azido-3-hydroxypropionate [(+)-19]. A mixture of 0.37 g (0.66 mmol) of nosylate **18** and 0.46 g (7.1 mmol) of NaN_3 in 12 mL of dry DMF was stirred vigorously under argon at 55 °C until TLC analysis indicated that no nosylate was still present. After addition of 30 mL of H_2O, the product was extracted with Et_2O (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (hexane/EtOAc 3:1) to give 0.20 g (75%) of 2-azido derivative **19** as a colorless oil: $[\alpha]^{25}_D$ +6.4° (*c* 1.6, $CHCl_3$); IR 3602, 2116, 1736 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, $J = 7.0$ Hz), 1.23 (m, 21H), 1.57 (m, 2H), 2.59 (t, 2H, $J = 7.9$ Hz), 2.82 (br s, 1H), 4.06 (d, 1H, $J = 7.1$ Hz), 4.22 (q, 2H, $J = 7.1$ Hz), 4.97 (d, 1H, $J = 7.0$ Hz), 7.16 (m, 3H), 7.26 (m, 1H); ^{13}C NMR δ 14.04, 14.11, 22.67, 29.30, 29.34, 29.49, 29.58, 29.62, 29.65, 31.45, 31.90, 35.92, 62.11, 66.69, 74.22, 123.84, 126.59, 128.51, 128.87, 138.81, 143.44, 168.97; HR-MS [DCI, MNH_4^+] *m/z* calcd for $C_{23}H_{41}O_3N_4$ 421.3179, found 421.3186.

***trans*-2-Ethoxycarbonyl-3-(3′-dodecylphenyl)aziridine [(−)-20].** A solution of 49 mg (0.12 mmol) of azide **19** and 65 mg (0.25 mmol) of Ph_3P in 10 mL of THF/H_2O 9:1 was stirred at room-temperature overnight under nitrogen. The solvents were removed and the residue was purified by column chromatography (hexane/EtOAc 4:1) to give 39 mg (90%) of aziridine **20** as a colorless liquid: $[\alpha]^{25}_D$ −141.1° (*c* 1.4, $CHCl_3$); IR 3689, 3283, 1715, 1600, 1222, 1200, 1025 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, $J = 7.0$ Hz), 1.23 (m, 18H), 1.30 (t, 3H, $J = 7.6$ Hz), 1.56 (m, 2H), 1.89 (br s, 1H), 2.55 (t, 2H, $J = 7.7$ Hz), 2.58 (s, 1H), 3.20 (d, 1H, $J = 2.0$ Hz), 4.23 (m, 2H), 7.06 (s, 1H), 7.06 (d, 2H, $J = 6.4$ Hz), 7.20 (t, 1H, $J = 7.6$ Hz); ^{13}C NMR δ 14.11, 14.15, 22.67, 29.33, 29.36, 29.48, 29.56, 29.62, 29.64, 31.49, 31.90, 35.88, 39.41, 40.45, 61.73, 123.49, 125.93, 127.88, 128.29, 137.65, 143.30, 171.75.

Ethyl (2*R*,3*R*)-3-(3′-Dodecylphenyl)-3-hydroxy-2-palmitoylamidopropionate [(−)-21]. To a solution of 49 mg (0.12 mmol) of azido ester **19** in 20 mL of absolute EtOH was added 15 mg of Lindlar catalyst (Pd−$CaCO_3$).[30] The apparatus was evacuated, then flushed with hydrogen from a H_2-filled balloon. The reaction mixture was stirred at room temperature until all of the starting azido ester **19** was consumed (TLC). After the solvent was removed, the residue was further dried under high vacuum (0.7 Torr, 1 h). The residue was dissolved in 10 mL of freshly distilled THF, and 98 mg (0.26 mmol) of *p*-nitrophenyl palmitate was added. The reaction mixture was stirred at room temperature for 60 h under nitrogen. The solvent was removed, and the residue was purified with chromatography (elution first with 100 mL of hexane/EtOAc 20:1, then with hexane/EtOAc 5:1), providing 41 mg (55%) of the desired product **21** as a white solid: mp 69.5−70.4 °C; $[\alpha]^{25}_D$ −25.2° (*c* 1.6, $CHCl_3$); IR 3521, 1728, 1666 cm^{-1}; ^1H NMR δ 0.86 (t, 6H, $J = 7.0$ Hz), 1.18−1.51 (m, 45H), 1.56 (m, 4H), 2.18 (dt, 2H, $J = 7.4, 2.7$ Hz), 2.54 (t, 2H, $J = 7.6$ Hz), 4.17 (q, 2H, $J = 7.2$ Hz), 4.97 (dd, 1H, $J = 6.7, 3.2$ Hz), 5.24 (d, 1H, J = 3.1 Hz), 6.19 (d, 1H, $J = 6.7$ Hz), 6.97 (d, 1H, $J = 7.7$ Hz), 7.01 (s, 1H), 7.06 (d, 1H, $J = 7.6$ Hz), 7.19 (t, 1H, $J = 7.6$ Hz); ^{13}C NMR δ 14.03, 14.11, 22.67, 25.60, 29.20, 29.35, 29.38, 29.45, 29.54, 29.62, 29.65, 29.68, 31.56, 31.91, 36.00, 36.31, 59.29, 62.02, 75.41, 123.12, 125.93, 128.06, 138.97, 142.90, 169.45, 174.92; HR-MS (FAB, MH^+) calcd for *m/z* $C_{39}H_{70}NO_4$ 616.5305, found 616.5305.

2-Bromo-6-(1′-hydroxydodecyl)pyridine (23). To a solution of 1.0 g (4.2 mmol) of 2,6-dibromopyridine (**22**) in 10 mL of dry THF at −78 °C was added 1.9 mL (4.75 mmol) of *n*-BuLi (2.5 M solution in hexane) under argon atmosphere. After the mixture was stirred for 30 min, a solution of 0.80 g (4.3 mmol) of dodecanal in 8 mL of dry THF was added. The mixture was stirred at −78 °C for 1 h, then at room temperature for 1 h. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, and vigorous stirring was maintained for 10 min. The product was extracted with Et_2O (3 × 15 mL), the combined extracts were dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (hexane/EtOAc 7:3) to give 1.15 g (80%) of **23** as a white solid: mp 39.0−40.0 °C; IR 3613, 3460, 1584, 1554, 1437, 1161, 1125 cm^{-1}; ^1H NMR δ 0.82 (t, 3H, $J =$ 7.0 Hz), 0.90−1.50 (m, 18H), 1.50−1.90 (m, 2H), 3.58 (br s, 1H), 4.63 (dd, 1H, $J = 8.0, 4.5$ Hz), 7.21 (d, 1H, $J = 7.6$ Hz), 7.29 (d, 1H, $J = 4.8$ Hz), 7.47 (t, 1H, $J = 7.7$ Hz);^{13}C NMR δ 14.01, 22.57, 25.26, 29.24, 29.43, 29.48, 29.51, 29.54, 31.80, 38.24, 73.10, 118.96, 126.35, 138.83, 140.99, 164.75.

2-Bromo-6-(1′-bromododecyl)pyridine (24). To a solution of 0.34 g (1.0 mmol) of alcohol **23** and 0.31 g (1.2 mmol) of Ph_3P in 15 mL of dry CH_2Cl_2 was added 0.20 g (1.1 mmol) of NBS at 0 °C under argon atmosphere. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with 30 mL of hexane and passed through a pad of silica gel to remove the

(30) Kunesch, G. *Tetrahedron Lett.* **1983**, *24*, 5211−5214.

precipitate of Ph_3PO. Concentration gave 0.38 g (93%) of **24** as a colorless oil. A small sample was purified by flash chromatography (hexane/EtOAc 9:1): ^{1}H NMR δ 0.85 (t, 3H, J = 7.0 Hz), 1.00−1.60 (m, 18H), 2.00−2.30 (m, 2H), 4.93 (dd, 1H, J = 8.2, 6.8 Hz), 7.38 (m, 2H), 7.52 (t, 1H, J = 7.7 Hz);^{13}C NMR δ 14.09, 22.65, 27.85, 28.83, 29.30, 29.32, 29.46, 29.56, 31.87, 38.09, 54.16, 120.96, 127.30, 139.15, 141.16, 161.98.

2-Bromo-6-dodecylpyridine (25). To a solution of 1.12 g (2.77 mmol) of crude **24** in 10 mL of dry DMSO was added 0.63 g (16.6 mmol) of $NaBH_4$ at room temperature under argon atmosphere. After the mixture was stirred at room temperature overnight, the mixture was diluted with 50 mL of Et_2O and washed with brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 9:1) to give 0.81 g (90%) of **25** as a colorless oil: ^{1}H NMR δ 0.83 (t, 3H, J = 7.0 Hz), 1.10−1.40 (m, 18H), 1.60−1.90 (m, 2H), 2.71 (t, 2H, J = 7.9 Hz), 7.05 (d, 1H, J = 7.4 Hz), 7.25 (d, 1H, J = 7.7 Hz), 7.39 (t, 1H, J = 7.7 Hz);^{13}C NMR δ 14.05, 22.62, 29.25, 29.29, 29.37, 29.47, 29.56, 29.60, 29.73, 31.85, 37.97, 121.36, 125.08, 138.48, 141.36, 164.22.

***N*-*tert*-Butoxylcarbonyl (4*S*)-4-[1′-(6″-Dodecylpyridin-2″-yl)-hydroxymethyl]-2,2-dimethyl-1,3-oxazolidine (26, 27).** To a solution of 0.39 g (1.2 mmol) of **25** in 10 mL of dry THF was added 0.5 mL (1.25 mmol) of *n*-BuLi (a 2.5 M solution in hexane) dropwise at −78 °C under argon atmosphere. After the mixture was stirred for 1 h, a solution of 0.23 g (1.0 mmol) of aldehyde **4** in 5 mL of dry THF was added dropwise over a 5-min period. The mixture was stirred at −78 °C for 3 h. The reaction was quenched with aqueous saturated $NaHCO_3$ solution (5 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed twice with brine, dried ($MgSO_4$), and evaporated. Column chromatography (hexane/EtOAc 4:1) gave 0.26 g (55%) of diastereoisomers **26** and **27**, which have very similar R_f values (0.56, hexane/EtOAc 4:1). ^{1}H NMR (C_6D_6, 60 °C) δ 0.90 (t, 3H, J = 7.0 Hz), 1.10−1.93 (m, 37H), 2.68 and 2.69 (two sets of t, 2H, J = 7.0 Hz), 3.66 (dd, 0.83H, J = 9.7, 6.4 Hz), 3.73 (dd, 0.17H, J = 9.3, 6.7 Hz), 4.19−4.40 (m, 1.67H), 4.36 (m, 0.34H), 4.18−5.22 (m, 1H), 6.72 (m, 1H), 6.90−7.20 (m, 2H).

3-(6′-Dodecylpyridin-2′-yl)-2-aminopropane-1,3-diol (28). A solution of 48 mg (1.0 mmol) of **26** and **27** in 3 mL of 1 M HCl and 3 mL of THF was heated at 70 °C under argon with stirring for 5 h. The reaction mixture was cooled to room temperature, and neutralized with 1 M NaOH (3 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine and dried (Na_2SO_4). Flash chromatography ($CHCl_3$/MeOH/concd NH_4OH 130:25:4) gave 28 mg (84%) of diastereomeric sphingosine analogue **28** as a white solid: mp 54.0−56.0 °C; R_f 0.52 ($CHCl_3$/MeOH/concd NH_4OH 130:25:4); ^{1}H NMR δ 0.84 (t, 3H, J = 7.0 Hz), 1.10−1.50 (m, 18H), 1.64 (t, 2H, J = 7.3 Hz), 2.71 (t, 2H, J = 7.9 Hz), 3.18 (m, 5H), 3.34 (dd, 1H, J = 11.2, 5.3 Hz), 3.58 (dd, 1H, J = 11.2, 6.2 Hz), 4.74 (d, 0.17H, J = 3.8 Hz), 4.78 (d, 0.83H, J = 4.8 Hz), 7.03 (d, 1H, J = 7.6 Hz), 7.16 (d, 0.17H, J = 7.7 Hz), 7.18 (d, 0.83H, J = 7.7 Hz), 7.58 (t, 1H, J = 7.7 Hz); ^{13}C NMR[31] δ 14.08, 22.65, 29.31, 29.43, 29.55, 29.61, 29.63, 31.88, 37.95, 57.20, (57.67), 63.42, (64.69), (73.49), 74.72, (117.77), 118.41, (121.53), 121.63, 137.16, (137.29), 158.77, (158.91), (161.17), 161.37.

(2*S*,3*S*)-3-(6′-Dodecylpyridin-2′-yl)-2-butanoylamidopropane-1,3-diol [(−)-3]. To a solution of 31 mg (0.92 mmol) of **28** in 3 mL of dry THF was added 35 mg (0.18 mmol) of *p*-nitrophenyl butyrate at room temperature. The reaction was stirred for 48 h and then concentrated under reduced pressure. TLC analysis ($CHCl_3$/MeOH 9:1) showed the formation of (−)-**3** (R_f 0.52) and its diastereoisomer (R_f 0.45). Purification by column chromatography (by gravity, $CHCl_3$/MeOH 9:1) afforded 24 mg (70%) of (−)-**3** as a white solid: mp 52.2−53.5 °C; $[\alpha]^{25}_D$ −100.5° (*c* 2.1, $CHCl_3$); IR 3425, 3305, 1644, 1507, 1096 cm^{-1}; ^{1}H NMR δ 0.74 (t, 3H, J = 7.4 Hz), 0.85 (t, 3H, J = 7.0 Hz), 0.90−1.40 (m, 18H), 1.40−1.60 (m, 2H), 1.60−1.80 (m, 2H), 1.90−2.20 (m, 2H), 2.60−2.90 (t, 2H, J = 7.9 Hz), 3.66 (dd, 1H, J = 11.8 Hz, 4.5 Hz), 4.00 (dd, 1H, J = 11.8, 2.2 Hz), 4.30 (m, 1H), 4.98 (s, 1H), 5.89 (br s, 1H), 6.46 (d, 1H, J = 6.3 Hz), 7.07 (d, 1H, J = 7.7 Hz), 7.46 (d, 1H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.8 Hz);^{13}C NMR δ 13.43, 14.08, 19.02, 22.65, 29.26, 29.31, 29.40, 29.54, 29.62, 29.72, 31.88, 37.51, 38.07, 57.33, 62.62, 77.25, 119.07, 121.78, 138.28, 150.78, 160.52, 174.94; HR-MS (FAB, MH$^+$) calcd for *m*/*z* $C_{24}H_{43}N_2O_3$ 407.3274, found 407.3269.

(2*S*,3*S*)-3-(6′-Dodecylpyridin-2′-yl)-2-*tert*-butyloxycarbonylaminopropane-1,3-diol [(−)-29]. Amberlyst 15 (0.15 g) was added to a solution of **26** and **27** (0.10 g, 0.21 mmol) in MeOH (5 mL). The mixture was stirred at room temperature for 48 h, filtered through Celite, and concentrated. The residue was purified by column chromatography (by gravity, $CHCl_3$/MeOH 9:1). Unreacted starting material was recovered, retreated with Amberlyst, and the product was purified as above. There was obtained 59 mg (65%) of diol **29** as a colorless oil: $[\alpha]^{25}_D$ −46.2° (*c* 3.4, $CHCl_3$); IR 3025, 1701, 1496, 1454, 1167 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.75 (t, 3H, J = 6.9 Hz), 1.10−1.50 (m, 27H), 1.60 (m, 2H), 2.57 (t, 2H, J = 7.6 Hz), 3.47 (m, 1H), 3.80 (dd, 1H, J = 11.3, 4.4 Hz), 4.11 (br s, 1H), 4.59 (br s, 1H), 5.02 (s, 1H), 5.55 (m, 2H), 6.55 (d, 1H, J = 7.6 Hz), 7.07 (t, 1H, J = 7.7 Hz), 7.28 (d, 1H, J = 7.7 Hz);^{13}C NMR δ 14.35, 23.09, 28.24, 29.57, 29.79, 29.83, 29.88, 29.99, 30.08, 30.11, 32.30, 38.00, 58.10, 62.71, 77.12, 79.41, 119.05, 121.43, 137.43, 157.36, 159.96, 160.93.

(4*S*,5*S*)-4-(6′-Dodecylpyridin-2′-yl)-5-*tert*-butyloxycarbonylamino-2,2-dimethyl-1,3-dioxane [(−)-31]. This compound was prepared in 66% yield by using the same procedure as described for (+)-**13**: $[\alpha]^{25}_D$ −25.0° (*c* 3.4, $CHCl_3$); IR 1713, 1214, 1161 cm^{-1}; ^{1}H NMR (C_6D_6, 60 °C) δ 0.88 (t, 3H, J = 6.8 Hz), 1.10−1.50 (m, 35H), 1.81 (m, 2H), 2.76 (t, 2H, J = 7.8 Hz), 3.71 (t, 1H, J = 10.2 Hz), 3.81 (br s, 1H), 4.40 (dd, 1H, J = 10.8, 4.8 Hz), 4.96 (d, 1H, $J_{4,5}$ = 9.6 Hz), 5.73 (s, 1H), 6.68 (d, 1H, J = 7.5 Hz), 7.18 (1H, overlap with C_6H_6), 7.35 (d, 1H, J = 7.6 Hz);^{13}C NMR δ 14.34, 19.06, 23.09, 28.36, 29.40, 29.79, 29.87, 29.95, 30.05, 30.08, 30.12, 32.30, 38.46, 51.51, 64.09, 74.71, 78.69, 99.09, 118.05, 121.78, 137.26, 155.58, 159.48, 160.69.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **2**, **3**, **6**−**8**, **10**, **11**, **13**, **16**−**21**, and **23**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) The values in parentheses represent the diastereoisomeric peaks.