JOC Article

First Asymmetric Synthesis of 6-Hydroxy-4-Sphingenine-Containing Ceramides. Use of Chiral Propargylic Alcohols To Prepare a Lipid Found in Human Skin

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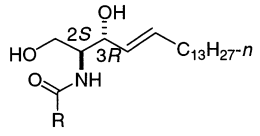
Received July 25, 2002

6-Hydroxy-(4*E*)-sphingenine-containing ceramides were found recently in human skin. We present here the first synthesis of the 6*S* and 6*R* diastereoisomers **2** and **3**, which represent analogues of (2*S*,3*R*)-ceramide (**1**) having two allylic hydroxyl groups. Chiral propargylic alcohols **8** and **11**, which were prepared by asymmetric dihydroxylation of α,*β*-unsaturated ester **13** and allylic chloride **22**, respectively, were employed as precursors of **2** and **3**. Nucleophilic addition of lithiated TBS-protected propargylic ethers **25** and **32** to L-serine-derived aldehyde **26**, respectively, afforded oxazolidine intermediates **27** and **33**. Acid-mediated deprotection of the oxazolidine, followed by *N*-acylation and Birch reduction, completed the syntheses of **2** and **3**.

Introduction

Ceramides (*N*-acylsphingosines) were reported to occur in human epidermis in 1975,[1] and ceramide (**1**) has since been discovered to be a potent lipid mediator of many cellular functions, including proliferation, differentiation, and apoptosis.[2] The role of ceramides in skin function, particularly in the regulation of the water content of the epidermis,[3] has led to the development of synthetic "pseudoceramides" as ceramide replacements in the cosmetic industry.[4] The sphingolipids in stratum corneum are structurally heterogeneous. A substantial proportion of skin ceramides are hydroxylated at various positions of the sphingoid base or at the α and *ω* positions of the *N*-linked fatty acyl chain.[5] A novel sphingoid base, (6*R*/6*S*)-6-hydroxy-(4*E*)-sphingenine, with predominately 18 and 20 carbon atoms, was identified in the ceramide fraction of human stratum corneum; ∼25% of these ceramides bear *ω*-hydroxy fatty acids,[6a−c] and ∼9% have nonhydroxylated fatty acids.[6d] We report here the first asymmetric synthesis of these diastereomeric ceramides of human stratum corneum. The amide chain of skin ceramides often contains as many as 30 carbons;[5] however, for ease of handling, we synthesized model ceramides **2** and **3** with an *N*-octanoyl chain (see Chart 1). The synthetic route to **2** and **3** described here can be applied to the preparation of other 6-hydroxy-substituted ceramides bearing longer *N*-acyl chains, thereby affording homogeneous stratum corneum sphingolipids for biophysical investigations.

CHART 1. (2*S*,3*R*)-Ceramide (1), 2-Octanoylamido-(2*S*,3*R*,6*S*)-6-hydroxy-(4*E*)-sphingenine (2), and 2-Octanoylamido-(2*S*,3*R*,6*R*)-6-hydroxy-(4*E*)-sphingenine (3)



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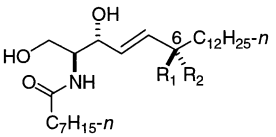

2 R_1 = H, R_2 = OH (2*S*,3*R*,6*S*)

3 R_1 = OH, R_2 = H (2*S*,3*R*,6*R*)

Results and Discussion

Synthetic Plan. As outlined in Scheme 1, our strategy for the preparation of ceramide **2** involves the key oxazolidine intermediate **27**, which is obtained by the addition of the acetylide ion derived from propargylic alcohol **11** to *N*-Boc-*N*,*O*-isopropylidene-L-serinal ((*S*)-

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(1) (a) Gray, G. M.; Yardly, H. *J. Lipid Res*. **1975**, *16*, 434−440. (b) Gray, G. M.; Yardly, H. *J. Lipid Res*. **1975**, *16*, 441−447.

(2) For reviews of ceramide biochemistry, see: (a) Perry, D. K.; Hannun, Y. A. *Biochim. Biophys. Acta* **1998**, *1436*, 233−243. (b) Kolesnick, R. N.; Goni, F. M.; Alonso, A. *J. Cell Physiol.* **2000**, *184*, 285−300. (c) Hannun, Y. A.; Obeid, L. M. *J. Biol. Chem*. **2002**, *277*, 25847−25850.

(3) Together with other lipids (primarily cholesterol and free fatty acids) in a multilamellar matrix with a complex phase behavior, ceramides are involved in providing skin with its barrier properties and water-binding capacity: Downing, D. T.; Stewart, M. E.; Wertz, P. W. *J. Invest. Dermatol*. **1987**, *88*, 2s−6s.

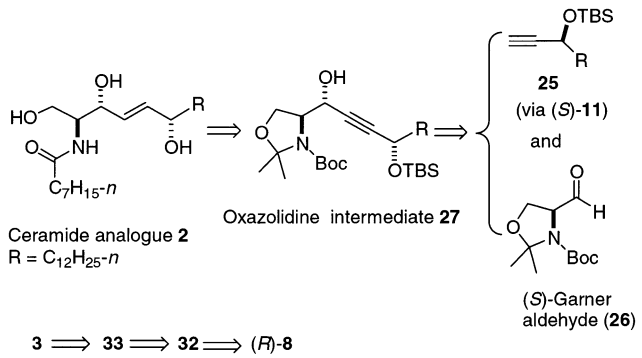
(4) (a) Suzuki, T. *Fragrance J*. **1993**, *21*, 23−33. (b) Mizushima, H.; Fukasawa, J.; Suzuki, T. *J. Colloid Interface Sci.* **1997**, *195*, 156−163. (c) Möller, H. The Chemistry of Natural and Synthetic Skin Barrier Lipids. *Cosmet. Sci. Technol. Ser.* **2002**, *24*, 1−35.

(5) Koller, T.; Sandhoff, K. *Angew. Chem., Int. Ed*. **1999**, *38*, 1532−1568.

(6) (a) Robson, K. J.; Stewart, M. E.; Michelsen, S.; Lazo, N. D.; Downing, D. T. *J. Lipid Res*. **1994**, *35*, 2060−2068. (b) Stewart, M. E.; Downing, D. T. *J. Invest. Dermatol*. **1995**, *105*, 613−618. (c) Bouwstra, J. A.; Gooris, G. S.; Dubbelaar, F. E. R.; Ponec, M. *J. Lipid Res*. **2001**, *42*, 1759−1770. (d) Stewart, M. E.; Downing, D. T. *J. Lipid Res*. **1999**, *40*, 1434−1439.

10.1021/jo026240+ CCC: $25.00
Published on Web 12/06/2002

SCHEME 1. Retrosynthetic Plan

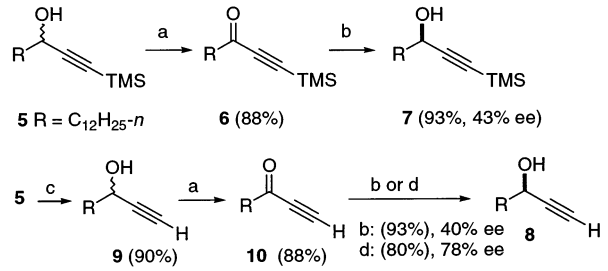


Garner aldehyde, **26**).[7] Similarly, diastereomer **3** arises via intermediate **33**, which is obtained by the reaction of the acetylide ion derived from **8** with aldehyde **26**. Thus, the success of this synthetic plan depends on the ability to prepare long-chain propargylic alcohols (*R*)-**8** and (*S*)-**11** in high enantiomeric purity (see below).

Synthesis of Chiral Propargylic Alcohols. Chiral propargylic alcohols are important synthons. They have been prepared by many methods, e.g., addition of an organometallic compound to an acetylenic aldehyde in the presence of chiral ligands,[8] enantioselective aldol addition to an α,*β*-ynal,[9] asymmetric reduction of an α,*β*-ynone,[10] resolution via enzymatic techniques,[11] Sharpless asymmetric epoxidation of an allylic alcohol,[12] and asymmetric dihydroxylation (AD) of an allylic chloride.[13]

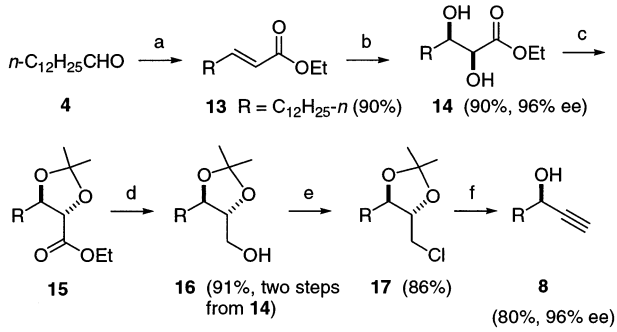
Attempted Enantioselective Reduction of Ynones 6 and 10 (Scheme 2). We first examined whether the enantioenriched propargylic alcohols **8** and **11** could be prepared by asymmetric reduction of α,*β*-ynones **6** and **10** (Scheme 2). Treatment of trimethylsilylacetylene with *n*-BuLi in THF at −78 °C followed by reaction with tridecanal **4** provided alcohol **5** in 92% yield. PCC oxidation of **5** afforded α,*β*-ynone **6** in 88% yield. Asymmetric reduction of ynone **6** with $LiAlH_4$ in diethyl ether in the presence of Darvon alcohol (Chirald)[10,14] gave alcohol **7**, but the resulting ee[15] was low (43%). As shown in Scheme 2, analogous treatment of ynone **10**, obtained by removal of the TBS group of **5** and PCC oxidation of the resulting alcohol **9**, also provided **8** in poor enantiomeric purity (40%). Similarly, reduction of ynone **10** with *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane ((*R*)-Alpine-Borane)[16] gave moderate enantioselectivity (78% ee).

SCHEME 2. Attempted Preparation of Alcohol 8 via Asymmetric Reduction[a]



[a] Reagents and conditions: (a) PCC, CH_2Cl_2, rt; (b) $LiAlH_4$, Chirald, Et_2O, −78 °C; (c) K_2CO_3, MeOH, rt; (d) (*R*)-Alpine-Borane, 0 °C to rt.

SCHEME 3. Synthesis of Propargylic Alcohol (*R*)-8[a]



[a] Reagents and conditions: (a) $(i\text{-PrO})_2P(O)CH_2CO_2Et$ (**12**), Et_3N, LiBr, THF, rt; (b) AD-mix-*β*, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), rt; (c) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, rt; (d) DIBAL-H, THF, 0 °C; (e) NCS, Ph_3P, CH_2Cl_2, 0 °C to rt; (f) *n*-BuLi, HMPA, THF, −42 °C to rt.

Therefore, we examined alternative routes for the preparation of chiral propargylic alcohols **8** and **11**. As outlined in Schemes 3 and 4, the routes we chose involve the AD reaction with an α,*β*-unsaturated ester[17] or an allylic chloride,[13] and conversion of the resultant diol to a 4-(chloromethyl)-1,3-dioxolane, followed by a double elimination reaction.

Synthesis of 8 via AD Reaction of α,*β*-Unsaturated Ester 13. On base-mediated double elimination, chloromethyl-1,3-dioxolanes (+)-**17** (Scheme 3) and (−)-**24** (Scheme 4) afforded alcohols **8** and **11**, respectively. α,*β*-Unsaturated ester **13** was prepared by Horner−Wadsworth−Emmons (HWE) reaction of tridecanal **4**

(7) For a review of the applications of the Garner aldehyde, see: Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136−2157.

(8) (a) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473−7484. (b) BouzBouz, S.; Pradaux, F.; Cossy, J.; Ferroud, C.; Falguieres, A. *Tetrahedron Lett.* **2000**, *41*, 8877−8880. (c) Lu, G.; Li, X.; Zhou, Z.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2147−2152.

(9) Singer, R. A.; Shepard, M. S.; Carreira, E. M. *Tetrahedron* **1998**, *54*, 7025−7032.

(10) (a) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582−588. (b) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 4913−4918.

(11) (a) Takano, S.; Setoh, M.; Yamada, O.; Ogasawara, K. *Synthesis* **1993**, *12*, 1253−1256. (b) Waldinger, C.; Schneider, M.; Botta, M.; Corelli, F.; Summa, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1485−1488.

(12) Takano, S.; Samizu, K.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1344−1345.

(13) Takano, S.; Yoshimitsu, T.; Ogasawara, K. *Synlett* **1994**, 119−120.

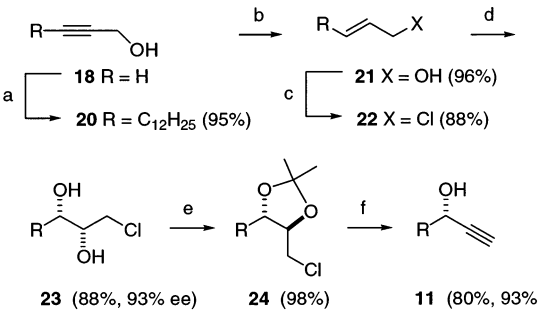
(14) Chirald is a trademark for Darvon alcohol. Propargylic ketones with a short-chain alkyl group were reduced with Chirald−$LiAlH_4$ to provide chiral alcohols in high ee;[10b] however, the enantiomeric purity was decreased when a long-chain alkyl group was present.

(15) The % ee was determined by ^1H and ^{19}F NMR analysis of the Mosher ester formed by the reaction of the alcohol with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) chloride in the presence of DMAP: Guivisdalsky, P. N.; Bittman, R. *J. Org. Chem.* **1989**, *54*, 4637−4642.

(16) Alpine-Borane is a trademark of Aldrich Chemical Co. For the preparation of (*R*)-Alpine-Borane and its use in the asymmetric reduction of 1-octyn-3-one, see: (a) Midland, M. M.; Graham, R. S. *Org. Synth.* **1985**, *63*, 57−65. (b) For a review of asymmetric reduction of propargyl ketones with Alpine-Borane, see: Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371−1380.

(17) (a) Kwong, H.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999−3002. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

SCHEME 4. Synthesis of Propargylic Alcohol (*S*)-11[a]

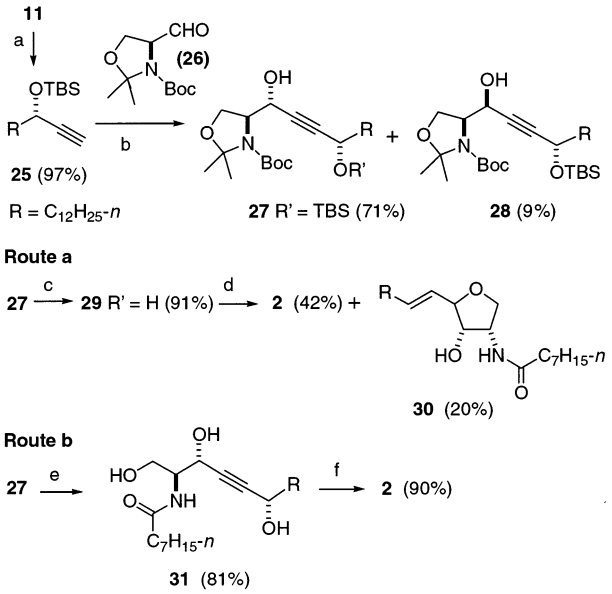


[a] Reagents and conditions: (a) Li, NH_3, $Fe(NO_3)_3$, $C_{12}H_{25}Br$ (**19**), THF, −78 °C; (b) $LiAlH_4$, THF, reflux; (c) NCS, Ph_3P, CH_2Cl_2, 0 °C to rt; (d) AD-mix-α, $NaHCO_3$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C; (e) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, rt; (f) *n*-BuLi, HMPA, THF, −42 °C to rt.

with diisopropyl ester phosphonate **12** (Scheme 3).[18] Reaction of **13** with AD-mix-*β* provided diol ester **14** in 90% yield and 96% ee. This result is consistent with previous reports of very high ee values attained in AD reactions of α,*β*-unsaturated esters.[17b] Treatment of diol **14** with 2,2-dimethoxypropane in the presence of *p*-TsOH gave acetonide ester **15**, which on reduction with DIBAL-H gave alcohol **16**. During the acetonide formation, a trace of the methyl ester analogue of **15** was formed by transesterification. However, subsequent reduction provided the same alcohol **16**. The latter was converted to chloride **17** in 88% yield by Mitsunobu reaction.[19] Propargylic alcohol (*R*)-**8** was obtained in good yield and high ee[20] by treatment of **17** with excess *n*-BuLi and HMPA in THF at low temperature.

Synthesis of 11 via Allylic Chloride 22 (Scheme 4). Takano et al. prepared short-chain propargylic alcohols from allylic chlorides.[13] We applied this method to the preparation of long-chain alcohol **11**. Thus, alkylation of propargyl alcohol (**18**) with dodecyl bromide (**19**) in THF[22a] gave propargylic alcohol **20** in 95% yield (Scheme 4). The latter was converted to (*E*)-allylic alcohol **21** in 96% yield by $LiAlH_4$ reduction[23] and then to chloride **22** in 88% yield by Mitsunobu reaction of **21**. Reaction of **22** with AD-mix-α[23] provided diol **23**[24] in 88% yield and 93% ee. To minimize epoxide formation, the AD reaction was carried out under "buffered" conditions (with 3 equiv of $NaHCO_3$).[25] Treatment of diol **23** with 2,2-dimethoxypropane in the presence of *p*-TsOH gave acetonide **24**, which was treated with excess *n*-BuLi in the presence of HMPA to provide alcohol (*S*)-**11** in 80% yield (93% ee).

SCHEME 5. Synthesis of Ceramide Analogue 2[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, rt; (b) *n*-BuLi, THF, −78 °C to rt; (c) *n*-Bu_4NF, THF, rt; (d) (i) Li, $EtNH_2$, −78 °C, (ii) 1 M HCl, dioxane, 100 °C, (iii) *p*-$O_2NC_6H_4CO_2C_7H_{15}$-*n*, THF, rt; (e) (i) 1 M HCl, dioxane, 100 °C, (ii) *p*-$O_2NC_6H_4CO_2C_7H_{15}$-*n*, THF, rt; (f) Li, $EtNH_2$, −78 °C.

Synthesis of Ceramide Analogue 2 (Scheme 5). Coupling of protected propargylic alcohols **8** and **11** with (*S*)-aldehyde **26**[7,26] led to ceramide analogues **2** and **3**. The C-2 and C-6 configurations in **2** and **3** are derived from the stereogenic centers in serinaldehyde **26** and the propargylic alcohols, respectively. The new stereocenter at C-3 is generated by the asymmetric addition of the lithium acetylide of **25** or **32** to the Boc-protected aldehyde. As shown in Scheme 5, protection of the hydroxy group of **11** (TBSCl, Im) gave ether **25**, which was lithiated (*n*-BuLi, THF, −78 °C) and reacted with aldehyde **26** to give an 8:1 mixture of *erythro*-**27** and *threo*-**28** in 80% overall yield.[27] The diastereoselectivity was improved significantly (ratio > 20:1) by the addition of 2 equiv of HMPA.[28] After diastereomers **27** and **28** were separated by chromatography, the TBS group of **27** was removed by treatment with *n*-Bu_4NF in THF to give diol **29**, and Birch reduction was used to convert the triple bond to a trans double bond. Acid hydrolysis (1 M HCl in dioxane, 100 °C) followed by *N*-acylation with *p*-nitrophenyl octanoate provided target ceramide analogue **2**

(18) Bonini, C.; Federici, C.; Rossi, L.; Righi, G. *J. Org. Chem.* **1995**, *60*, 4803−4812.

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

(20) For a preliminary account of the preparation of both *R* and *S* long-chain propargylic alcohols in high ee via AD reaction of α,*β*-unsaturated esters with either AD-mix-α or AD-mix-*β*, see: Chun, J.; Byun, H.-S.; Bittman, R. *Tetrahedron Lett.* **2002**, *43*, 8043−8045.

(21) Takano, S.; Sugihara, T.; Ogasawara, K.*Heterocycles* **1990**, *31*, 1721−1725.

(22) (a) van Aar, M. P. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 11223−11234. (b) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766−4770.

(23) Zhang, Z.-B.; Wang, Z.-M.; Wang, Y.-X.; Liu, H.-Q.; Lei, G.-X.; Shi, M. *J. Chem. Soc., Perkin Trans.* 1 **2000**, 53−57.

(24) Zhang et al.[23] assigned the 2*S*,3*S* configuration to compound **23**; however, it should be 2*R*,3*S*. Moreover, because of the discrepancy between the mp and [α] values and those of ref 23, we prepared the enantiomer of **23**, (2*S*,3*R*)-1-chloropentadecane-2,3-diol, by the reaction of **22** with AD-mix-*β*, and found no change in mp (64.5−65.5 °C) and the same magnitude of specific rotation but opposite sign ($[\alpha]^{25}_D$ +8.9° (*c* 1.0, MeOH)).

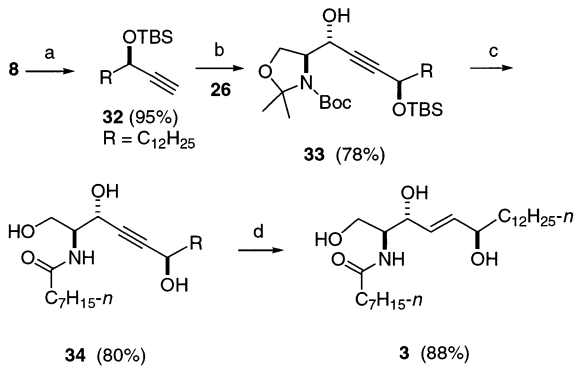
(25) For the "buffered" AD reaction of allylic halides, see: Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 3469−3472.

(26) (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.

(27) The ratio of **27** to **28** was estimated by high-temperature ^1H NMR spectroscopy.

(28) For examples of high *anti*:*syn* ratios in the addition of alkynyllithium reagents to **26** in the presence of HMPA, see: (a) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354−362. (b) Gruza, H.; Kiciak, K.; Krasinski, A.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2627−2631.

SCHEME 6. Synthesis of Ceramide Analogue 3[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, rt; (b) *n*-BuLi, HMPA, THF, −78 °C to rt; (c) (i) 1 M HCl, dioxane, 100 °C, (ii) *p*-$O_2NC_6H_4CO_2C_7H_{15}$-*n*, THF, rt; (d) Li, $EtNH_2$, −78 °C.

(route a). Unexpectedly, we found the yield of **2** to be only 42%; about 20% byproduct **30** was also formed. A much better result (route b) was obtained when we changed the sequence of these reactions: acid hydrolysis of **27** followed by *N*-acylation provided 4-alkynylceramide analogue **31**. In the last step, Birch reduction of **31** (Li, $EtNH_2$, THF, −78 °C) gave ceramide analogue **2** in 90% yield.

Synthesis of Ceramide Analogue 3 (Scheme 6). Protection of the hydroxy group of **8** as the TBS ether followed by lithiation (*n*-BuLi, THF, −78 °C) and reaction with aldehyde **26** in the presence of HMPA afforded **33** in 78% yield (Scheme 6). Acid hydrolysis (1 M HCl in dioxane, 100 °C) of **33** followed by *N*-acylation with *p*-nitrophenyl octanoate afforded 4-alkynylceramide analogue **34**, which on Birch reduction provided ceramide analogue **3** in 88% yield.

In summary, we have reported the first synthesis of naturally occurring sphingolipids with the 6(*R*/*S*)-hydroxysphing-(4*E*)-enine backbone, a novel long-chain base bearing allylic hydroxy groups at C-3 and C-6. The key precursors were the propargylic alcohols **8** and **11**, which were prepared by AD reactions with α,*β*-unsaturated ester **13** and allylic chloride **22**, respectively, followed by acetonide formation and elimination. The target ceramide analogues **2** and **3** were obtained with high stereoselectivity and good yields.

Experimental Section

General Information. See the previous paper for general experimental details.[29] (*S*)-Garner aldehyde (**26**) was prepared from *N*-Boc-L-serine methyl ester as described previously.[26b,c] Mosher esters were prepared as described previously.[15] ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The solvent was $CDCl_3$ unless otherwise noted. IR spectra were recorded in chloroform. The mobile phase used in electrospray mass spectrometry contained ∼50 *μ*M NH_4OAc and 0.1% HOAc.

***rac*-1-(Trimethylsilyl)pentadecyn-3-ol (5).** To a solution of 0.43 mL (3.0 mmol) of (trimethylsilyl)acetylene in 15 mL of dry THF was added 1.3 mL (3.2 mmol) of *n*-BuLi (2.5 M solution in hexanes) at −78 °C under N_2. After 30 min, a solution of 0.48 g (2.8 mmol) of tridecanal (**4**) in 10 mL of THF was added dropwise. After the mixture was stirred for 2 h at −78 °C and for 1 h at rt, the reaction was quenched by the addition of aqueous saturated NH_4Cl solution. The product was extracted with EtOAc (3 × 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Pentadecynyl alcohol **5** (0.77 g, 92%) was obtained by chromatography on silica gel (hexane/EtOAc, 9:1): IR 3597, 3302, 2169 cm^{-1}; ^1H NMR *δ* 0.14 (br s, 9H), 0.84 (t, 3H, *J* = 6.7 Hz), 1.10−1.50 (m, 20H), 1.64 (m, 2H), 2.12 (br s, 1H), 4.31 (t, 1H, *J* = 6.6 Hz); ^{13}C NMR *δ* −0.2, 14.1, 22.6, 22.7, 25.1, 27.8, 29.2, 29.3, 29.5, 29.61, 29.64, 31.9, 37.1, 37.6, 62.8, 89.1, 107.1; HR-MS [DCI/NH_3, MNH_4^+] *m*/*z* calcd for $C_{18}H_{14}NOSi$ 314.1879, found 314.1879.

1-(Trimethylsilyl)pentadecyn-3-one (6). To a solution of 0.30 g (1.0 mmol) of **5** in 10 mL of CH_2Cl_2 was added 0.43 g (2.0 mmol) of PCC. The mixture was stirred at rt for 5 h and then filtered through a pad of silica gel, which was washed with CH_2Cl_2. The filtrate was concentrated to give a residue that was purified by flash chromatography (hexane/EtOAc, 9:1), affording 0.26 g (88%) of ynone **6**: IR 2172, 1665, 1256 cm^{-1}; ^1H NMR *δ* 0.16 (s, 9H), 0.82 (t, 3H, *J* = 6.6 Hz), 1.10−1.60 (m, 18H), 1.57 (m, 2H), 2.46 (t, 1H, *J* = 7.4 Hz); ^{13}C NMR *δ* −0.9, 14.0, 22.2, 22.6, 22.7, 23.7, 23.8, 28.8, 29.1, 29.2, 29.3, 29.4, 29.51, 29.52, 31.8, 42.3, 42.6, 45.1, 97.1, 102.0, 187.6; MS [ESI] *m*/*z* 295.2 (M^+), 312.2 (MNH_4^+), 317.1 (MNa^+).

1-(Trimethylsilyl)pentadecyn-3-ol (7). To a solution of Chirald (1.70 g, 6.0 mmol) in 10 mL of dry Et_2O was added dropwise 2.8 mL (2.8 mmol) of $LiAlH_4$ (a 1.0 M solution in Et_2O) at 0 °C. After being stirred for 5 min, the mixture was chilled to −78 °C, and a solution of ketone **6** (590 mg, 2.0 mmol) in 10 mL of Et_2O was added over a 15 min period. The mixture was stirred at −78 °C for 6 h. Saturated aqueous NH_4Cl solution was added to quench the reaction. The product was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (hexane/EtOAc, 4:1) gave 275 mg (93%) of **7** as a colorless oil: IR 3597, 2158 cm^{-1}; MS [ESI] *m*/*z* 314.2 (MNH_4^+), 319.2 (MNa^+).

***rac*-1-Pentadecyn-3-ol (9).** A mixture of 0.60 g (2.0 mmol) of TMS acetylide **5** and 0.62 g (4.6 mmol) of K_2CO_3 in 4 mL of MeOH was stirred at rt for 4 h. After the solvent was removed, the residue was dissolved in 30 mL of Et_2O, washed with water, and dried ($MgSO_4$). Concentration and purification of the residue by column chromatography (hexane/EtOAc, 9:1) gave 0.40 g (90%) of **9** as a white solid: mp 44.0−45.0 °C; IR 3597, 3302, 1457 cm^{-1}; ^1H NMR *δ* 0.84 (t, 3H, *J* = 6.6 Hz), 1.20−1.60 (m, 20H), 1.68 (m, 2H), 2.31 (br s, 1H), 2.42 (d, 1H, *J* = 3.7 Hz), 4.32 (dt, 1H, *J* = 6.7, 2.1 Hz); ^{13}C NMR *δ* 14.1, 22.6, 25.1, 29.3, 29.5, 29.62, 29.69, 29.7, 32.0, 37.6, 62.2, 72.7, 85.1; HR-MS [DCI/NH_3, MNH_4^+] *m*/*z* calcd for $C_{15}H_{32}NO$ 242.2484, found 242.2477.

1-Pentadecyn-3-one (10). This compound was prepared in 88% yield by using the same procedure as described for **6**: IR 3291, 2093, 1681 cm^{-1}; ^1H NMR *δ* 0.82 (t, 3H, *J* = 6.6 Hz), 1.10−1.60 (m, 18H), 1.61 (m, 2H), 2.51 (t, 1H, *J* = 7.4 Hz), 3.17 (s, 1H); ^{13}C NMR *δ* 14.0, 22.6, 23.7, 28.8, 29.2, 29.3, 29.48, 29.53, 29.54, 31.8, 45.3, 78.2, 81.4, 187.3; HR-MS [DCI/NH_3, MNH_4^+] *m*/*z* calcd for $C_{15}H_{30}NO$ 240.2327, found 240.2333.

Ethyl (2*E*)-Pentadecenoate (13). To a nitrogen-flushed solution of 10.5 g (122 mmol) of LiBr in 100 mL of dry THF was injected 7.2 mL (7.6 g, 30 mmol) of $(i\text{-PrO})_2P(O)CH_2CO_2$-Et (**12**) at rt. After the solution was stirred at rt for 10 min, 6.8 mL (49 mmol) of Et_3N was added, and stirring was continued for 10 min. A solution of 4.3 g (25 mmol) of **4** in 10 mL of dry THF was added. The reaction mixture was stirred vigorously at rt until the full consumption of tridecanal was observed (TLC). The precipitate was removed by passing the reaction mixture through a pad of silica gel in a sintered glass funnel. The pad was washed with hexane/EtOAc (10:1). Concentration gave a pale yellow oil that was purified by column chromatography (hexane/EtOAc, 20:1), providing 6.0 g (90%) of ester **13** as a colorless oil. The NMR data are in full accord with the literature data.[18]

(29) Chun, J.; He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem*. **2002**, *67*, 2600−2605.

Ethyl (2*S*,3*R*)-2,3-Dihydroxypentadecanoate [(+)-14]. To a solution of 14.0 g of AD-mix-β in 200 mL of *t*-BuOH/H_2O (1:1) that had been stirred vigorously at rt for 30 min was added 950 mg (10.0 mmol) of $MeSO_2NH_2$. Stirring was continued for 10 min at rt. Then 2.7 g (10.0 mmol) of α,β-unsaturated ester **13** was added. The reaction mixture was stirred vigorously until the disappearance of ester **13** was noted (TLC). Sodium sulfite (15.0 g, 14.6 mmol) was added to quench the reaction, and stirring was continued for another 30 min. The product was extracted with EtOAc (3 × 80 mL), and the combined extracts were dried (Na_2SO_4) and concentrated to give a yellow residue. Purification of the residue by column chromatography (hexane/EtOAc, 2:1) gave 2.7 g (90%) of diol ester **14** as a white solid: mp 69.0−70.0 °C; $[\alpha]^{25}_D$ +8.3° (*c* 1.0, $CHCl_3$); IR 3629, 3019, 2398, 1518, 1425, 1212 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.5 Hz), 1.10−1.70 (m, 25H), 3.06 (d, 1H, J = 8.4 Hz), 3.86 (m, 2H), 4.06 (dd, 1H, J = 6.5, 2.3 Hz), 4.24 (q, 2H, J = 7.1 Hz); ^{13}C NMR δ 14.15, 14.17, 22.8, 25.9, 29.5, 29.70, 29.72, 29.74, 29.76, 29.8, 32.0, 33.6, 61.8, 72.8, 73.6, 173.8; MS [ESI] *m*/*z* 320.2 (MNH_4^+), 325.2 (MNa^+).

(4*S*,5*R*)-5-Dodecyl-4-ethoxycarbonyl-2,2-dimethyl-1,3-dioxolane (15). To a solution of 2.4 g (8.0 mmol) of diol ester **14** in 60 mL of dry CH_2Cl_2 were added 1.67 g (16.0 mmol) of 2,2-dimethoxypropane and 50 mg (0.26 mmol) of *p*-TsOH at rt. The mixture was stirred at rt for 2 h and then passed through a pad of silica gel in a sintered glass funnel. The pad was washed with 50 mL of CH_2Cl_2. Concentration gave ester **15** as a colorless oil, which was used without further purification in the subsequent reaction.

(4*R*,5*R*)-5-Dodecyl-4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane [(+)-16]. To a solution of ester **15** obtained above in 15 mL of dry THF was added dropwise 10.7 mL (16.0 mmol) of DIBAL-H (a 1.5 M solution in toluene) at 0 °C under N_2. The reaction mixture was stirred for 2 h at 0 °C until TLC analysis showed the reaction to be complete. The reaction was quenched by slow addition of 2 mL of MeOH followed by 15 mL of cold 5% aqueous potassium sodium tartrate solution. The product was extracted with EtOAc (3 × 40 mL), and the combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (hexane/EtOAc, 4:1) gave 2.18 g (91%) of **16** as a colorless oil: $[\alpha]^{25}_D$ +18.8° (*c* 1.8, $CHCl_3$); IR 3597, 1463, 1382, 1103 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.10−1.70 (m, 28H), 2.90 (t, 1H, J = 6.0 Hz), 3.59 (m, 1H), 3.72 (m, 2H), 3.84 (m, 1H); ^{13}C NMR δ 14.1, 22.7, 26.0, 27.1, 27.4, 29.4, 29.58, 29.63, 29.70, 29.73, 29.8, 32.0, 33.2, 62.2, 77.1, 81.8, 108.6; HR-MS [DCI, MH^+] *m*/*z* calcd for $C_{18}H_{37}O_3$ 301.2743, found 301.2751.

(4*S*,5*R*)-4-Chloromethyl-5-dodecyl-2,2-dimethyl-1,3-dioxolane [(+)-17]. To a solution of 1.74 g (5.8 mmol) of alcohol **16** and 1.83 g (6.9 mmol) of Ph_3P in 30 mL of dry CH_2Cl_2 was added 930 mg (6.9 mmol) of NCS at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to rt, and stirred for 2 h. The mixture was diluted with 100 mL of hexane and passed through a pad of silica gel to remove the precipitate of Ph_3PO. Concentration and purification of the residue by column chromatography (hexane/EtOAc, 9:1) gave 1.59 g (86%) of **17** as a colorless oil: $[\alpha]^{25}_D$ +14.2° (*c* 0.9, $CHCl_3$); IR 1464, 1376, 1218, 1098 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.20−1.70 (m, 28H), 3.58 (d, 2H, J = 4.9 Hz), 3.88 (m, 2H); ^{13}C NMR δ 14.1, 22.7, 26.0, 27.0, 27.5, 29.4, 29.5, 29.6, 29.7, 32.0, 33.5, 44.4, 79.4, 80.3, 109.1; HR-MS [DCI, MH^+] *m*/*z* calcd for $C_{18}H_{36}O_2Cl$ 319.2404, found 319.2407.

(3*R*)-1-Pentadecyn-3-ol [(+)-8]. To a stirred solution of 4.5 mL (26.1 mmol) of HMPA in 20 mL of dry THF was added 10.4 mL (26.1 mmol) of *n*-BuLi (a 2.5 M solution in hexane) at −42 °C under N_2. After 10 min, a solution of 1.19 g (3.73 mmol) of chloride **17** in 10 mL of THF was added dropwise over 5 min. After 0.5 h, the reaction mixture was warmed to rt and stirred for another 0.5 h. Saturated aqueous NH_4Cl solution was added to quench the reaction. The product was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (hexane/EtOAc, 7:1) gave 668 mg (80%) of **8** as a white solid: mp 40.0−41.0 °C; $[\alpha]^{25}_D$ +2.60° (*c* 1.0, $CHCl_3$); IR 3597, 3302, 1458 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.20−1.60 (m, 20H), 1.72 (m, 2H), 2.41 (br s, 1H), 2.44 (d, 1H, J = 3.7 Hz), 4.36 (m, 1H); ^{13}C NMR δ 14.1, 22.7, 25.1, 29.3, 29.5, 29.62, 29.69, 29.7, 32.0, 37.6, 62.3, 72.8, 85.1; HR-MS [DCI/NH_3, MNH_4^+] *m*/*z* calcd for $C_{15}H_{32}NO$ 242.2484, found 242.2489.

2-Pentadecyn-1-ol (20). This compound was prepared in 95% yield by a slight modification of the procedure of van Aar et al.;[22a] we used 3 equiv of propargyl alcohol (**18**) rather than 1.5 equiv; mp 44.2−45.2 °C (lit.[22a] mp 38−41 °C, lit.[22b] mp 43−45 °C). The NMR data are in full accord with the literature data.[22a,b]

(2*E*)-Pentadecen-1-ol (21). This compound, which is a low-melting-point white solid, was prepared in 96% yield as described previously, and the NMR data are in full accord with the literature data.[23]

(2*E*)-1-Chloropentadecene (22). To a solution of 5.0 g (22.1 mmol) of alcohol **21** and 7.0 g (26.7 mmol) of Ph_3P in 50 mL of dry CH_2Cl_2 was added 3.3 g (24.4 mmol) of NCS at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to rt, and stirred for 2 h. The mixture was diluted with 150 mL of hexane and passed through a pad of silica gel with suction to remove the precipitate of Ph_3PO. The filtrate was concentrated, and the resulting residue was dissolved in 100 mL of hexane and passed through a pad of silica gel to remove the precipitate of Ph_3PO again. Concentration gave 4.79 g (88%) of allylic chloride **22** as a colorless oil. This compound was used in the next step without further purification.

(2*R*,3*S*)-1-Chloropentadecane-2,3-diol [(−)-23]. After a solution of 14.0 g of AD-mix-α[23,30] in 200 mL of *t*-BuOH/H_2O (1:1) was stirred vigorously at rt for 30 min, 2.52 g (30.0 mmol) of $NaHCO_3$ was added. After 15 min, 950 mg (10.0 mmol) of $MeSO_2NH_2$ was added, and stirring was continued for 10 min at rt. The reaction mixture was chilled to 0 °C, and 2.47 g (10.0 mmol) of allylic chloride **22** was added. The reaction mixture was stirred vigorously for 8 h. Sodium sulfite (15.0 g, 14.6 mmol) was added to quench the reaction, and stirring was continued for another 30 min. The product was extracted with EtOAc (3 × 80 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a yellow solid residue, which was purified by column chromatography (hexane/EtOAc, 2:1), giving 2.45 g (88%) of diol **23** as a white solid: mp 64.5−65.5 °C (lit.[23] mp 92−93 °C); $[\alpha]^{25}_D$ −9.6° (*c* 1.25, $CHCl_3$); $[\alpha]^{25}_D$ −8.9° (*c* 1.0, MeOH) (lit.[23] $[\alpha]^{25}_D$ −7.0° (*c* 1.0, MeOH)).[24] The NMR data are in full accord with the literature data.[23]

(4*R*,5*S*)-4-Chloromethyl-5-dodecyl-2,2-dimethyl-1,3-dioxolane [(−)-24]. This compound was prepared in 98% yield by using the same procedure as described for **15**: $[\alpha]^{25}_D$ −10.93° (*c* 2.1, $CHCl_3$); IR and ^1H and ^{13}C NMR spectra essentially identical to those of (+)-**17**; HR-MS [DCI, MH^+] *m*/*z* calcd for $C_{18}H_{36}O_2Cl$ 319.2404, found 319.2400.

(3*S*)-1-Pentadecyn-3-ol [(−)-11]. This compound was prepared in 80% yield by using the same procedure as described for **8**: mp 40.0−41.0 °C; $[\alpha]^{25}_D$ −2.59° (*c* 1.0, $CHCl_3$); IR and ^1H and ^{13}C NMR spectra essentially identical to those of (+)-**8**; HR-MS [DCI, MH^+] *m*/*z* calcd for $C_{15}H_{29}O$ 225.2218, found 225.2211.

(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-pentadecyne [(−)-25]. To a solution of 0.45 g (2.0 mmol) of **11** and 0.29 g (4.2 mmol) of imidazole in 4 mL of DMF under N_2 was added 0.33 g (2.2 mmol) of *tert*-butylchlorodimethylsilane. After the solution was stirred at rt overnight, it was diluted with water (5 mL), and the product was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine and water,

(30) 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.

dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography (hexane) to give 0.66 g (97%) of **25** as a colorless oil: $[\alpha]^{25}_D$ −26.9° (*c* 1.7, $CHCl_3$); IR 1714, 1463, 1256, 1093, 837 cm^{-1}; ^1H NMR δ 0.10 (s, 3H), 0.13 (s, 3H), 0.89 (m, 12H), 1.20−1.40 (m, 20H), 1.65 (m, 2H), 2.34 (d, 1H, J = 2.1 Hz), 4.32 (dt, 1H, J = 6.5, 2.1 Hz); ^{13}C NMR δ −5.1, −4.5, 14.1, 18.2, 22.7, 25.2, 25.8, 29.3, 29.4, 29.61, 29.64, 29.71, 29.74, 32.0, 38.6, 62.8, 71.8, 85.8; HR-MS [DCI, MH^+] *m*/*z* calcd for $C_{21}H_{43}SiO$ 339.3083, found 339.3086.

***N*-*tert*-Butoxycarbonyl-(4*S*,1′*R*,4′*S*)-4-[4′-(*tert*-butyldimethylsilyloxy)-1′-hydroxy-2′-hexadecynyl]-2,2-dimethyl-1,3-oxazolidine [(−)-27].** To a solution of 1.01 g (3.0 mmol) of alkyne **25** in 15 mL of dry THF was slowly added 1.3 mL (3.2 mmol) of *n*-BuLi (2.5 M solution in hexanes) at −78 °C under N_2. The mixture was stirred for 30 min at −78 °C, and a solution of 0.69 g (3.0 mmol) of **26** in 10 mL of THF was added dropwise with stirring. The mixture was kept at −78 °C for 2 h and then allowed to warm to rt for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The major diastereomer **27** was isolated by chromatography on silica gel (hexane/EtOAc, 4:1): $[\alpha]^{25}_D$ −41.1° (*c* 2.9, $CHCl_3$); IR 3334, 3012, 1688, 1380, 1256, 1152 cm^{-1}; ^1H NMR (C_6D_6, 70 °C)[31] δ 0.13 (s, 3H), 0.19 (s, 3H), 0.88 (t, 3H, J = 6.1 Hz), 0.96 (s, 9H), 1.20−1.80 (m, 37H), 3.79 (t, 1H, J = 7.5 Hz), 4.00 (br s, 2H), 4.41 (t, 1H, J = 6.1 Hz), 4.70 (br s, 1H); ^{13}C NMR (C_6D_6)[32] δ −5.2, −4.9, 14.3, 18.1, 18.4, 18.5, 18.7, 23.1, 23.3, 25.7, 25.9, 26.0, 26.3, 28.3, 29.5, 29.7, 29.8, 30.00, 30.05, 30.07, 30.1, 32.3, 38.2, 39.2, (62.0) 63.3, 64.2 (64.6), 67.1, (79.9) 81.7, 83.0 (83.5), 87.6 (88.1), 101.0, (151.7) 154.3; HR-MS [FAB, MH^+] *m*/*z* calcd for $C_{32}H_{62}NO_5Si$ 568.4397, found 568.4366.

Data for the minor diastereomer 28: IR 3597, 3008, 1692, 1398, 1256, 1163, 1092 cm^{-1}; ^1H NMR (C_6D_6, 70 °C) δ 0.14 (s, 3H), 0.20 (s, 3H), 0.88 (t, 3H, J = 6.1 Hz), 0.99 (s, 9H), 1.20−1.80 (m, 37H), 3.26 (br s, 1H), 3.49 (t, 1H, J = 6.4 Hz), 3.83 (dd, 1H, J = 9.5, 6.5 Hz), 4.13 (m, 2H), 4.46 (m, 1H), 4.76 (d, 1H, J = 6.4 Hz); HR-MS [FAB, MNa^+] *m*/*z* calcd for $C_{32}H_{61}NO_5SiNa$ 590.4217, found 590.4236.

***N*-*tert*-Butoxycarbonyl-(4*S*,1′*R*,4′*S*)-4-[1′,4′-dihydroxy-2′-hexadecynyl]-2,2-dimethyl-1,3-oxazolidine [(−)-29].** To a solution of 0.47 g (0.82 mmol) of **27** in 5.0 mL of THF was added 1.64 mL (1.64 mmol) of a 1.0 M solution of *n*-Bu_4NF in THF at rt under N_2. After the mixture was stirred for 1 h, and the reaction was quenched with 5 mL of water. The product was extracted with EtOAc (3 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (EtOAc/hexane, 2:3) to give 0.34 g (91%) of **29** as a colorless oil: $[\alpha]^{25}_D$ −41.1° (*c* 1.9, $CHCl_3$); IR 1666, 1467, 1394, 1368, 1245, 1167, 1082 cm^{-1}; ^1H NMR (C_6D_6, 70 °C) δ 0.89 (t, 3H, J = 6.6 Hz), 0.96 (s, 9H), 1.20−1.80 (m, 37H), 2.22 (d, 1H, J = 4.6 Hz), 3.78 (dd, 1H, J = 9.0, 7.0 Hz), 3.96 (br s, 1H), 4.05 (br s, 1H), 4.31 (dd, 1H, J = 11.1, 5.2 Hz), 4.69 (br s, 1H); ^{13}C NMR (C_6D_6) δ 14.3, 14.8, 22.9, 23.0, 23.1, 23.3, 23.5, 25.3, 25.8, 26.1, 26.7, 28.3, 29.8, 30.09, 30.1, 30.2, 32.1, 32.3, 34.5, 38.2, (62.0) 62.3, 62.9, 63.7, (64.8) 65.2, (79.9) 80.9, 83.6, 87.9 (88.4), 94.9 (95.4), (151.9) 154.2; HR-MS [FAB, MH^+] *m*/*z* calcd for $C_{26}H_{48}NO_5$ 454.3532, found 454.3517.

(2*S*,3*R*,6*S*)-2-Octanoylamido-4-octadecyne-1,3,6-triol [(−)-31]. A solution of 113 mg (0.20 mmol) of **27** in 5 mL of 1 M HCl and 5 mL of dioxane was heated at 100 °C with stirring for 1 h under N_2. The reaction mixture was cooled to rt and neutralized with 1 M NaOH (5 mL). The product was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine and dried (Na_2SO_4). Removal of the solvent provided a crude sphingosine analogue as a white solid, which was dissolved in 6 mL of dry THF. After 108 mg (0.40 mmol) of *p*-nitrophenyl octanoate was added at rt, the reaction mixture was stirred for 24 h and concentrated. Purification by flash chromatography ($CHCl_3$/MeOH, 9:1) afforded 71 mg (81%, two steps) of 4-alkynylceramide analogue **31** as a white solid: mp 95.2−96.2 °C; $[\alpha]^{25}_D$ −13.6° (*c* 1.1, $CHCl_3$/MeOH, 4:1); IR 3426, 1659, 1509, 1052 cm^{-1};^1H NMR ($CDCl_3$/MeOD) δ 0.88 (t, 6H, J = 6.5 Hz), 1.20−1.70 (m, 32H), 2.24 (t, 2H, J = 7.5 Hz), 3.67 (dd, 1H, J = 11.5, 4.7 Hz), 3.90 (dd, 1H, J = 11.5, 4.6 Hz), 4.06 (d, 1H, J = 4.7 Hz), 4.30 (m, 1H), 4.53 (dd, 1H, J = 4.8, 1.3 Hz); ^{13}C NMR ($CDCl_3$/MeOD) δ 14.1, 22.7, 22.8, 25.4, 25.8, 29.1, 29.3, 29.5, 29.7, 31.8, 32.0, 36.66, 36.7, 37.6, 55.2, 61.5, 61.8, 62.8, 82.3, 87.8, 175.3; HR-MS [FAB, MNa^+] *m*/*z* calcd for $C_{26}H_{49}NO_4Na$ 462.3559, found 462.3552.

(2*S*,3*R*,6*S*)-2-Octanoylamido-(4*E*)-octadecene-1,3,6-triol [(+)-2]. To the blue solution prepared by addition of 50 mg (7.2 mmol) of lithium metal to 5 mL of liquid $EtNH_2$ was added a solution of **31** (44 mg, 0.10 mmol) in 5 mL of dry THF at −78 °C. After the mixture was stirred for 1 h, the reaction was quenched by addition of 400 mg (7.5 mmol) of NH_4Cl. After removal of $EtNH_2$ by a stream of N_2, the mixture was diluted with 50 mL of $CHCl_3$ and washed with water. The organic layer was dried (Na_2SO_4) and concentrated. Purification by column chromatography ($CHCl_3$/MeOH, 9:1) gave 40 mg (90%) of **2** as a white solid: mp 119.5−121.0 °C; $[\alpha]^{25}_D$ +5.1° (*c* 1.1, $CHCl_3$/MeOH, 4:1); IR 3427, 1659, 1509, 1465, 1222 cm^{-1}; ^1H NMR ($CDCl_3$/MeOD) δ 0.88 (t, 6H, J = 6.4 Hz), 1.20−1.70 (m, 32H), 2.21 (t, 2H, J = 7.4 Hz), 3.63 (dd, 1H, J = 10.9, 3.4 Hz), 3.84 (m, 2H), 4.06 (q, 1H, J = 6.1 Hz), 4.20 (t, 1H, J = 5.3 Hz), 5.65 (dd, 1H, J = 15.5, 5.8 Hz), 5.73 (dd, 1H, J = 16.7, 6.0 Hz); ^{13}C NMR ($CDCl_3$/MeOD) δ 14.1, 22.7, 22.8, 25.6, 25.9, 29.1, 29.4, 29.5, 29.7, 29.8, 31.8, 32.0, 36.7, 37.1, 54.7, 61.6, 71.9, 72.6, 129.5, 135.6, 174.9; HR-MS [FAB, MNa^+] *m*/*z* calcd for $C_{26}H_{51}NO_4Na$ 464.3716, found 464.3707.

Data for (3*S*,4*S*)-2-[(1′*E*)-1′-Tetradecenyl]-3-hydroxy-4-octanoylamidotetrahydrofuran [(+)-30]: mp 142.0−143.0 °C; $[\alpha]^{25}_D$ +12.9° (*c* 0.9, $CHCl_3$/MeOH, 4:1); IR 1665, 1510, 1467, 1223 cm^{-1}; ^1H NMR ($CDCl_3$/MeOD) δ 0.88 (t, 6H, J = 6.4 Hz), 1.20−1.70 (m, 30H), 2.08 (q, 2H, J = 6.9 Hz), 2.21 (t, 2H, J = 7.4 Hz), 3.62 (t, 1H, J = 8.2 Hz), 3.79 (br s, 3H), 4.06 (m, 2H), 4.29 (q, 1H, J = 3.0 Hz), 4.53 (m, 1H), 5.60 (dd, 1H, J = 15.4, 7.4 Hz), 5.83 (dt, 1H, J = 15.4, 8.5 Hz); ^{13}C NMR ($CDCl_3$/ MeOD) δ 13.56, 13.6, 22.2, 22.3, 25.4, 28.6, 28.7, 28.8, 28.9, 29.2, 29.27, 29.3, 31.3, 31.6, 32.2, 36.0, 52.4, 69.4, 71.8, 83.1, 124.0, 136.4, 174.3; HR-MS [DCI, $MH^+ - H_2O$] *m*/*z* calcd for $C_{26}H_{48}NO_2$ 406.3685, found 406.3669; MS [ESI, MH^+] *m*/*z* calcd for $C_{26}H_{50}NO_3$ 424.3, found 424.3. The configuration at C-2 was not determined.

(3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-pentadecyne [(+)-32]. This compound was prepared in 95% yield by using the same procedure as described for **25**: $[\alpha]^{25}_D$ +20.7° (*c* 0.7, $CHCl_3$); IR 1708, 1467, 1256, 1093, 837 cm^{-1}; ^1H NMR δ 0.10 (s, 3H), 0.13 (s, 3H), 0.89 (m, 12H), 1.20−1.40 (m, 20H), 1.65 (m, 2H), 2.34 (d, 1H, J = 2.1 Hz), 4.32 (m, 1H); ^{13}C NMR δ −5.1, −4.5, 14.1, 18.2, 22.7, 25.2, 25.8, 29.3, 29.4, 29.61, 29.64, 29.71, 29.74, 32.0, 38.6, 62.8, 71.8, 85.8; MS [ESI] *m*/*z* 356.3 (MNH_4^+).

***N*-*tert*-Butoxycarbonyl-(4*S*,1′*R*,4′*R*)-4-[4′-(*tert*-butyldimethylsilyloxy)-1′-hydroxy-2′-hexadecynyl]-2,2-dimethyl-1,3-oxazolidine [(−)-33].** To a solution of 1.01 g (3.0 mmol) of alkyne **32** in 15 mL of dry THF was slowly added 1.3 mL (3.2 mmol) of *n*-BuLi (a 2.5 M solution in hexanes) at −78 °C under N_2. After the mixture was stirred for 30 min at −78 °C, HMPA (1.05 mL, 6.0 mmol) was added, followed by a solution of 0.69 g (3.0 mmol) of **26** in 10 mL of dry THF. The mixture was kept at −78 °C for 2 h, and then allowed to warm to rt for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. *N*-Boc-1,3-oxazolidine **33** was isolated by chromatography on silica gel (hexane/EtOAc, 4:1): $[\alpha]^{25}_D$ −4.3° (*c* 1.8, $CDCl_3$); IR 1696, 1375, 1010 cm^{-1}; ^1H NMR (C_6D_6, 70 °C) δ 0.13 (s, 3H),

(31) The 1,3-oxazolidine carbamate system exists as a pair of rotamers, the interconversion of which is enhanced at high temperature; therefore, proton NMR spectra were recorded at 70 °C.

(32) Some of the signals in the ambient-temperature ^{13}C NMR spectra appear as a pair of singlets (denoted in parentheses).

0.18 (s, 3H), 0.88 (t, 3H, J = 6.1 Hz), 0.96 (s, 9H), 1.20−1.80 (m, 37H), 3.79 (t, 1H, J = 7.1 Hz), 4.00 (br s, 2H), 4.41 (t, 1H, J = 5.0 Hz), 4.70 (br s, 1H); ^{13}C NMR (C_6D_6) δ −4.8, −3.9, 14.4, 18.4, 23.1, 23.4, 24.0, 25.5, 25.7, 26.1, 26.3, 28.2, 28.4, 29.7, 29.8, 30.0, 30.1, 37.0, (63.1) 63.4, 64.2 (64.6), (65.0) 65.2, (79.8) 80.8, 83.6 (83.7), 87.5 (88.0), 95.0, (151.7) 154.3; HR-MS [FAB, MNa^+] m/z calcd for $C_{32}H_{61}NO_5SiNa$ 590.4217, found 590.4231.

(2*S*,3*R*,6*R*)-2-Octanoylamido-4-octadecyne-1,3,6-triol [(−)-34]. This compound was prepared in 80% yield by using the same procedure as described for **31**: mp 82.5−83.5 °C; $[\alpha]^{25}_D$ −1.56° (*c* 1.8, $CDCl_3$); IR 3427, 1657, 1512, 1463, 1053 cm^{-1};^{1}H NMR δ 0.85 (t, 6H, J = 6.4 Hz), 1.20−1.70 (m, 32H), 2.22 (t, 2H, J = 7.5 Hz), 3.71 (dd, 1H, J = 10.9, 3.4 Hz), 4.04 (m, 2H), 4.32 (t, 1H, J = 6.5 Hz), 4.59 (d, 1H, J = 3.6 Hz), 6.65 (d, 1H, J = 7.9 Hz); ^{13}C NMR δ 14.06, 14.1, 22.6, 22.7, 25.4, 25.7, 29.1, 29.3, 29.4, 29.67, 29.72, 31.7, 32.0, 36.7, 37.7, 54.9, 61.8, 62.0, 63.2, 82.5, 88.1, 174.9; HR-MS [DCI, MH^+] m/z calcd for $C_{26}H_{50}NO_4$ 440.3740, found 440.3742.

(2*S*,3*R*,6*R*)-2-Octanoylamido-(4*E*)-octadecene-1,3,6-triol [(−)-3]. This compound was prepared in 88% yield by using the same procedure as described for **2**: mp 92.0−93.0 °C; $[\alpha]^{25}_D$ −10.0° (*c* 1.0, $CHCl_3$); IR 3426, 1658, 1510, 1467, 1224 cm^{-1}; ^{1}H NMR δ 0.88 (t, 6H, J = 6.4 Hz), 1.20−1.70 (m, 32H), 2.23 (t, 2H, J = 7.5 Hz), 3.70 (dd, 1H, J = 10.9, 3.4 Hz), 3.94 (m, 2H), 4.13 (q, 1H, J = 6.1 Hz), 4.37 (t, 1H, J = 4.1 Hz), 5.79 (dd, 1H, J = 15.5, 5.8 Hz), 5.81 (dd, 1H, J = 16.7, 6.0 Hz), 6.38 (d, 1H, J = 7.4 Hz); ^{13}C NMR δ 14.1, 22.6, 22.7, 25.5, 25.7, 29.0, 29.2, 29.4, 29.6, 29.7, 31.7, 31.9, 36.8, 37.3, 54.4, 62.1, 71.9, 73.8, 129.4, 135.6, 174.2; HR-MS [FAB, MNa^+] m/z calcd for $C_{26}H_{51}NO_4Na$ 464.3716, found 464.3700.

Acknowledgment. This work was supported by National Institutes of Health Grant HL 16660.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **2**, **3**, **5**, **8**, **10**, **11**, **14**, **16**, **17**, **24**, **25**, **27**, and **29**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026240+