Stereoselective Preparation of Ceramide and Its Skeleton Backbone Modified Analogues via Cyclic Thionocarbonate Intermediates Derived by Catalytic Asymmetric Dihydroxylation of α,β-Unsaturated Ester Precursors

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A novel and efficient synthetic route to ceramide **1a** and skeleton backbone modified ceramide analogues **1b**,**c** is reported. The syntheses utilize osmium-catalyzed asymmetric dihydroxylation of (*E*)-α,*β*-unsaturated ester **5a**−**c** as the chiral induction step, with the desired configurations in the products **1a**−**c, 2a**, and **13** being generated by regioselective azide substitution at the α position of α,*β*-dihydroxyesters **6a**−**c** via a cyclic thionocarbonate intermediate. Azido esters **10a**−**c** are converted to the corresponding ceramides **1a**−**c** by a sequence of azide reduction, *N*-acylation, ester reduction ($NaBH_4$/LiBr), and Birch reduction of the triple bond (Li, $EtNH_2$). These seven- to eight-step syntheses afford the target compounds **1a**−**c** with excellent stereocontrol and in 30−42% overall yields. Furthermore, propargylic α-azido-*β*-hydroxyester **10a** is converted to D-*erythro*-sphingosine **2a** via simultaneous reduction of the triple bond, azido, and ester functional groups with $LiAlH_4$, providing a highly concise and practical four-step synthesis of this key naturally occurring sphingolipid. The L-erythro stereoisomers are also available in high enantiomeric purity by the method described herein.

Introduction

Sphingolipids are distributed ubiquitously in the membranes of eukaryotic cells,[1] where they were previously thought to play only a structural role. In recent years, however, a great deal of attention has been devoted to studies of the biological processes regulated by sphingolipids, and evidence of newly discovered roles of these compounds in cell functions is continually being demonstrated. In response to stress stimuli such as inflammatory cytokines, chemotherapeutic agents, heat shock, and UV−C and ionizing radiation, a cell-line dependent (e.g., endothelial, lymphoid, and hematopoietic) increase in sphingosine and ceramide (*N*-acylsphingosine, **1a**) levels takes place, leading to cell growth arrest and initiation of programmed cell death (apoptosis).[2] Ceramide, which is produced by stimulation of sphingomyelinases or by de novo synthesis, is a second messenger that triggers multiple receptor-mediated cell signaling pathways.[3] In contrast to the wealth of information available concerning the functions of ceramide in various cell types, the molecular mechanisms by which ceramide exerts its activities are not well understood. Potential targets for ceramide action include protein phosphatases, protein kinases, and other membrane-associated enzymes.[2b,c,3,4]

In view of their biological importance, sphingolipids have attracted the attention of many synthetic chemists. Many routes to enantiomerically pure sphingolipids have been described; L-serine and carbohydrates have been used extensively as the chiral synthons, and approaches involving asymmetric induction to control the stereochemistry are also available.[5,4,5] Unnatural ceramide analogues may be useful in the investigation of ceramide's modes of action and also may provide opportunities for modulating the cellular responses mediated by ceramide. As an extension of our work on the syntheses of phytosphingolipids[6] and of ceramides bearing a C(5)−C(6) double bond,[7] we describe here an efficient, stereocontrolled synthesis of Δ^4-ceramide **1a** and analogues **1b**,**c**, which are modified in the sphingolipid backbone by having the trans double bond positioned at C(7)−C(8)

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(1) Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins, and Membranes*; Vance, D. E., Vance, J. E., Eds.; Elsevier: Amsterdam, 1991; pp 327−361.

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(5) For recent reviews, see: (a) Jung, K.-H.; Schmidt, R. R. In *Lipid Synthesis and Manufacture*; Gunstone, F. D., Ed.; Sheffield Academic Press: Sheffield, U. K.; CRC Press: Boca Raton, FL, 1999; pp 208−249. (b) Curfman, C.; Liotta, D. *Methods Enzymol.* **2000**, *311*, 391−457. (c) Koskinen, P. M.; Koskinen, A. M. P. *Methods Enzymol.* **2000**, *311*, 458−479.

(6) He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7618−7626.

(7) He, L.; Byun, H.-S.; Smit, J.; Wilschut, J.; Bittman, R. *J. Am. Chem. Soc.* **1999**, *121*, 3897−3903.

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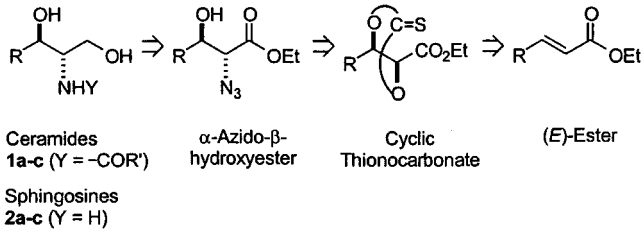
Scheme 1. Retrosynthetic Plan



and C(15)−C(16), respectively. We also now report a practical synthesis of D-*erythro*-(2*S*,3*R*)-sphingosine (**2a**), the backbone component of various sphingolipids, from 1-pentadecyne.

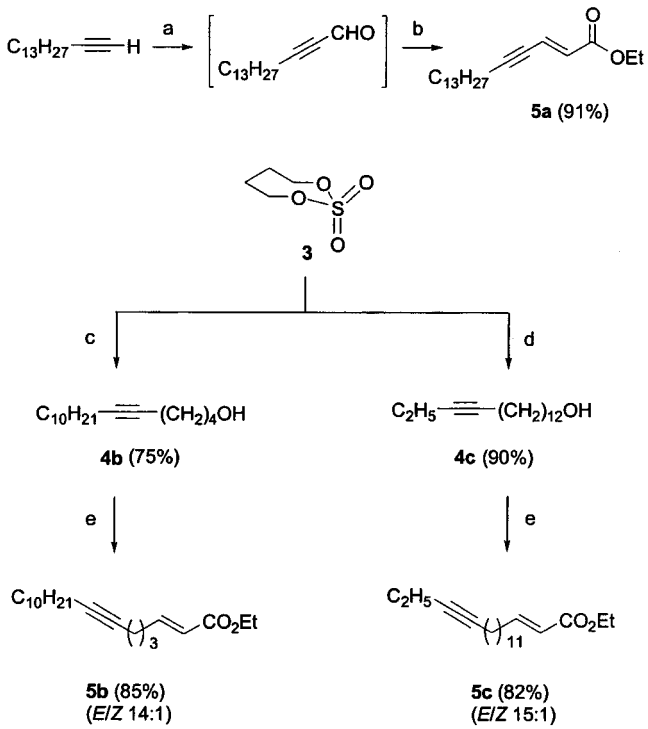
Results and Discussion

Synthetic Plan. As outlined in Scheme 1, the strategy for the preparation of ceramides **1a**−**c** involves three major reactions: (1) asymmetric dihydroxylation of an (*E*)-α,*β*-unsaturated ester as the chiral induction stage,[8] (2) regioselective introduction of the azido group at the α position, with inversion, via a cyclic thionocarbonate intermediate, and (3) selective reduction of the ester functional group after the azido group has been converted to a long-chain amido group. The synthetic route has the advantage of being simple, efficient, and highly enantioselective.

Synthesis of (*E*)-α,*β*-Unsaturated Esters 5a−c. Since an isolated double bond is more reactive in the asymmetric dihydroxylation reaction than the C(2)−C(3) double bond in conjugation with an ester functional group,[9] a synthon with a triple bond was chosen for the construction of (*E*)-α,*β*-unsaturated esters **5a**−**c** (Scheme 2). The required trans geometry was generated subsequently by Birch reduction of the triple bond. The Horner−Wadsworth−Emmons (HWE)[10] reaction was employed for the construction of the α,*β*-unsaturated ester via coupling of the corresponding aldehyde with a phosphonate reagent.[11] As shown in Scheme 2, the required precursors 5-hexadecyn-1-ol (**4b**) and 13-hexadecyn-1-ol (**4c**) were obtained in 90% and 75% yields, respectively, via ring opening of cyclic sulfate **3**[12] with lithium 1-dodecyne and 9-dodecynylmagnesium bromide, respectively, in the presence of a catalytic amount of CuI.[13] During the preparation of 9-dodecynylmagnesium bromide, a small amount of 9-dodecyn-1-ol was reproducibly formed, which made it difficult to purify the desired product **4b**. Fortunately, the directly obtained ring-opened product is a sulfate salt, which is insoluble in hexane−THF mixtures, whereas the byproduct (9-dodecyn-1-ol) is soluble. Therefore, the latter could be removed by simply adding hexane to the reaction mixture when the reaction was completed and separating the solid and liquid phases. Ynols **4b**,**c** were converted to the corresponding aldehydes in almost quantitative yield via Swern oxidation.[14] Although hexadec-2-yn-1-ol (**4a**) can be prepared by coupling of propargyl alcohol with 1-bromotridecane using lithium amide,[15] we found that Swern and PCC oxidation of alcohol **4a** provided the desired aldehyde in only moderate yield. Alternatively, formylation of lithium 1-pentadecyne with 1-formylpiperidine provided the desired hexadec-2-ynal in almost quantitative yield. HWE olefination of hexadec-2-ynal and of the aldehydes derived from alcohols **4b**,**c** with triethyl phosphonoacetate provided enyne esters **5a**−**c** in high yield and good *E*/*Z* ratio (10:1−15:1). Use of diisopropyl (ethoxycarbonylmethyl)phosphonate in the HWE reaction improved the *E*/*Z* ratio significantly; for example, *E*-**5a** was formed (in 91% yield) exclusively.[16]

Asymmetric Dihydroxylation of (2*E*)-α,*β*-Unsaturated Esters 5a−c. Asymmetric dihydroxylation of

Scheme 2. Synthesis of α,*β*-Unsaturated Esters 5a−c[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −23 to 0 °C, (ii) 1-formylpiperidine; (b) (*i*-PrO)$_2$P(O)CH$_2$CO$_2$Et, LiBr, Et$_3$N, THF, rt; (c) (i) 1-dodecyne, *n*-BuLi, THF, −23 °C, then CuI (cat.), **3**, rt; (d) 1-bromododec-9-yne, Mg, THF, reflux; then CuI (cat.), **3**, rt; (e) (i) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78 to −42 °C, (ii) (EtO)$_2$P(O)CH$_2$CO$_2$Et, LiBr, Et$_3$N, THF, rt.

(8) The Sharpless asymmetric aminohydroxylation (AA) reaction of olefins, such as (*E*)-α,*β*-unsaturated esters **5**, is a powerful reaction for the stereocontrolled construction of a vicinal hydroxyamido moiety. For AA reactions of olefins, see: Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483−1486, and references therein. However, the AA reaction produces a 3-amido-2-hydroxyester instead of the desired 2-amido-3-hydroxyester. Although Morgan et al. (Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949−1952) demonstrated recently that the AA reaction of 4-haloaryl esters provided a 2-amido-3-hydroxyester as the major product, the chemical yield and the % ee are generally unsatisfying. Furthermore, the AA reaction produces the threo instead of the desired erythro stereochemistry.

(9) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(10) For a review of the HWE reaction, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

(11) (a) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624−2626. (b) The *Z* and *E* stereoisomers were separated by column chromatography (elution with hexane/EtOAc 25:1) and characterized by ^{1}H NMR.

(12) Cyclic sulfate **3** was prepared from 1,4-butanediol in 72% yield by using the Gao and Sharpless procedure (ref 19).

(13) For recent reviews of cyclic sulfate chemistry, see: (a) Lohray, B. B.; Bhushan, V. *Adv. Heterocycl. Chem.* **1997**, *68*, 89−180. (b) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051−7091.

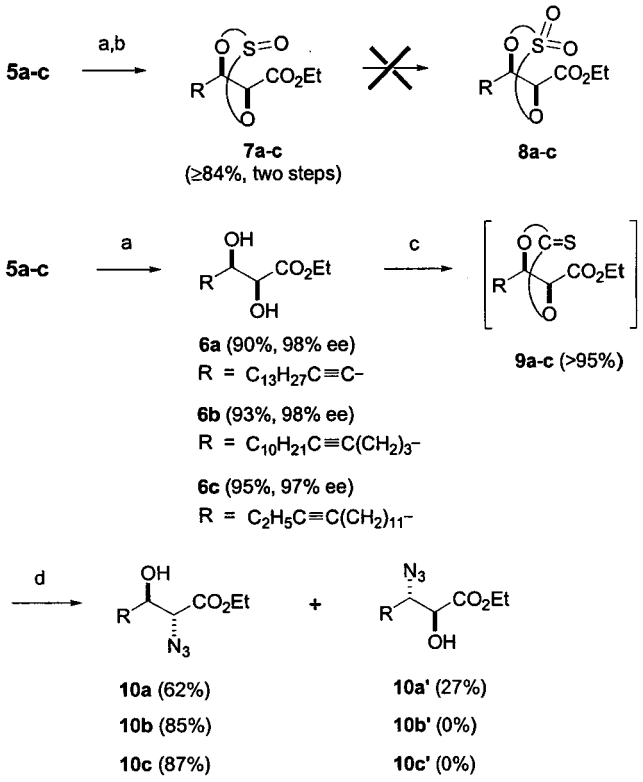
(14) For reviews of the Swern oxidation, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857−870. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572.

(15) Ruan, Z.-S. Ph.D. Thesis, The City University of New York, 1990.

enyne esters **5b**,**c** proceeded smoothly, affording the desired 2,3-diol esters in excellent yield and chiral purity. However, under the optimized conditions reported by Sharpless and co-workers in 1992,[17] asymmetric dihydroxylation of enyne ester **5a** was unsuccessful. In view of the electron deficiency of the double bond, it is not surprising that the reaction using commercial AD-mix (both α and β) proceeded very slowly and was incomplete. Thus, only a very low yield (~20%) of diol ester **6a** was obtained initially, even after prolonged reaction. The yield was not improved by changing the solvent system, e.g., by varying the *t*-BuOH/H_2O ratio or by using other solvents such as MeCN/H_2O or MeCN/H_2O/EtOAc. This problem was overcome by the addition of more osmium reagent ($K_2OsO_4 \cdot 2H_2O$) and chiral ligand [$(DHDQ)_2$−PHAL or $(DHQ)_2$−PHAL] to the commercial AD-mix-β/α. The desired diol ester **6a** was obtained in 90% yield and 98% ee.[18] Although asymmetric dihydroxylation of both conjugated enynes and α,β-unsaturated esters has been well documented,[9] to the best of our knowledge this is the first reported example of the asymmetric dihydroxylation reaction at a conjugated olefin located between a triple bond and an ester functional group.

Regioselective α-Azidation of Diol Esters 6a−c (Scheme 3). Regioselective α-azidation of diol esters **6a**−**c** via a cyclic sulfate intermediate was attempted. However, the desired cyclic sulfate intermediate **8a**−**c** of all three diols **6a**−**c** could not be formed, since under the oxidation conditions ($NaIO_4$, cat. $RuCl_3$, MeCN, H_2O) required for the conversion of a cyclic sulfite to the corresponding cyclic sulfate,[19] the triple bond was also oxidized.[20] Attempts to achieve a kinetic differentiation of the triple bond and cyclic sulfite also failed. The triple bond became oxidized just as quickly as the sulfite group in the same molecule. Several other oxidants were also tried for the oxidation of cyclic sulfite **7** to cyclic sulfate **8**.[21] Direct azidation of cyclic sulfite **7a**−**c**[13] at high temperature (e.g., 90−120 °C) was also unsuccessful. Regioselective monoazidation of **6a** via Mitsunobu reaction using Ph_3P, DIAD, and $TMSN_3$ in CH_2Cl_2[22] furnished β-azido ester **10a′** instead of the desired α-azido ester **10a** as the major product. Although α-azido esters **10b**,**c** could be obtained in moderate yields (~60%) via nucleophilic azide substitution of ethyl α-(*p*-nitrophenylsulfonyloxy)-β-hydroxyoctadec-7/15-ynoate (derived from the regioselective reaction of diol ester **6b** or **6c** with *p*-nitrophenylsulfonyl chloride in the presence of Et_3N),[23] the same reaction conditions provided the α-nosylate intermediates of diol **6a** in only low yield (due to the formation of α,β-bissulfonate and α-sulfonyloxy-α,β-unsaturated ester). Finally, cyclic thionocarbonate chemistry[24] was found to be the best choice (Scheme 3). Thus, diols **6a**−**c** were quantitatively converted to the corresponding cyclic thionocarbonates **9a**−**c** by reaction with thiophosgene in the presence of a catalytic amount of DMAP; then the crude cyclic thionocarbonate was subjected to a ring-opening reaction with NaN_3. In the ring opening of cyclic thionocarbonates **9b**,**c** with N_3^-, the nucleophile attacked the α position exclusively, providing **10b**,**c** in high yield (85% and 87%, respectively). Although the overall monoazidation of diol **6a** was also achieved in 89% yield (**10a** + **10a′**) via cyclic thionocarbonate **9a**, only a moderate degree of regioselectivity (α/β 2.4/1) was achieved. Presumably, the triple bond in cyclic thionocarbonate **9a** activates the β position toward nucleophilic substitution.

Scheme 3. Synthesis of (2*S*,3*R*)-α-Azido-β-hydroxyesters 10a−c via Cyclic Thionocarbonate Intermediates 9a−c[a]



[a] Reagents and conditions: (a) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, rt; (b) $SOCl_2$, py, CH_2Cl_2, 0 °C; (c) $Cl_2C{=}S$, py, DMAP (cat.), CH_2Cl_2, 0 °C; (d) NaN_3, DMF, PPTS, 0 °C.

Synthesis of Ceramides 1a−c. As shown in Scheme 4, α-azido-β-hydroxyesters **10a**−**c** were converted to ceramide **1a** and ceramide analogues **1b**,**c** in high yields via Staudinger reduction followed by in situ *N*-acylation, selective reduction of the ester functional group with $NaBH_4$/LiBr/THF, and Birch reduction using Li/$EtNH_2$.

(16) Generally, use of a larger phosphonoester reagent in the HWE reaction gives a higher *E*/*Z* ratio (Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873−3888).

(17) 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.

(18) The ee of diols **6a**−**c** was determined by ^1H NMR analysis of the corresponding bis-Mosher esters derived from these diols and their enantiomers.

(19) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1538−1539.

(20) (a) Carlsen, P. H. J.; Katsuki, T.; Martín, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938. (b) Martín, V. S.; Palazón, J. M.; Rodríguez, C. M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, U.K., 1995; pp 4415−4422. (c) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2607−2624.

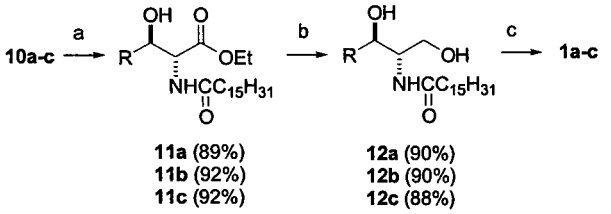
(21) Attempts to oxidize cyclic sulfite **7** to **8** by using $K_3[Fe(CN)_6]$, $NaIO_4$, CrO_3, or CrO_3 on silica gel were unsuccessful.

(22) He, L.; Wanunu, M.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1999**, *64*, 6049−6055.

(23) Regioselective α-nosylation of an α,β-dihydroxyester may result from the acidity difference of the two hydroxyl groups or from intramolecular hydrogen bonding of the β-hydroxy group with the carboxylate oxygen: (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. (c) Hoffman, R. V.; Kim, H.-O. *J. Org. Chem.* **1991**, *56*, 6759−6764.

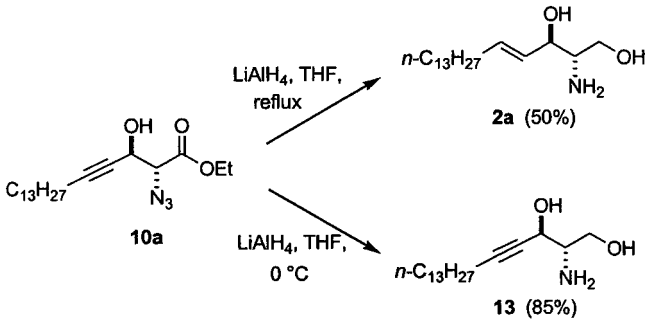
(24) Ko, S. Y. *J. Org. Chem.* **1995**, *60*, 6250−6251.

Scheme 4. Syntheses of D-*erythro*-*trans*-Δ^4-, Δ^7-, and Δ^{15}-Ceramides 1a−c[a]



[a] Reagents and conditions: (a) Ph_3P, *n*-$C_{15}H_{31}CO_2C_6H_4NO_2$-*p*, THF/$H_2O$ 9:1, rt; (b) $NaBH_4$, LiBr, THF, rt; (c) Li, $EtNH_2$, THF, −78 °C.

Scheme 5. One-Pot Conversion of Azido Ester 10a to Sphingosine Analogue 13 and Sphingosine 2a



This seven-step synthesis provided ceramide **1a** in 30% overall yield[25] and ceramide analogues **1b** and **1c** in 38% and 42% yields. Moreover, the triple bond, azido, and ester functional groups in azido ester **10a** were reduced simultaneously by $LiAlH_4$ in THF at reflux, furnishing D-*erythro*-sphingosine **2a** in 50% yield (Scheme 5). (The triple-bond analogue of sphingosine **13** was obtained in 85% yield when the reduction was carried out at 0 °C. Selective *N*-acylation of **13** provided the triple-bond ceramide analogue **12a**.) Thus, starting from the inexpensive precursor 1-pentadecyne, we developed a practical four-step synthesis of D-*erythro*-sphingosine **2a** in 23% overall yield. The structure of **2a** was confirmed by the identity of its physical data (^1H and ^{13}C NMR, IR, $[\alpha]^{25}_D$, mp) with those reported in the literature.[26]

L-*erythro*-Sphingosine and L-*erythro*-ceramide were prepared in similar yields by the same reaction sequence by simply using AD-mix-α rather than AD-mix-*β* in the dihydroxylation step.

The strategy used for the efficient syntheses of **1b** and **1c** represents a versatile methodology for moving the trans double bond (which is between C(4) and C(5) in ceramide **1a**) to other positions in the long-chain base. As noted previously,[7] there are several examples of biological processes that are affected differentially by the double-bond position in substrates, inhibitors, and other ligands. Thus it will be of interest to examine the biological properties of trans double-bond regioisomers of sphingolipids.

Conclusions

A novel and efficient synthetic route has been developed for the synthesis of D-*erythro*-ceramide **1a**. The requisite chirality was introduced in two key steps: asymmetric dihydroxylation of an α,*β*-unsaturated ester and regioselective introduction of azide ion to the α position of a cyclic thionocarbonate intermediate. Using a similar synthetic strategy, ceramide analogues bearing a *E* double bond at different positions along the sphingoid backbone (e.g., **1b** and **1c**) were synthesized in high yield and chiral purity. Simultaneous reduction of the triple bond, azido, and ester functional groups in **10a** by $LiAlH_4$ furnished D-*erythro*-sphingosine **2a** (four steps, 23% overall yield), completing a practical and concise route to this important sphingolipid.

Experimental Section

General Information. See the previous reports for general experimental details.[6,7] Thiophosgene was purchased from Acros. NMR spectra were recorded in $CDCl_3$ unless otherwise noted.

5-Hexadecyn-1-ol (4b). To a stirred solution of 5.9 g (34.2 mmol) of 1-dodecyne in 200 mL of freshly distilled THF at −23 °C was injected 13.7 mL (34.2 mmol) of *n*-BuLi (a 2.5 M solution in hexane). The reaction mixture was stirred for 4.5 h at this temperature under nitrogen, during which time a milk-like suspension was obtained. After 300 mg (1.6 mmol) of CuI was added, the cold bath was removed. Stirring was continued, and 15 min later a solution of 2.6 g (17.1 mmol) of cyclic sulfate **3** in 20 mL of THF was injected. The reaction mixture was stirred overnight under nitrogen at room temperature. After most of the THF was blown out by using a gentle stream of air, 200 mL of Et_2O and 80 mL of 20% aqueous H_2SO_4 were added. The heterogeneous solution was stirred vigorously at room temperature for 24 h. The two layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layer was treated with anhydrous K_2CO_3 to remove the dissolved sulfuric acid, dried (Na_2SO_4), and concentrated. The liquid residue was purified by column chromatography (elution with hexane/EtOAc 4:1), affording 3.2 g (75%) of alkynol **4b** as a pink oil: IR 3563 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 15H), 1.45 (m, 2H), 1.54 (m, 2H), 1.66 (m, 2H), 2.10 (tt, 2H, J = 7.1, 2.3 Hz), 2.17 (tt, 2H, J = 7.0, 2.3 Hz), 3.65 (t, 2H, J = 6.5 Hz); ^{13}C NMR δ 14.11, 18.53, 18.73, 22.68, 25.35, 28.89, 29.13, 29.16, 29.32, 29.55, 29.58, 31.88, 31.90, 62.54, 79.69, 80.77.

Hexadec-13-yn-1-ol (4c). To a solution of 8.9 g (36.5 mmol) of 1-bromo-9-dodecyne in 140 mL of freshly distilled THF in a 500-mL three-neck round-bottomed flask was added 1.6 g (65.8 mmol) of magnesium turnings and two drops of 1,2-dibromoethane. After being flushed with nitrogen, the reaction mixture was stirred vigorously under reflux until the shiny magnesium metal became dark or gray (1.5−2 h). After the reaction mixture was cooled to about room temperature, a catalytic amount of CuI (250 mg, 1.3 mmol) was added, which made the light yellow solution turn to purple. After stirring was continued for another 10 min, the reaction mixture was chilled to −23 °C, and a solution of 3.7 g (24.3 mmol) of cyclic sulfate **3** in 30 mL of dry THF was injected. The reaction mixture was stirred at this temperature until cyclic sulfate **3** was completely consumed (TLC). After most of the THF was removed by using a gentle stream of air, 300 mL of hexane was added to the

(25) The ^1H NMR spectra, IR, specific rotation, and melting point of **1a** were in accord with those reported in the literature.[26a,g] The ^{13}C NMR spectrum was consistent with that reported in ref 26a; Ohashi et al.[26g] did not report the ^{13}C NMR spectrum.

(26) (a) Shibuya, H.; Kawashima, K.; Narita, N.; Ikeda, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1992**, *40*, 1154−1165. (b) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510−520. (c) Murakami, T.; Hato, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 823−827. (d) Enders, D.; Whitehouse, D. L.; Runsink, J. *Chem. Eur. J.* **1995**, *5*, 382−388. (e) Katsumara, S.; Yamamoto, N.; Fukuda, E.; Iwama, S. *Chem. Lett.* **1995**, 393−394. (f) Solladié-Cavallo, A.; Koessler, J. L. *J. Org. Chem.* **1994**, *59*, 3240−3242. (g) Ohashi, K.; Kosai, S.; Arizuka, M.; Watanabe, T.; Yamagiwa, Y.; Kamikawa, T.; Kates, M. *Tetrahedron* **1989**, *45*, 2557−2570. (h) Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5320−5327. (i) Groth, U.; Schöllkopf, U.; Tiller, T. *Tetrahedron* **1991**, *47*, 2835−2842. (j) Zimmermann, P.; Schmidt, R. R. *Liebigs Ann. Chem.* **1988**, 633−667.

slurry. The heterogeneous solution was stirred vigorously for 10 min and then allowed to stand for precipitation. The clear top solution was separated. The precipitate (i.e., slurry) was washed again with another 300 mL of hexane. After separation, Et_2O (200 mL) and 20% aqueous H_2SO_4 (80 mL) were added to the precipitate. The heterogeneous solution was stirred vigorously at room temperature for 24 h. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 150 mL). The combined ether layers were treated with anhydrous K_2CO_3 to remove the dissolved H_2SO_4, dried (Na_2SO_4), and concentrated. Purification of the light yellow residue by flash chromatography (elution with hexane/EtOAc 4:1) provided 5.2 g (90%) of the desired alcohol **4c** as a white solid: mp 40.8−41.2 °C; IR 3560 cm^{-1}; ^1H NMR δ (t, 3H, J = 7.4 Hz), 1.24 (m, 14H), 1.49 (m, 6H), 2.12 (m, 4H), 3.61 (t, 2H, J = 6.6 Hz); ^{13}C NMR δ 12.41, 14.37, 18.71, 25.72, 28.85, 29.13, 29.41, 29.50, 29.58, 32.76, 63.06, 79.57, 81.56.

Ethyl (2*E*)-Octadec-2-en-4-ynoate (5a). Hexadec-2-ynal (Scheme 2) was prepared by formylation of 1-pentadecyne as follows. To a solution of 1-pentadecyne (5.21 g, 25.0 mmol) in 100 mL of dry THF was added 11 mL (27.5 mmol) of *n*-BuLi (a 2.5 M solution in hexane) at −23 °C. The mixture was stirred at −23 °C for 2 h, then at room temperature for another 2 h. To the pentadecynyllithium suspension was added 3.1 mL (27.9 mmol) of 1-formylpiperidine at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 100 mL of 10% aqueous $NaHSO_4$ solution. The product was extracted with Et_2O (4 × 100 mL). The organic layer was washed with 10% aqueous $NaHSO_4$ solution (3 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The product, 2-hexadecynal, was obtained as a pale yellow liquid, which was thoroughly dried under high vacuum (0.7 Torr) and used without further purification in the subsequent HWE reaction (see the general procedure outlined below for the preparation of **5b**,**c**). **5a**: IR 2215, 1711, 1620 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 20H), 1.28 (t, 3H, J = 7.2 Hz), 1.49−1.56 (m, 2H), 2.34 (t, 2H, J = 6.7 Hz), 4.19 (q, 2H, J = 7.2 Hz), 6.12 (d, 1H, J = 15.9 Hz), 6.73 (d, 1H, J = 15.9 Hz); ^{13}C NMR δ 14.11, 14.20, 19.75, 22.68, 28.30, 28.86, 29.08, 29.35, 29.48, 29.60, 29.64, 29.67, 31.91, 60.55, 77.91, 100.87, 126.13, 129.21, 166.17; HR-MS (FAB, MH^+) m/z calcd for $C_{20}H_{35}O_2$ 307.2637, found 307.2644.

Ethyl (2*E*)-Octadec-2-en-7-ynoate (5b) and Ethyl (2*E*)-Octadec-2-en-15-ynoate (5c). These two compounds were prepared from alkynols (**4b**,**c**, respectively) via Swern oxidation and subsequent HWE olefination as follows. **a. Swern Oxidation.** To a solution of 780 mg (10.0 mmol) of DMSO in 40 mL of dry CH_2Cl_2 at −78 °C was injected 0.44 mL (5.0 mmol) of oxalyl chloride under nitrogen. The reaction mixture was stirred at this temperature for 10 min, followed by the injection of 2.0 mmol of alcohol **4b** or **4c** in 5−8 mL of dry CH_2Cl_2. The reaction temperature was then changed from −78 to −42 °C, and the reaction mixture was stirred at the latter temperature until the complete consumption of alcohol was noticed by TLC (<3 h). After 3 mL (28.0 mmol) of Et_3N was injected, the cold bath was removed and stirring was continued while the reaction mixture was allowed to warm to room temperature. The reaction mixture was transferred to a separatory funnel containing 50 mL of saturated aqueous $NaHCO_3$ solution, and the product was extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The crude aldehyde was dried thoroughly under high vacuum (0.7 Torr) and used without further purification in the subsequent reaction. **b. HWE Reaction.** To a nitrogen-flushed solution of 870 mg (10.0 mmol) of LiBr in 50 mL of freshly distilled THF was injected 2.4 mmol of $(EtO)_2P(O)CH_2CO_2Et$ or $(i\text{-}PrO)_2P(O)CH_2CO_2Et$ at room temperature. After the solution was stirred at room temperature for 10 min, 0.42 mL (4.0 mmol) of Et_3N was injected, and stirring was continued for another 15 min. A solution of the thoroughly dried crude aldehyde in 10 mL of dry THF was injected. A white precipitate was formed several minutes after the addition of the aldehyde. The reaction mixture was stirred vigorously at room temperature until the full consumption of the aldehyde 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 400 mL of hexane/EtOAc 6:1. Concentration gave a pale yellow oil that was purified by column chromatography (elution with a gradient of hexane/EtOAc 100:1−25:1).

5b: IR 2220, 1715, 1650 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.29 (m, 17H), 1.45 (m, 2H), 1.62 (m, 2H), 2.11 (tt, 2H, J = 7.1, 2.2 Hz), 2.17 (tt, 2H, J = 7.0, 2.3 Hz), 2.29 (ddt, 2H, J = 6.7, 6.6, 0.9 Hz), 4.17 (q, 2H, J = 7.1 Hz), 5.82 (dt, 1H, J = 15.6, 1.3 Hz), 6.94 (dt, 1H, J = 15.6, 7.0 Hz); ^{13}C NMR δ 14.11, 14.26, 18.25, 18.71, 22.67, 27.39, 28.88, 29.09, 29.15, 29.32, 29.55, 29.58, 31.12, 31.90, 60.16, 79.02, 81.21, 121.79, 148.38, 166.63; HR-MS (FAB, MH^+) m/z calcd for $C_{20}H_{35}O_2$ 307.2637, found 307.2629.

5c: IR 1707, 1648 cm^{-1}; ^1H NMR δ 1.09 (t, 3H, J = 7.5 Hz), 1.08−1.51 (m, 21H), 2.05−2.21 (m, 6H), 4.15 (q, 2H, J = 7.1 Hz), 5.78 (dt, 1H, J = 15.6, 1.3 Hz), 6.94 (dt, 1H, J = 15.6, 7.0 Hz); ^{13}C NMR δ 12.39, 14.26, 14.37, 18.71, 28.00, 28.84, 29.13, 29.37, 29.48, 29.54, 32.18, 60.10, 79.57, 81.56, 121.17, 149.50, 166.80; HR-MS (DEI, M^+) m/z calcd for $C_{20}H_{34}O_2$ 306.2559, found 306.2551.

General Procedures for Asymmetric Dihydroxylation of an α,β-Unsaturated Ester. After a solution of 14.0 g of AD-mix-β (or AD-mix-α) in 300 mL of *t*-BuOH/H_2O 1:1 was stirred vigorously at room temperature for 1 h, 950 mg (10.0 mmol) of methanesulfonamide was added, and stirring was continued for an additional 10 min at room temperature. After the reaction mixture was chilled with an ice−water bath, 10.0 mmol of the α,β-unsaturated ester (**5a**, **5b**, or **5c**) was added, and the reaction mixture was stirred vigorously at this temperature until the disappearance of the α,β-unsaturated ester was noticed (TLC). After sodium sulfite (15.0 g, 146.0 mmol) was added to quench the reaction, stirring was continued for another 30 min while the reaction mixture was allowed to warm to room temperature. The product was extracted with EtOAc or $CHCl_3$ (3 × 150 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a yellow solid residue, which was dissolved in a minimum volume of $CHCl_3$ and passed through a pad of silica gel in a sintered glass funnel to remove the ligand. The pad was washed with hexane/EtOAc 3:1 to collect the product. Concentration of the eluent provided an almost pure product. The % ee of diols **6a**−**c** was determined by ^1H NMR or ^{19}F NMR analysis of the corresponding bis-Mosher esters derived from both enantiomers.

Ethyl (2*S*,3*R*)-2,3-dihydroxyoctadec-4-ynoate [(−)-6a]: [27] 90% yield (98% ee); mp 57.3−57.9 °C; $[\alpha]^{25}_D$ −3.81° (*c* 3.15, $CHCl_3$); IR 3560, 2228, 1735 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 20H), 1.30 (t, 3H, J = 7.1 Hz), 1.48 (m, 2H), 2.20 (dt, 2H, J = 7.26, 2.0 Hz), 2.73 (br s, 2H), 4.22 (d, 1H, J = 2.8 Hz), 4.28 (q, 2H, J = 7.1 Hz), 4.62 (dt, 1H, J = 2.4, 2.0 Hz); ^{13}C NMR δ 14.10, 14.14, 18.68, 22.67, 28.46, 28.86, 29.11, 29.34, 29.49, 29.61, 29.63, 31.90, 62.40, 64.05, 73.80, 87.36, 171.82; HR-MS (FAB, MH^+) m/z calcd for $C_{20}H_{37}O_4$ 341.2692, found 341.2693.

Ethyl (2*S*,3*R*)-2,3-dihydroxyoctadec-7-ynoate [(+)-6b]: 94% yield (96% ee); mp 52.6−53.2 °C; $[\alpha]^{25}_D$ +12.63° (*c* 1.18, $CHCl_3$); IR 3563, 1732 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 14H), 1.30 (t, 3H, J = 7.0 Hz), 1.43−1.72 (m, 6H), 2.10 (tt, 2H, J = 7.1, 2.2 Hz), 2.20 (m, 2H), 3.90 (dt, 1H, J = 6.5, 1.9 Hz), 4.06 (d, 1H, J = 1.9 Hz), 4.27 (q, 2H, J = 7.1 Hz); ^{13}C NMR δ 14.15, 18.73, 25.28, 29.12, 29.31, 29.54, 31.89, 32.95, 62.17, 72.10, 73.11, 79.43, 80.91, 173.53; HR-MS [FAB, MH^+] m/z calcd for $C_{20}H_{37}O_4$ 341.2692, found 341.2699.

Ethyl (2*S*,3*R*)-2,3-dihydroxyoctadec-15-ynoate [(+)-6c]: 95% yield (96% ee); mp 62.0−62.5 °C; $[\alpha]^{25}_D$ +8.8° (*c* 1.72, $CHCl_3$); IR 3560, 1731 cm^{-1}; ^1H NMR δ 1.09 (t, 3H, J = 7.4 Hz), 1.24 (m, 15H), 1.30 (t, 3H, J = 7.2 Hz), 1.45 (m, 3H), 1.59 (m, 2H), 2.12 (m, 4H), 3.86 (dt, 1H, J = 7.5, 1.9 Hz), 4.05 (d, 1H, J = 1.9 Hz), 4.27 (q, 2H, J = 7.1 Hz); ^{13}C NMR δ 12.41, 14.16, 14.38, 18.72, 25.71, 28.86, 19.14, 29.50, 29.53, 29.57,

(27) For asymmetric dihydroxylation of 3.07 g (10.0 mmol) of enyne ester **5a** (Scheme 3), 160 mg of $(DHQ)_2$−PHAL/$(DHQD)_2$−PHAL and 30 mg of $K_2OsO_4{\cdot}(H_2O)_2$ were added to 15 g of commercial AD-mix-α/β before the reaction.

33.83, 62.13, 72.51, 72.98, 79.59, 81.57, 173.69; HR-MS [FAB, MH^+] *m/z* calcd for $C_{20}H_{37}O_4$ 341.2692, found 341.2693.

General Procedure for the α-Azidation of a Diol Ester via a Cyclic Thionocarbonate Intermediate. a. Preparation of a Cyclic Thionocarbonate. To a solution of 1.0 mmol of diol ester (**6a**, **6b**, or **6c**) in 18 mL of dry CH_2Cl_2 was added sequentially 325 mL (4.0 mmol) of pyridine, 10 mg (0.05 mmol) of DMAP, and 103 μL (1.3 mmol) of thiophosgene at 0 °C. The reaction mixture was stirred at this temperature under nitrogen until the total consumption of the diol ester was noted by TLC (<2 h). The reaction mixture was filtered through a pad of silica gel in a sintered glass funnel to remove the salts. The pad was washed with hexane/EtOAc 6:1, and the filtrate was concentrated under reduced pressure and dried under high vacuum (0.7 Torr, 3 h). The cyclic thionocarbonate was used directly in the subsequent azidation reaction without further purification. **b. Nucleophilic Ring Opening.** To a solution of the crude cyclic thionocarbonate in 8 mL of dry DMF was added 277 mg (1.1 mmol) of PPTS and 195 mg (3.0 mmol) of NaN_3 at 0 °C. The reaction mixture was stirred at this temperature under nitrogen until the disappearance of the cyclic thionocarbonate was noticed by TLC. [Alternatively, to a solution of 232 mg of crude cyclic thionocarbonate derived from diol **6a** in 12 mL of THF/DMF 5:1 were added 90 μL (0.68 mmol) of $TMSN_3$ and 2 mg (0.036 mmol) of NaN_3 at 0 °C. The reaction mixture was stirred at this temperature under nitrogen. *n*-Bu_4NF (1 mL, 1.0 M solution in THF) was added at 0 °C after the ring-opening reaction was completed.] The reaction mixture was diluted with 30 mL of H_2O and extracted with Et_2O (3 × 60 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The product was purified on silica gel (elution with hexane/EtOAc 20:1).

Ethyl (2*R*,3*R*)-2-azido-3-hydroxyoctadec-4-ynoate [(+)-10a]: $[\alpha]^{25}_D$ +17.4° (*c* 1.9, $CHCl_3$); IR 3575, 2227, 2111, 1740 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.22 (m, 20H), 1.30 (t, 3H, *J* = 7.1 Hz), 1.46 (tt, 2H, *J* = 7.4, 7.1 Hz), 2.17 (dt, 2H, *J* = 7.1, 1.9 Hz), 2.65 (br s, 1H), 3.99 (d, 1H, *J* = 5.1 Hz), 4.27 (m, 2H), 4.72 (dt, 1H, *J* = 5.1, 2.6 Hz); ^{13}C NMR δ 14.07, 18.60, 22.64, 28.18, 28.76, 29.05, 29.30, 29.46, 29.58, 29.60, 29.63, 31.87, 62.19, 63.35, 65.87, 75.97, 88.85, 167.59; HR-MS (FAB) *m/z* calcd for $C_{20}H_{36}O_3N_3$ 366.2757, found 366.2756. **10a′**: ^1H NMR δ 0.86 (*t*, 3H, *J* = 7.0 Hz), 1.15−1.40 (m, 24H), 1.49 (tt, 2H, *J* = 7.4, 7.1 Hz), 2.23 (dt, 2H, *J* = 7.0, 2.0 Hz), 3.08 (br s, 1H), 4.20−4.34 (m, 4H); ^{13}C NMR δ 14.10, 18.53, 22.65, 28.46, 28.67, 29.04, 29.32, 29.46, 29.58, 29.61, 29.64, 31.88, 55.70, 62.35, 69.98, 73.56, 91.34, 170.66.

Ethyl (2*R*,3*R*)-2-azido-3-hydroxyoctadec-7-ynoate [(+)-10b]: $[\alpha]^{25}_D$ +45.3° (*c* 2.38, $CHCl_3$); IR 3605, 2113, 1732 cm^{-1}; ^1H NMR δ 0.85 (t, 3H, *J* = 7.0 Hz), 1.24 (m, 16H), 1.32 (t, 5H, *J* = 7.1 Hz), 1.42−1.69 (m, 6H), 2.10 (tt, 3H, *J* = 7.0, 2.3 Hz), 2.18 (m, 2H), 3.94 (m, 2H), 4.28 (q, 2H, *J* = 7.0 Hz); ^{13}C NMR δ 14.11, 14.15, 18.49, 18.72, 22.67, 24.93, 28.90, 29.10, 29.17, 29.32, 29.54, 29.59, 31.90, 32.09, 62.11, 66.17, 71.49, 79.28, 81.09, 168.95; HR-MS (FAB) *m/z* calcd for $C_{20}H_{35}O_3N_3$ 365.2678, found 365.2693.

Ethyl (2*R*,3*R*)-2-azido-3-hydroxyoctadec-15-ynoate [(+)-10c]: $[\alpha]^{25}_D$ +43.54° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3590, 2113, 1735 cm^{-1}; ^1H NMR δ 1.09 (t, 3H, *J* = 7.5 Hz), 1.24 (m, 18H), 1.32 (t, 3H, *J* = 7.1 Hz), 1.47 (m, 6H), 1.82 (br s, 1H), 2.12 (m, 4H), 3.92 (m, 2H), 4.27 (q, 2H, *J* = 7.1 Hz); ^{13}C NMR δ 12.41, 14.17, 14.39, 18.72, 25.35, 28.86, 29.15, 29.37, 29.47, 29.52, 29.56, 33.02, 62.09, 66.18, 71.90, 79.59, 81.57, 168.99; HR-MS [FAB, M^+] *m/z* calcd for $C_{20}H_{35}O_3N_3$ 365.2678, found 365.2654.

General Procedure for the One-Pot Conversion of an Azido to an Amido Group. To a solution of 1.0 mmol of α-azidoester (**10a**, **10b**, or **10c**) and 944 mg (2.5 mmol) of *p*-nitrophenyl palmitate in 30 mL of THF/H_2O 9:1 was added 314 mg (1.2 mmol) of Ph_3P. The reaction mixture was stirred at room temperature under nitrogen for 48 h. After the solvents were removed in vacuo (2-PrOH was used to remove the H_2O residue), the light yellow residue was dissolved in 100 mL of Et_2O and washed with 1% aqueous Na_2CO_3 solution (4 × 20 mL) to remove the 4-nitrophenol byproduct. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (elution with hexane/EtOAc 5:1).

Ethyl (2*R*,3*R*)-2-palmitoylamido-3-hydroxyoctadec-4-ynoate [(−)-11a]: mp 82.4−83.1 °C; $[\alpha]^{25}_D$ −41.2° (*c* 1.5, $CHCl_3$); IR 3419, 2229, 1736, 1655, 1505 cm^{-1}; ^1H NMR δ 0.84 (t, 6H, *J* = 6.9 Hz), 1.23 (m, 44H), 1.28 (t, 3H, *J* = 7.3 Hz), 1.40 (tt, 2H, *J* = 7.6, 7.2 Hz), 1.60 (tt, 2H, *J* = 7.4, 6.8 Hz), 2.09 (dt, 2H, *J* = 7.1, 2.1 Hz), 2.17 (t, 2H, *J* = 7.4 Hz), 3.04 (br s, 1H), 4.23 (m, 2H), 4.81 (m, 2H), 6.03 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR δ 14.06, 14.11, 18.47, 22.64, 25.49, 28.45, 28.73, 29.07, 29.19, 29.31, 29.45, 29.49, 29.57, 29.61, 29.64, 31.71, 31.88, 36.50, 44.93, 62.19, 72.28, 73.72, 86.01, 171.32, 172.26; HR-MS (DCI, MH^+) *m/z* calcd for $C_{36}H_{68}NO_4$ 578.5148, found 578.5127.

Ethyl (2*R*,3*R*)-2-palmitoylamido-3-hydroxyoctadec-7-ynoate [(−)-11b]: mp 60.8−61.3 °C; $[\alpha]^{25}_D$ −23.3° (*c* 1.05, $CHCl_3$); IR 3426, 1731, 1668, 1508 cm^{-1}; ^1H NMR δ 0.85 (t, 6H, *J* = 7.0 Hz), 1.23 (m, 38H), 1.28 (t, 3H, *J* = 7.1 Hz), 1.41−1.64 (m, 8H), 2.08 (tt, 2H, *J* = 7.2, 2.2 Hz), 2.14 (m, 2H), 2.25 (t, 2H, *J* = 7.5 Hz), 2.92 (br s, 1H), 3.96 (m, 1H), 4.22 (m, 2H), 4.65 (dd, 1H, *J* = 6.6, 3.0 Hz), 6.45 (d, 1H, *J* = 6.6 Hz); ^{13}C NMR δ 14.11, 18.49, 18.72, 22.67, 25.16, 25.56, 28.92, 29.16, 29.21, 29.30, 29.34, 29.46, 29.54, 29.59, 29.64, 29.67, 31.89, 32.09, 36.38, 57.91, 61.98, 72.79, 79.32, 80.84, 170.31, 174.35; HR-MS (FAB, MH^+) calcd for *m/z* $C_{36}H_{68}NO_4$ 578.5148, found 578.5175.

Ethyl (2*R*,3*R*)-2-palmitoylamido-3-hydroxyoctadec-15-ynoate [(−)-11c]: mp 70.5−71.2 °C; $[\alpha]^{25}_D$ −25.1° (*c* 0.95, $CHCl_3$); IR 3421, 1732, 1669, 1507 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.09 (t, 3H, *J* = 7.4 Hz), 1.23 (m, 42H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.44 (m, 2H), 1.62 (m, 2H), 2.14 (m, 5H), 2.25 (t, 2H, *J* = 7.8 Hz), 3.92 (m, 1H), 4.22 (m, 2H), 4.65 (dd, 1H, *J* = 6.6, 3.0 Hz), 6.41 (d, 1H, *J* = 6.6 Hz); ^{13}C NMR δ 12.40, 14.11, 14.12, 14.37, 18.71, 22.67, 25.57, 25.65, 28.85, 29.14, 29.20, 29.30, 29.34, 29.47, 29.51, 29.54, 29.57, 29.59, 29.64, 29.67, 31.90, 33.20, 36.40, 57.88, 61.94, 73.23, 79.58, 81.57, 170.44, 174.28; HR-MS (FAB, MH^+) calcd for *m/z* $C_{36}H_{68}NO_4$ 578.5148, found 578.5162.

General Procedure for Selective Reduction of an Ester with $NaBH_4$−LiBr in the Presence of an Amide. To a heterogeneous mixture of 1.0 mmol of α-amido ester (**11a**, **11b**, or **11c**) and 868 mg (10.0 mmol) of LiBr in 40 mL of freshly distilled THF was added 454 mg (12.0 mmol) of $NaBH_4$ at 0 °C. The suspension was stirred vigorously at room temperature under nitrogen until the full consumption of starting ester was noticed (TLC). The reaction mixture was transferred to a sintered glass funnel containing a pad of silica gel with a Pasteur pipet. The pad was washed with 400 mL of $CHCl_3$/MeOH 15:1 by gravity to collect the product. The filtrate was concentrated, and the residue was purified by column chromatography (elution with $CHCl_3$/MeOH 50:1). The product was dissolved in $CHCl_3$ (15−25 mL) and passed through a Cameo filter (Fisher Scientific) to remove the dissolved silica gel.

(2*S*,3*R*)-2-Palmitoylamido-4-octadecyn-1,3-diol [(−)-12a]: mp 102.0−102.5 °C; $[\alpha]^{25}_D$ −8.2° (*c* 2.0, $CHCl_3$/MeOH 9:1); IR 3609, 3429, 2229, 1660, 1500 cm^{-1}; ^1H NMR δ 0.86 (t, 6H, *J* = 7.0 Hz), 1.24 (m, 44H), 1.48 (m, 2H), 1.61 (m, 2H), 2.20 (m, 4H), 2.30 (br s, 2H), 3.74 (dd, 1H, *J* = 11.3, 3.9 Hz), 4.02 (m, 1H), 4.11 (dd, 1H, *J* = 11.4, 3.8 Hz), 4.58 (m, 1H), 6.27 (d, 1H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 13.92, 18.53, 22.53, 25.60, 28.46, 28.82, 29.02, 29.13, 29.21, 29.24, 29.37, 29.41, 29.52, 29.54, 31.77, 36.50, 55.01, 61.68, 63.19, 77.62, 87.28, 174.71; HR-MS (DCI, MH^+) *m/z* calcd for $C_{34}H_{66}NO_3$ 536.5043, found 536.5046.

(2*R*,3*R*)-2-Palmitoylamido-7-octadecyn-1,3-diol [(+)-12b]: mp 88.2−88.9 °C; $[\alpha]^{25}_D$ +5.4° (*c* 1.3, $CHCl_3$); IR 3453, 1663, 1510 cm^{-1}; ^1H NMR δ 0.85 (t, 6H, *J* = 7.0 Hz), 1.23 (m, 38H), 1.44 (m, 2H), 1.63 (m, 6H), 2.10 (t, 2H, *J* = 7.1 Hz), 2.19 (m, 4H), 2.54 (br s, 2H), 3.72−3.83 (m, 3H), 3.99 (dd, 1H, *J* = 11.3, 3.1 Hz), 6.43 (d, 1H, *J* = 7.0 Hz); ^{13}C NMR δ 14.11, 18.59, 18.73, 22.67, 25.44, 25.76, 28.93, 29.13, 29.17, 29.32, 29.35, 29.50, 29.56, 29.65, 29.68, 31.90, 33.46, 36.83, 53.87, 62.44,

73.63, 79.42, 81.06, 173.72; HR-MS (FAB, MH^+) calcd for *m/z* $C_{34}H_{66}NO_3$ 536.5043, found 536.5021.

(2*S*,3*R*)-2-Palmitoylamido-15-octadecyn-1,3-diol [(+)-12c]: mp 90.5−91.5 °C; $[\alpha]^{25}_D$ +6.4° (*c* 1.54, $CHCl_3$); IR 3440, 1664, 1510 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.09 (t, 3H, *J* = 7.5 Hz), 1.23 (m, 40H), 1.46 (m, 4H), 1.61 (m, 2H), 2.11 (m, 4H), 2.26 (t, 2H, *J* = 7.8 Hz), 2.87 (br s, 2H), 3.72 (m, 2H), 3.80 (m, 1H), 3.95 (dd, 1H, *J* = 11.4, 3.5 Hz), 6.47 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR δ 12.39, 14.10, 14.36, 18.70, 22.66, 25.77, 25.98, 28.86, 29.13, 29.15, 29.29, 29.34, 29.36, 29.51, 29.58, 29.64, 29.68, 31.90, 34.42, 36.83, 53.81, 62.35, 73.99, 79.56, 81.54, 173.78; HR-MS (FAB, MH^+) *m/z* calcd for $C_{34}H_{66}NO_3$ 536.5043, found 536.5016.

General Procedure for Reduction of an Alkyne to an (*E*)-Alkene by Li/$EtNH_2$. In a 100-mL, two-necked round-bottomed flask was collected 20 mL of $EtNH_2$ at −78 °C. Then small pieces of lithium metal were added (100 mg, 14.4 mmol; the lithium bar was pretreated first with hexane, then with Et_2O, and finally with MeOH until it was shiny). The reaction mixture was stirred under nitrogen at −78 °C until the deep blue color was sustained for at least 30 min. At this moment an yne-diol solution (250 mg of **12a**, **12b**, or **12c** in 10 mL of dry THF) was injected slowly. The reduction was run for 40 min and then quenched by MeOH (added dropwise until the blue color completely disappeared) at −78 °C. Stirring was continued while the reaction mixture was allowed to warm to room temperature. After most of the solvents were blown out by air, H_2O (30 mL) and Et_2O (30 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated (2-PrOH was used to remove the residual H_2O). The white solid residue was purified by column chromatography (elution with $CHCl_3$/MeOH 100:1). The product was dissolved in a minimum volume of $CHCl_3$ and passed through a Cameo filter to remove dissolved silica gel. Finally, the product was lyophilized from benzene to give a white powder.

D-*erythro*-Δ^4-Ceramide [(2*S*,3*R*)-*N*-palmitoylsphingosine, (−)-1a]: mp 96.5−97.4 °C [lit.[26a] mp 95−96 °C, lit.[26g] mp 95.0−96.0 °C]; $[\alpha]^{25}_D$ −5.4° (*c* 1.5, $CHCl_3$/MeOH 9:1) [lit.[26a] $[\alpha]^{23}_D$ −5.4° (*c* 0.9, $CHCl_3$/MeOH 9:1), lit.[26g] $[\alpha]^{25}_D$ −5.82° (*c* 0.98, $CHCl_3$/MeOH 9:1)]; IR 3433, 1653 cm^{-1}; ^1H NMR δ 0.85 (t, 6H, *J* = 7.0 Hz), 1.23 (m, 46H), 1.61 (m, 2H), 2.02 (dt, 2H, *J* = 7.1, 7.1 Hz), 2.21 (t, 2H, *J* = 7.8 Hz), 2.46 (br s, 2H), 3.67 (dd, 1H, *J* = 11.1, 3.1 Hz), 3.84−3.95 (m, 2H), 4.29 (t, 1H, *J* = 5.4 Hz), 5.49 (dd, 1H, *J* = 15.5, 6.4 Hz), 5.76 (dt, 1H, *J* = 15.5, 6.5 Hz), 6.29 (d, 1H, *J* = 7.3 Hz); ^{13}C NMR δ 14.12, 22.68, 25.76, 28.93, 29.12, 29.23, 29.28, 29.36, 29.50, 29.51, 29.66, 29.69, 31.92, 32.29, 36.82, 54.50, 62.45, 74.57, 128.72, 134.29, 174.03.

D-*erythro*-Δ^7-Ceramide [(+)-1b]: mp 92.5−94.3 °C; $[\alpha]^{25}_D$ +5.8° (*c* 1.4, $CHCl_3$); IR 3430, 1654 cm^{-1}; ^1H NMR δ 0.83 (t, 6H, *J* = 7.0 Hz), 1.21 (m, 42H), 1.46−1.62 (m, 4H), 1.86−2.16 (m, 4H), 2.18 (t, 2H, *J* = 7.5 Hz), 2.98 (br s, 2H), 3.68 (m, 2H), 3.80 (m, 1H), 3.95 (dd, 1H, *J* = 11.5, 3.6 Hz), 5.35 (m, 2H), 6.60 (d, 1H, *J* = 7.9 Hz); ^{13}C NMR δ 14.10, 18.73, 22.67, 25.77, 25.91, 28.93, 29.17, 29.23, 29.31, 29.34, 29.37, 29.52, 29.64, 29.69, 31.90, 32.36, 32.60, 33.81, 36.84, 53.90, 62.34, 73.61, 129.53, 130.94, 173.62; HR-MS (FAB, MH^+) calcd for *m/z* $C_{34}H_{68}NO_3$ 538.5199, found 538.5180.

D-*erythro*-Δ^{15}-Ceramide [(+)-1c]: mp 97.8−99.0 °C; $[\alpha]^{25}_D$ +7.12° (*c* 1.93, $CHCl_3$/MeOH 9:1); IR 3427, 1654 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.5 Hz), 1.23 (m, 42H), 1.50 (m, 2H), 1.62 (m, 2H), 1.95 (m, 4H), 2.21 (t, 2H, *J* = 7.3 Hz), 2.38 (br s, 2H), 3.74 (m, 2H), 3.81 (m, 1H), 3.98 (d, 1H, *J* = 10.6 Hz), 5.39 (m, 2H), 6.43 (d, 1H, *J* = 6.5 Hz); ^{13}C NMR δ 13.99, 14.11, 22.68, 25.59, 25.77, 25.97, 29.18, 29.29, 29.35, 29.52, 29.57, 29.65, 29.68, 31.91, 32.56, 34.49, 36.86, 53.71, 62.48, 74.20, 129.36, 131.82, 173.61; HR-MS (FAB, MH^+) calcd for *m/z* $C_{34}H_{68}NO_3$ 538.5199, found 538.5182.

D-*erythro*-Sphingosine [(−)-2a]. To an ice-cooled suspension of 83 mg (2.2 mmol) of $LiAlH_4$ in 15 mL of freshly distilled THF under nitrogen was injected a solution of 80 mg (0.22 mmol) of azido ester **10a** in 4 mL of THF. The reaction mixture was stirred at room temperature for 2 h and then refluxed overnight. After the addition of 10 mL dry THF, the reaction mixture was chilled with an ice−water bath and filtered through a pad of silica gel (∼7 g) slurry in hexane in a sintered glass funnel (3 cm × 6 cm) to remove the salt and the excess $LiAlH_4$ by gentle suction. Note: It was found that this workup procedure was very efficient for small-scale reactions. 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 column chromatography (elution with $CHCl_3$/MeOH/concd NH_4OH 130:25:4), providing 33 mg (50%) of sphingosine **2a** as a white solid. The product was dissolved in a minimum volume of $CHCl_3$ and passed through a Cameo filter to remove dissolved silica gel. **2a:** mp 80.7−82.1 °C [lit.[26a] mp 81−82 °C, lit.[26f] mp 76−77 °C, lit.[26h] mp 72−75 °C, lit.[26i] mp 75−80 °C]; $[\alpha]^{25}_D$ −2.7° (*c* 1.2, $CHCl_3$) [lit.[26a] $[\alpha]^{28}_D$ −2.8° (*c* 1.0, $CHCl_3$), lit.[26h] $[\alpha]^{21}_D$ −1.3° (*c* 3.5, $CHCl_3$), lit.[26i] $[\alpha]^{20}_D$ −6° (*c* 0.84, $CHCl_3$), lit.[26j] $[\alpha]^{22}_D$ −2.5° (*c* 6, $CHCl_3$)]; IR 3616, 3412, 1587, 1463, 1040, 970 cm^{-1}; ^1H NMR δ 0.85 (t, 3H, *J* = 7.0 Hz), 1.23 (m, 20H), 1.35 (m, 2H), 2.02 (q, 2H, *J* = 7.0 Hz), 2.64 (br s, 4H), 2.84 (q, 1H, *J* = 5.2 Hz), 3.64 (m, 2H), 4.04 (t, 1H, *J* = 6.0 Hz), 5.44 (dd, 1H, *J* = 15.4, 7.2 Hz), 5.71 (dt, 1H, *J* = 15.4, 7.2 Hz); ^{13}C NMR δ 14.11, 22.67, 29.17, 29.26, 29.35, 29.48, 29.62, 29.65, 29.68, 31.91, 32.35, 56.15, 63.66, 75.06, 129.11, 134.67.

(2*S*,3*R*)-2-Amino-1,3-dihydroxyoctadec-4-yne [(+)-13]: mp 58.6−59.4 °C; $[\alpha]^{25}_D$ −5.4° (*c* 1.0, $CHCl_3$); IR 3605, 3390, 2214, 1581, 1463, 1029, 834 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.23 (m, 15H), 1.48 (tt, 2H, *J* = 7.6, 7.1 Hz), 2.18 (dt, 2H, *J* = 7.1, 1.6 Hz), 2.83 (br s, 4H), 2.92 (m, 1H), 3.67 (m, 2H), 4.37 (br s, 1H); ^{13}C NMR δ 14.10, 18.69, 22.67, 28.66, 28.97, 29.12, 29.34, 29.52, 29.64, 29.67, 29.86, 31.90, 56.85, 63.56, 64.56, 78.14, 87.70.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **1a**−**c**, **3**, **4b**−**c**, **5a**−**c**, **6a**−**c**, **10a**−**c**, **10a′**, **11a**−**c**, **12a**−**c**, **13**, and **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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