General and Efficient Syntheses of C_{18}-4,8-Sphingadienines via S_N2'-Type Homoallylic Coupling Reactions Mediated by Thioether-Stabilized Copper Reagents

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Received August 9, 2000

The stereoselective syntheses of C_{18}-4,8-sphingadienines **3** and **4** as analogues of sphingosine **1** are described. The key step in these syntheses involved a novel S_N2'-type homoallylic coupling reaction between the corresponding thioether-stabilized allylic copper reagents and the allylic mesylate **7**. The thioether-stabilized allylic copper reagents were easily prepared and retained the configuration of their double bond during the coupling reactions, thus overcoming the problem of isomerization which was normally associated with the use of allylic organometallic reagents in such applications.

Introduction

Sphingolipids exist widely in the membranes of eukaryotic cells and play important roles in many physiological processes. Sphingolipid structurally consists of three components, i.e., a sphingoid base, a polar headgroup, and a fatty acid.[1] The number and the diversity of sphingolipids are greatly enhanced by the structural variations in each of their three components. There are more than 300 sphingolipids that have been identified to occur in nature, and new ones are still being discovered. As far as the sphingoid base is concerned, D-erythrosphingosine **1** and D-ribophytosphingosine **2** are the most abundant core structures in sphingolipids found in mammals and the plant kingdom. In addition to the common D-erythrosphingosine **1** and D-ribophytosphingosine **2**, there are also more than 60 other sphingoid structures existing in nature[1b,2] with microorganisms and marine organisms having been clearly demonstrated as new sources of novel natural products and having provided particularly exciting sphingosine analogues with unusual structures. Recently, some cerebrosides, glycosphingolipids with only one sugar unit as the polar headgroup, had been isolated from a variety of higher fungi and their culture broth and were found to contain (4*E*,8*E*)-9-methyl-4,8-sphingadienine **3** as a novel long-chain sphingoid base.[3] A number of marine sources including sea stars, sea anemones, sponges, corals, and truncates have been identified to produce glycosphingolipids by utilizing sphingadienines and sphingatrienines, such as (4*E*,8*E*)-9-methyl-4,8-sphingadienine **3**, (4*E*,8*E*)-4,8-sphingadienine **4**,[4] (4*E*,8*E*,10*E*)-9-methyl-4,8,10-sphingatrienine **5**,[5] and (4*E*,8*E*,10*E*)-4,8,10-sphingatrienine **6**,[6] as their sphingoid base. The precise function of these characteristic cerebrosides *in vivo* is not clear. Due to the vast variety of sphingolipids in nature and their tedious isolation from microheterogeneous mixtures, there is great demand for pure materials for detailed structural

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10.1021/jo005602f CCC: $19.00
Published on Web 11/27/2000

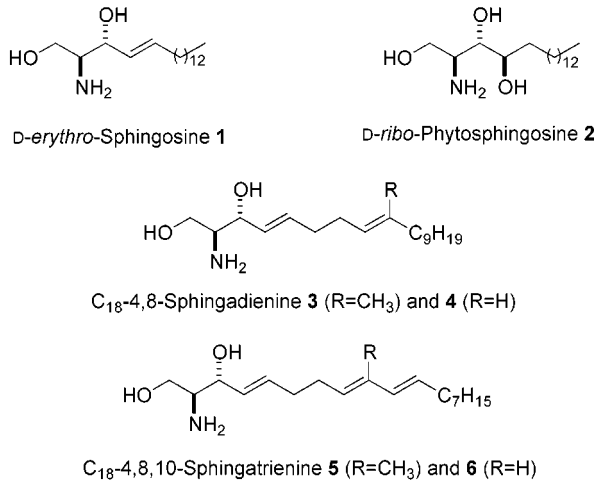
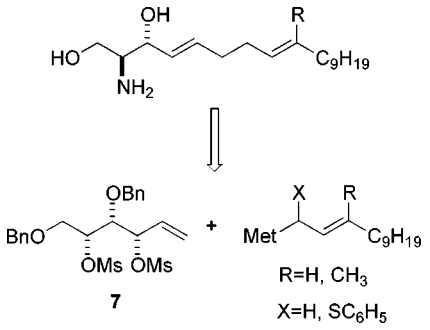


Figure 1.

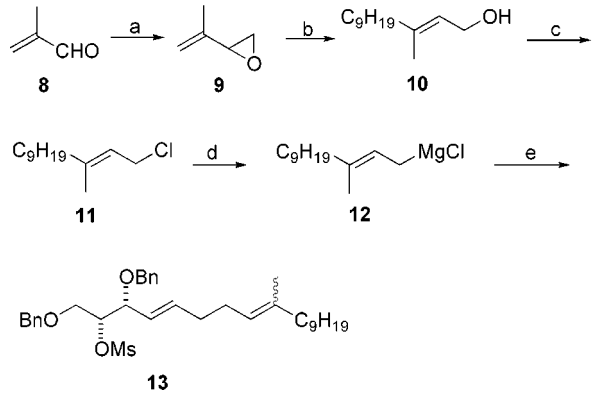
Scheme 1



elucidation and biological evaluations. Therefore, there is a strong requirement for chemical synthesis of cerebrosides, ceramides, and sphingoid bases.[7]

The S_N2- or S_N2'-type nucleophilic displacement reaction between copper-catalyzed Grignard reagent and allylic substrate has been an effective protocol for construction of a new carbon−carbon bond[8] and has attracted a number of mechanistic studies over the years dealing with its regio- and stereochemistry.[9] With general formation or retention of *E*-configuration double bond, the reaction has been widely used in the synthesis of sphingosine and its analogues.[10] Scheme 1 shows our retrosynthetic analysis of sphingadienines using a homoallylic coupling strategy. Successful application of such homoallylic coupling reactions between allylic organometallic compounds and allylic substrates in stereoselective synthesis very much depends on the minimization of the stereoisomerization of the allylic carbanions. As part of our efforts on the stereoselective synthesis of sphingosine and its analogues, we describe in this paper a highly convergent route for the stereoselective construction of sphingadienines by employing thioether-stabilized allylic copper reagents.

Scheme 2[a]



[a] Reagents and conditions: (a) Li, $BrCH_2Cl$, −78 °C to rt; (b) $C_8H_{17}MgBr$, CuCN (5 mol %), THF−Me_2S (20:1), −20 °C, 88%; (c) PPh_3, CCl_4, CH_3CN, 0 °C, 98%; (d) activated Mg, Et_2O, 0 °C; (e) dimesylate **7**, CuCN (5 mol %), THF, 0 °C, 84%.

Results and Discussion

Our retrosynthetic analysis revealed that the trans C4−C5 and C8−C9 double bonds in sphingadienines can be constructed by the copper(I)-mediated S_N2'-type homoallylic coupling between the dimesylate **7** and the corresponding allylic Grignard reagent with concomitant chain elongation in a single step. The dimesylate **7** has been used in our previous synthesis of D-erythrosphingosine **1**.[10c] The preparation of Grignard reagent **12** is summarized in Scheme 2. The isoprene epoxide **9** was prepared by reacting methacrolein **8** with (chloromethyl)-lithium (generated in situ from lithium and bromochloromethane).[11] Due to the volatile nature of the isoprene epoxide **9**, it was used directly for the next reaction without any purification. This method has advantages over the previous preparations of **9**, which were tedious and low yielding.[12] Treatment of the crude isoprene epoxide **9** with octylmagnesium bromide in THF−Me_2S (20:1) in the presence of CuCN (5 mol %) produced almost exclusively the desired *E*-configuration alcohol **10** in 88% yield with only traces of the corresponding *Z*-isomer.[12a] The alcohol **10** was converted to chloride **11** in 97% yield by reacting with triphenylphosphine and carbon tetra-

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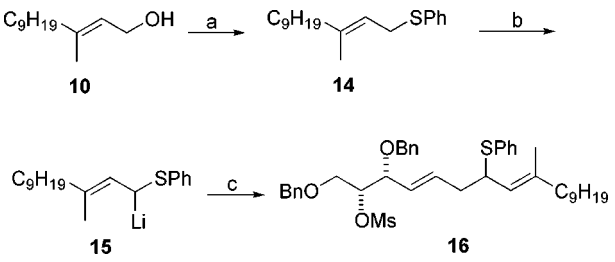
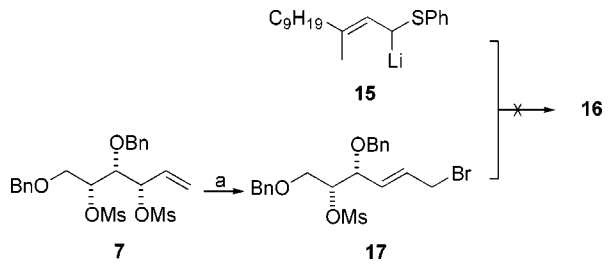
Scheme 3[a]



[a] Reagents and conditions: (a) PhSCN, *n*-Bu_3P, THF, −20 °C, 98%; (b) *n*-BuLi, HMPA, THF, −78 °C; (c) dimesylate **7**, CuCN (5 mol %), THF, −78 °C, 15%.

Scheme 4[a]



[a] Reagents and conditions: (a) $MgBr_2$, CuCN (5 mol %), THF, 0 °C, 96%.

chloride in acetonitrile.[13] Due to its instability on silica gel column, the crude **11** was purified by Kugelrohr distillation. The Grignard reagent **12**, prepared from allylic chloride **11** and activated magnesium,[14] was added to a solution of dimesylate **7** in THF at 0 °C in the presence of CuCN (5 mol %) to afford the α′,γ-product **13** in 84% yield with excellent *E*- and γ-selectivities. However, ^{1}H NMR analysis revealed diene **13** as a 5:2 mixture of diastereoisomers that derived from the differences of the double-bond configuration at C8−C9. The ratio was based on the integration of the 9-CH_3 signals appearing at δ 1.58 ppm for the 8*E*-isomer and δ 1.67 ppm for the 8*Z*-isomer. This diastereoisomeric mixture, which resulted from the isomerization of the allylic Grignard reagent **12**, could not be separated by flash chromatography, and subsequent attempts to separate their azide derivatives were also unsuccessful.

It has been known that the stereoisomerization of allylmetal compounds is dependent on temperature, the substitutions on the allyl group, and the metal species.[15] For example, high stereoretention was observed for disubstituted allylmagnesium at temperature below −95 °C, while rapid stereoisomerization occurred for the monosubstituted allylmagnesium even at −100 °C.[15a] In contrast to the allylmagnesium or allyllithium, the double-bond geometry of allylpotassium was well retained even at 0 °C, and that of the allylbarium was completely retained at −78 °C.[15] However, the harsh conditions for the preparation of stereochemically homogeneous allylmetals directly from allylic halides limited its applications in synthesis. Therefore, we directed our attention to heteroatom-stabilized allylic metal reagents that have been known to generally retain the configuration of the double bond at low temperature and can easily be prepared by deprotonation.[16] Literature studies indicated that thioether-stabilized allylic carbanions have less tendency to interconvert between the *E*- and *Z*-forms at −78 °C,[17] and this has already found application in terpene synthesis where reaction generally occurs via a S_N2-type coupling route.[16a] To obtain the thioether-stabilized allylic carbanion (Scheme 3), alcohol **10** was treated with phenyl thiocyanate[18] and tri-*n*-butylphosphine in THF at −20 °C to give the thioether **14** (98%), which was then deprotonated with *n*-butyllithium at −78 °C to form the thioether-stabilized allyllithium reagent **15**.[19] However, when the dimesylate **7** was added to the solution of **15** in THF at −78 °C in the presence of a catalytic amount of CuCN, a very low yield (15%) of the S_N2' homocoupling product **16** was obtained after workup. Alternatively, following the protocols in terpene synthesis, dimesylate **7** was first converted in 96% yield to the allylic bromide **17**, a solution of which was then added to allylic lithium **15** at −78 °C. Unfortunately, the reaction failed to produce the desired diene **16** (Scheme 4). We reasoned that the problem probably lay with the hard property of the lithium reagent which damaged the sensitive mesylate group in allylic bromide **17**.

The organocopper reagent has been known to be softer in property than the corresponding lithium reagent and generally give better results in S_N2'-type coupling reactions.[20] Although heteroatom-stabilized allylic lithium reagents have been extensively investigated and used widely in natural product synthesis,[16] the use of heteroatom-stabilized allylcopper reagents in S_N2- or S_N2'-type coupling reactions has not been fully exploited. In our work, we decided to convert the thioether-stabilized allyllithium **15** to the corresponding copper reagent by treating it with stoichiometric amount of CuCN·2LiCl. The completion of the transmetalation was indicated by the changing color of the solution going from being orange to pale. The S_N2' coupling between the allylic copper reagent and the dimesylate **7** readily occurred to yield the diene **16**. After examining various reaction conditions, we found that compound **16** could be prepared in excellent yield (89%) by adding a solution of dimesylate **7** to the copper reagent at −78 °C. Reverse addition resulted in the formation of a small amount of the 8*Z*-isomer (at the C8−C9 double bond, with the 9-CH_3 signal appearing in the ^{1}H NMR at δ 1.63 ppm), which was caused by the slight isomerization of the allylic copper reagent during the course of its addition to the dimesylate **7**. The structure of diene **16** followed its ^{1}H NMR and NOESY spectra where the trans configuration of the C4−C5 double bond was confirmed with $J_{4,5}$ as 15.4 Hz and the trans configuration of the C8−C9 double bond was confirmed by the 9-CH_3 signal appearing at δ 1.38 ppm. The S_N2 replacement of the mesylate group in diene **16** by sodium azide gave the azide compound **18** in 78%

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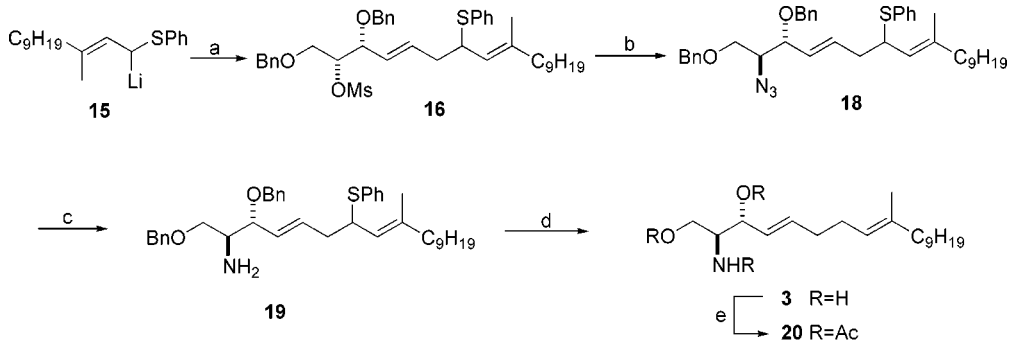
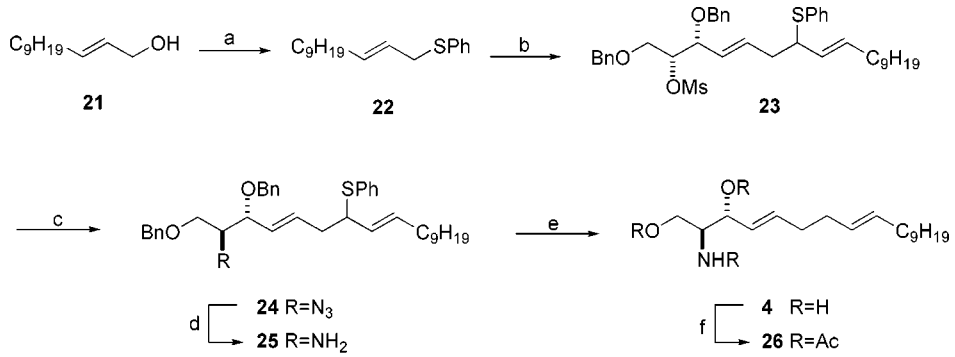
Scheme 5[a]



[a] Reagents and conditions: (a) CuCN·2LiCl (1.1 equiv), then dimesylate **7**, −78 °C, 89%; (b) NaN_3, DMF, 100 °C, 78%; (c) $LiAlH_4$, Et_2O, 0 °C, 100%; (d) Na, liquid NH_3, dibenzo-18-crown-6 (10 mol %); (e) Ac_2O, DMAP (cat.), Et_3N, CH_2Cl_2, 0 °C, 84% for two steps.

Scheme 6[a]



[a] Reagents and conditions: (a) PhSCN, *n*-Bu_3P, THF, −20 °C, 95%; (b) *n*-BuLi, HMPA, THF, −78 °C, then CuCN·2LiCl (1.1 equiv.), and then dimesylate **7**, −78 °C, 94%; (c) NaN_3, DMF, 100 °C, 81%; (d) $LiAlH_4$, Et_2O, 0 °C, 100%; (e) Na, liquid NH_3, dibenzo-18-crown-6 (10 mol %); (f) Ac_2O, DMAP (cat.), Et_3N, CH_2Cl_2, 0 °C, 82% for two steps.

yield. Desulfurization of azide **18** with nickel boride (generated in situ from nickel chloride hexahydrate and sodium borohydride) did not work.[21] Instead of desulfurization, the nickel boride actually reduced the C4−C5 double bond and the azide group in compound **18**. Lithium aluminum hydride reduction of the azide group in **18** afforded quantitatively the corresponding amine **19**, which was then treated with sodium in liquid ammonia in the presence of dibenzo-18-crown-6 (10 mol %)[22] to furnish the sphingadienine **3** with debenzylation and desulfurization in one step. The crude sphingadienine **3** was subsequently acetylated to provide the triacetate **20** for further characterization. We later found that the azide reduction, debenzylation and desulfurization of compound **18** could be accomplished with sodium in liquid ammonia in the presence of dibenzo-18-crown-6 (10 mol %) in a single step, though a slightly lower yield (43%) was obtained after further acetylation of the crude sphingadienine **3** (Scheme 5).

In a similar fashion, the sphingadienine **4** was also prepared through the S_N2'-type homoallylic coupling reaction between dimesylate **7** and the allylic copper reagent derived from thioether **22** (Scheme 6). Phenylsulfenation of the alcohol **21**[23] with phenyl thiocyanate and tri-*n*-butylphosphine at THF gave thioether **22** in 95% yield. Metalation of **22** with *n*-butyllithium and further transmetalation with stoichiometric amount of CuCN·2LiCl provided the thioether-stabilized allylic copper reagent, to which the dimesylate **7** was added to give the S_N2' homoallylic coupling product **23** in 94% yield. The diene **23** was further converted to the triacetate **26** via sphingadienine **4**, in much the same way as adopted for the synthesis of the triacetate **20**.

Conclusion

In summary, the stereoselective syntheses of sphingadienines **3** and **4** have been achieved. Thioether-stabilized allylic copper reagents have been used in the S_N2' type homoallylic coupling reactions with an allylic substrate, the dimesylate **7**, for the efficient construction of the 1,5-diene unit in sphingadienines. The high regio- and stereoselectivities of these syntheses are attributed to the useful properties of these thioether-stabilized allylic copper reagents that could well retain their double-bond geometry at low reaction temperature.

Experimental Section

General Methods. All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gastight syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. Melting points are uncorrected. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^1H NMR spectra were recorded at 270, 300, and 600 MHz and were assigned in ppm (δ) downfield relative to TMS as internal standard. Elemental analyses were performed at Shanghai Institute of Organic Chemistry. Flash

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column chromatography was performed on silica gel (10−40 μm) using a mixture of petroleum ether and ethyl acetate as the eluent. Compounds **7**[10c] and **21**[23] were prepared according to published procedures.

(2*R*,3*R*,4*E*,8*E*)-1,3-Di-*O*-benzyl-9-methyl-2-*O*-methylsulfonyl-7-(phenylthio)-4,8-octadecadiene-1,2,3-triol (16). *n*-Butyllithium (2.5 M in hexanes, 2.8 mL, 7 mmol) was added dropwise to a stirred solution of phenyl sulfide **14** (2.03 g, 7 mmol) and HMPA (1.22 mL) in dry THF (20 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h and gave a deep orange colored solution, to which CuCN·2LiCl (1 M in THF, 8 mL, 8 mmol) was added, followed, after 10 min, by the dropwise addition of the dimesylate **7** (2.912 g, 6 mmol) in THF (15 mL). After addition, the reaction mixture was stirred further for 30 min and quenched with saturated aqueous ammonium chloride (20 mL). The mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by flash column chromatography (petroleum ether/ethyl acetate 5:1) afforded **16** (3.62 g, 89%) as a white solid: mp 83−84 °C; $[\alpha]_D$ −4.6 (*c* 1.14, $CHCl_3$); IR (KBr) ν_{max} 2927, 2854, 1497, 1455, 1353, 1176, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 15H), 5.80 (dt, *J* = 15.4, 7.1 Hz, 1H), 5.40 (dd, *J* = 15.4, 8.0 Hz, 1H), 5.05 (d, *J* = 10.2 Hz, 1H), 4.73 (m, 1H), 4.60−4.30 (m, 4H), 4.08 (t, *J* = 7.1 Hz, 1H), 3.90 (m, 1H), 3.70 (m, 2H), 2.94 (s, 3H), 2.40 (m, 2H), 1.88 (t, *J* = 7.7 Hz, 2H), 1.38 (s, 3H), 1.20 (m, 14H), 0.88 (t, *J* = 6.3 Hz, 3H); MS (ESI) *m*/*z* 611 (M^+ − Bn + Na), 639 (M^+ − OSO_2CH_3 + K). Anal. Calcd for $C_{40}H_{54}S_2O_5$: C, 70.76; H, 8.01. Found: C, 70.61; H, 8.25.

(2S,3*R*,4*E*,8*E*)-2-Azido-1,3-di-*O*-benzyl-9-methyl-7-(phenylthio)-4,8-octadecadiene-1,3-diol (18). The mixture of mesylate **16** (2.954 g, 3.82 mmol) and sodium azide (1.5 g, 23 mmol) in dry DMF (40 mL) was heated at 100 °C for 24 h. Upon cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between water (30 mL) and diethyl ether (3 × 50 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether/ethyl acetate 30:1) afforded the azide **18** (1.88 g, 78%) as a coluorless oil: $[\alpha]_D$ −29.1 (*c* 1.26, $CHCl_3$); IR (film) ν_{max} 2920, 2850, 2100, 1630, 1590, 1495, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 15H), 5.20 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.48 (dd, *J* = 15.5, 8.4 Hz, 1H), 5.05 (d, *J* = 10.0 Hz, 1H), 4.60 (m, 1H), 4.51-(d, *J* = 2.1 Hz, 2H), 4.30 (m, 1H), 3.90 (m, 2H), 3.62 (m, 3H), 2.45 (m, 2H), 1.90 (dt, *J* = 7.44, 7.38 Hz, 2H), 1.38 (s, 3H), 1.22 (m, 14H), 0.88 (t, *J* = 7.0 Hz, 3H); MS (EI) *m*/*z* 599 (M^+ − N_2, 1.6), 489 (M^+ - N_2 − PhS, 15.7), 488 (M^+ − N_2 − PhSH, 15.9), 289 (32.7), 308 (0.86), 91 (100). Anal. Calcd for $C_{39}H_{51}N_3SO_2$: C, 74.84; H, 8.21; N, 6.71. Found: C, 75.02; H, 8.40; N, 6.88.

(2S,3*R*,4*E*,8*E*)-2-Amino-1,3-di-*O*-benzyl-9-methyl-7-(phenylthio)-4,8-octadecadiene-1,3-diol (19). A solution of azide **18** (783 mg, 1.25 mmol) in anhydrous diethyl ether (8 mL) was added dropwise to a slurry of lithium aluminum hydride (48 mg, 1.25 mmol) in anhydrous diethyl ether (8 mL) at 0 °C. After being stirred at room temperature for 12 h, the reaction was quenched with careful addition of cold water (3 mL), diluted with ethyl acetate (20 mL), and dried (Na_2SO_4). The solids were filtered off and washed with ethyl acetate (3 × 10 mL). The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to afford the amine **19** (750 mg, 100%) as a colorless oil: $[\alpha]_D$ −19.8 (*c* 1.62, $CHCl_3$); IR (film) ν_{max} 2930, 2870, 1590, 1450, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 15H), 5.72 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.45 (dd, *J* = 15.5, 8.4 Hz, 1H), 5.08 (d, *J* = 10.2 Hz, 1H), 4.57 (m, 1H), 4.49 (s, 2H), 4.30 (m, 1H), 3.95 (m, 1H), 3.75 (m, 1H), 3.62 (m, 1H), 3.49 (m, 1H), 3.10 (m, 1H), 2.45 (m, 2H), 1.90 (m, 2H), 1.75 (s, 2H), 1.38 (s, 3H), 1.25 (m, 14H), 0.90 (t, *J* = 7.0 Hz, 3H); MS (EI) *m*/*z* 600 (M^+, 4.8), 583 (M^+ − NH_3, 1.0), 490 (M^+ − PhSH, 5.7), 382 (12.1), 289 (11.8), 150 (100), 91 (89.2). Anal. Calcd for $C_{39}H_{53}NSO_2$: C,78.08; H, 8.90; N, 2.33. Found: C, 78.14; H, 8.95; N, 2.52.

(2*S*,3*R*,4*E*,8*E*)-*N*,*O*,*O*-Triacetyl-9-methyl-4,8-sphingadienine (20). To a solution of sodium (260 mg, 11 mmol) and dibenzo-18-crown-6 (31 mg, 0.09 mmol) in liquid ammonia (10 mL) at −78 °C was added a solution of amine **19** (510 mg, 0.85 mmol) in dry THF (10 mL). After addition, the reaction mixture was stirred at −78 °C for 40 min and was then quenched with solid ammonium chloride to decompose the excessive sodium. The mixture was left to rise to room temperature during which time nitrogen was bubbled into the solution to expel the ammonia. The residue was taken with chloroform (3 × 20 mL), and the extracts were concentrated under reduced pressure to give the crude sphingadienine **3**. Without further purification, the crude **3** was dissolved in dichloromethane (10 mL) and mixed with DMAP (5 mg, 0.04 mmol), triethylamine (1 mL, 7.17 mmol), and actetic anhydride (0.5 mL, 5.30 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 10 h and then partitioned between water (15 mL) and dichloromethane (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a residue that was purified by flash chromatography (petroleum ether/ethyl acetate, 3:2) to give the triacetate **20** (314 mg, 84%) as a white solid: mp 62−63 °C; $[\alpha]_D$ −13.8 (*c* 1.13, $CHCl_3$); IR (KBr) ν_{max} 3290, 2922, 2852, 1736, 1656, 1553, 1375, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.65 (d, *J* = 9.1 Hz, 1H), 5.42 (dd, *J* = 15.2, 7.4 Hz, 1H), 5.30 (dd, *J* = 7.1, 5.85 Hz, 1H), 5.08 (m, 1H), 4.45 (m, 1H), 4.30 (dd, *J* = 11.6, 6.3 Hz, 1H), 4.05 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.10 (s, 6H), 2.0 (s, 3H), 2.15−1.95 (m, 6H), 1.55 (s, 3H), 1.25 (m, 14H), 0.90 (t, *J* = 6.9 Hz, 3H); MS (EI) *m*/*z* 438 (M^+ + 1), 378 (M^+ − CH_3CO_2), 318, 102, 84. Anal. Calcd for $C_{25}H_{43}NO_5$: C, 68.61; H, 9.90; N, 3.20. Found: C, 68.59; H, 9.96; N, 3.35.

(2*R*,3*R*,4*E*,8*E*)-1,3-Di-*O*-benzyl-2-*O*-methylsulfonyl-7-(phenylthio)-4,8-octadecadiene-1,2,3-triol (23). Under the same reaction conditions as for the preparation of compound **16**, phenyl sulfide **22** (1.325 g, 4.8 mmol), *n*-BuLi (1.6 M in hexanes, 3 mL, 4.8 mmol), CuCN·2LiCl (1 M in THF, 5.5 mL, 5.5 mmol), and dimesylate **7** (1.94 g, 4.0 mmol) gave, after purification by flash column chromatography (petroleum ether/ethyl acetate, 5:1), the mesylate **23** (2.513 g, 94%) as a white solid: mp 48−49 °C; $[\alpha]_D$ −1.97 (*c* 3.35, $CHCl_3$); IR (KBr) ν_{max} 3030, 2923, 2852, 1498, 1455, 1438, 1350, 1175, 1092, 981, 930, 748 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 (m, 15H), 5.83 (dt, *J* = 7.2, 15.6 Hz, 1H), 5.42 (dd, *J* = 7.8, 15.6 Hz, 1H), 5.29 (m, 2H), 4.73 (m, 1H), 4.64−4.30 (m, 4H), 4.08 (m, 1H), 3.70 (m, 2H), 3.61 (m, 1H), 2.95 (s, 3H), 2.42 (m, 2H), 1.90 (m, 2H), 1.20 (m, 14H), 0.88 (t, *J* = 6.6 Hz, 3H); MS (EI) *m*/*z* 257 (94.95), 201 (100), 77 (12.8), 91 (4.7); MS (ESI) 687.7 (M^+ + Na), 665.9 (M^+ + H). Anal. Calcd for $C_{39}H_{52}S_2O_5$: C, 70.44; H, 7.88. Found: C, 70.50; H, 8.00.

(2S,3*R*,4*E*,8*E*)-2-Azido-1,3-di-*O*-benzyl-7-(phenylthio)-4,8-octadecadiene-1,3-diol (24). Under the same reaction conditions as for compound **18**, mesylate **23** (1.661 g, 2.50 mmol) and sodium azide (1.63 g, 25 mmol) gave, after purification by flash column chromatography (petroleum ether/ethyl acetate, 30:1), the azide **24** (1.24 g, 81%) as a colorless oil: $[\alpha]_D$ −29.8 (*c* 2.90, $CHCl_3$); IR (film) ν_{max} 2910, 1870, 2105, 1590, 1475, 1095, 970, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 15H), 5.73 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.50 (dd, *J* = 15.5, 8.35 Hz, 1H), 5.31 (m, 2H), 4.60 (m, 1H), 4.52 (d, *J* = 2.2 Hz, 2H), 4.34 (m, 1H), 3.89 (m, 1H), 3.63 (m, 4H), 2.45 (m, 2H), 1.90 (m, 2H), 1.20 (m, 14H), 0.88 t, *J* = 6.6 Hz, 3H); MS (EI) *m*/*z* 584 (M^+ − N_2, 0.44), 475 (M^+ − N_2 − SPh, 2.9), 275 (52.18), 149 (17.6), 148 (11.6), 123 (11.4), 109 (7.58), 91 (100). Anal. Calcd for $C_{38}H_{49}N_3SO_2$: C, 74.59; H, 8.07. Found: C, 74.85; H, 8.22.

(2S,3*R*,4*E*,8*E*)-2-Amino-1,3-di-*O*-benzyl-7-(phenylthio)-4,8-octadecadiene-1,3-diol (25). Under the same reaction conditions as for compound **19**, azide **24** (1.073 g, 1.75 mmol) and lithium aluminum hydride (67 mg, 1.75 mmol) afforded, after flash column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1), the amine **25** (1.02 g, 100%) as a colorless oil: $[\alpha]_D$ −17.03 (*c* 2.58, $CHCl_3$); IR (film) ν_{max} 2900, 2850, 1445, 1090, 740, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 15H), 5.74 (apparent dt, *J* = 15.5, 7.63 Hz, 1H),

5.45 (dd, J = 15.5, 8.3 Hz, 1H), 5.33 (m, 2H), 4.60 (m, 1H), 4.53 (s, 2H), 4.32 (m, 1H), 3.72 (m, 1H), 3.60 (m, 2H), 3.48 (m, 1H), 3.08 (m, 1H), 2.47 (m, 2H), 1.93 (m, 2H), 1.72 (s, 2H), 1.25 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H); MS (EI) m/z 587 (M^+ + H, 2.7), 586 (M^+, 5.7), 478 (M^+ − PhSH, 2.9), 367 (2.3), 274 (5.3), 150 (100), 91 (97.1). Anal. Calcd for $C_{38}H_{51}NSO_2$: C, 77.90; H, 8.77; N, 2.39. Found: C, 77.87; H, 8.67; N, 2.57.

(2*S*,3*R*,4*E*,8*E*)-*N*,*O*,*O*-Triacetyl-4,8-sphingadienine (26). Under the same reaction conditions as for compound **20**, amine **25** (265 mg, 0.45 mmol), sodium (117 mg, 5.09 mmol), and dibenzo-18-crown-6 (16 mg, 0.04 mmol) produced the crude sphingadienine **4**, which was then derivatized with acetic anhydride (0.5 mL, 5.3 mmol), DMAP (5 mg, 0.04 mmol), and triethylamine (1.0 mL, 7.17 mmol) to give, after purification by flash chromatography (petroleum ether/ethyl acetate, 3:2), the triacetate **26** (156 mg, 82%) as a white solid: mp 97−98 °C; $[\alpha]_D$ −13.3 (*c* 0.25, $CHCl_3$); IR (KBr) ν_{max} 3286, 2955, 2922, 2851, 1737, 1658, 1553, 1375, 1268, 1232, 1030, 966 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.79 (dt, J = 15.6, 6.6 Hz, 1H), 5.67-(d, J = 9.0 Hz, 1H), 5.42 (dd, J = 15.6, 6.6 Hz, 1H), 5.41 (dt, J = 15.6, 7.2 Hz, 1H), 5.35 (dt, J = 15.6, 6.6 Hz, 1H), 5.28 (dd, J = 7.2, 6.6 Hz, 1H), 4.43 (m, 1H), 4.29 (dd, J = 11.4, 6.0 Hz, 1H), 4.04 (dd, J = 11.4, 4.2 Hz, 1H), 2.08 (m, 2H), 2.07 (s, 6H), 1.98 (s, 3H), 1.96(m, 4H), 1.26 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H); MS (EI) m/z 364 ($M^+ - CH_3CO_2$), 304, 262, 144, 102, 85, 84, 43. Anal. Calcd for $C_{24}H_{41}NO_5$: C, 68.05; H, 9.75; N, 3.31. Found: C, 68.05; H, 9.66; N, 3.22.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (29790126), the Chinese Academy of Sciences (95-A1-504-03), and the Ministry of Science and Technology of China (970211006-6, G2000077502) for financial support.

Supporting Information Available: HNMR spectra for compounds **16**, **18**−**20**, and **23**−**26** and experimental details for compounds **10**, **11**, **13**, **14**, **17**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005602F