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SYNTHESIS OF (4E,8E,2S,3R,2'R)-N-2'-HYDROXYHEXADECANOYL-1-O-β-D-GLUCOPYRANOSYL-9-METHYL-4,8-SPHINGADIENINE, THE FRUITING-INDUCING CEREBROSIDE IN A BASIDIOMYCETE *SCHIZOPHYLLUM COMMUNE*†

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Abstract—The title compound was synthesized by employing (R)-2-aminohexadecanoic acid, D-glucose and (S)-serine as the chiral sources, and the synthetic sample was found to be chemically and biologically identical with the fruiting-inducing cerebroside isolated from Schizophyllum commune.

In 1982 some cerebrosides in the mycelia of Schizophyllum commune (Japanese name: Suéhiro také) were found by Kawai et al. to stimulate its own fruiting body formation.[1] One of the active principles was identified as (4E,8E,2S,3R,2'R)-N-2'-hydroxyhexadecanoyl-1-O-β-D-glucopyranosyl-9-methyl-4,8-sphingadienine **1a**,[2] which had previously been isolated from a sea anemone (Metridium senile) by Karlsson et al.[3] Very recently we reported the synthesis of the ceramide portion **1b** of the bioactive cerebroside **1a**.[4,5] Herein is described a synthesis of the cerebroside **1a** itself. The present work unambiguously established the absolute configuration of the cerebroside **1a** as depicted in Fig. 1.

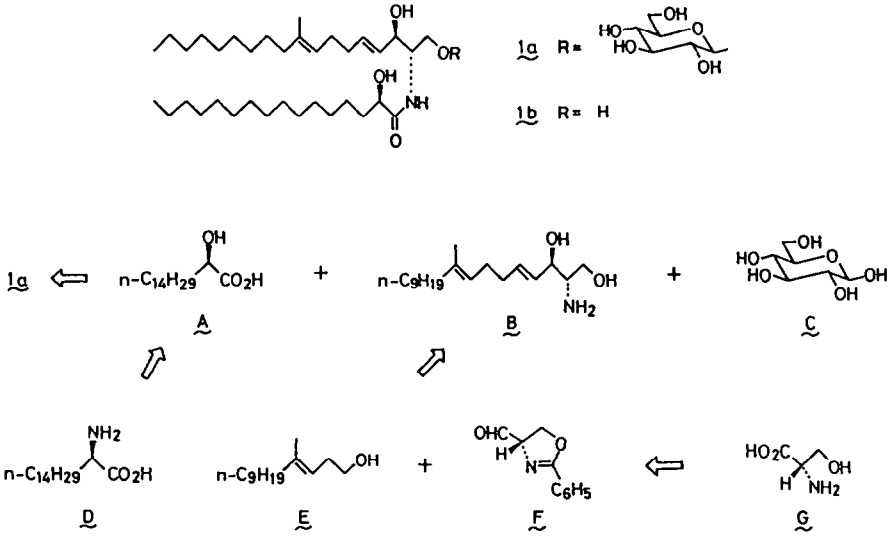

Fig.1. Synthetic plan for the cerebroside 1a.

†Synthesis of Sphingosine Relatives—III. Part II, K. Mori and Y. Funaki, Tetrahedron the preceding paper. The experimental part of this work was taken from the forthcoming doctoral dissertation of Y. F.

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Our synthetic plan for **1a** was different from that employed in our previous synthesis of **1b**.[4,5] Instead of resolving the sphingadienine (±)-**B** after acylation with (R)-**A**, we envisaged a chiral synthesis of **B** from **E** and the known oxazoline **F**[6] derived from (S)-serine **G**. The α-hydroxy acid moiety **A** could be obtained from **D** as described previously.[4,5] Acylation of **B** with **A** would lead to the single desired isomer **1b**, whose glucosidation with D-glucose **C** would eventually yield the bioactive cerebroside **1a**.

Synthesis of the optically active sphingadienine portion 13. In the present synthesis, the chirality at C-2 of **1a** originated from (S)-serine **2a** (Fig. 2). The use of (S)-serine in sphingolipid synthesis was first reported by Newman[6] and then by Thornton.[7] Conversion of (S)-**2a** to its Me ester·HCl **2b**[8] was followed by its treatment with benzimino Et ether for the protection of both NH_2 and OH groups.[9] Under Elliott's condition, no racemization at C-2 had been observed in the course of the oxazoline formation.[7,9] The resulting phenyloxazoline ester **3** was reduced with DIBAL-H to give an unstable aldehyde **4** (=**F**), which had to be used immediately in the next step due to its instability.

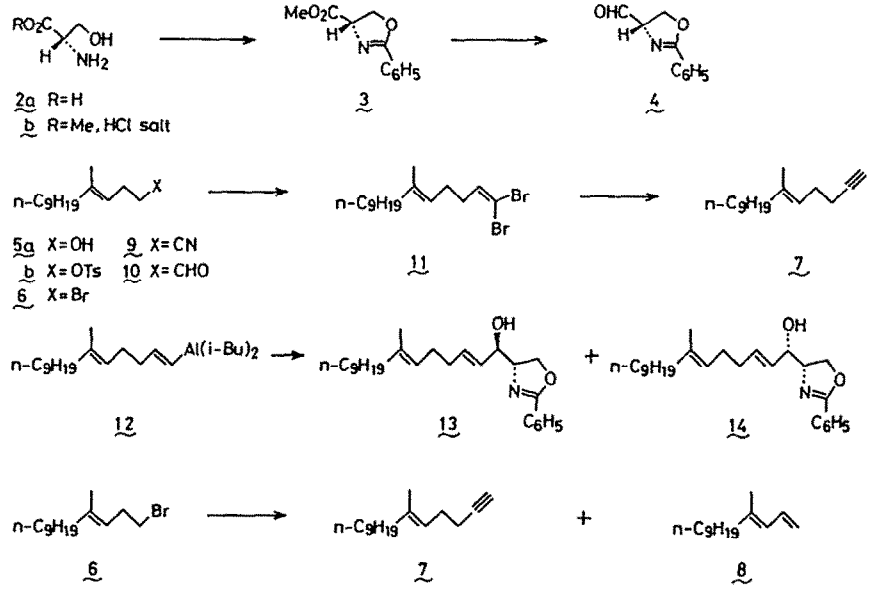

Fig. 2. Synthesis of the sphingadienine portion.

The starting material **5a** for the preparation of the achiral portion of **B** was synthesized from homoprenyl acetate in 3 steps (36 % overall yield) as reported by us.[4,5] An alkenylalane **12** was the reagent of choice for the formation of the C-C bond between C-3 and C-4.[cf.6,7] This was prepared in the following manner. The alcohol **5a** was converted to a bromide **6** in the conventional manner *via* a tosylate **5b**. Alkylation of LiC≡CH[10] with **6** yielded a mixture of the expected alkyne **7** (25 %) and an unwanted β-elimination product **8** (63 %). In view of this unsatisfactory yield of **7** together with the difficulty encountered in separating **7** and **8**, we sought for an alternative method. The bromide **6** was converted to a nitrile **9**, whose reduction with DIBAL-H furnished an aldehyde **10**. Treatment of **10** with Ph_3P and CBr_4 according to Corey[11] yielded a dibromodiene **11**. This gave the alkyne **7** when treated with n-BuLi. The overall yield of **7** from **6** by this 4-step process was 64 %. Addition of DIBAL-H to the alkyne **7** by the established procedure[6,7,12,13] afforded the desired alkenylalane **12**. Alkenylation of the phenyloxazoline aldehyde **4** with **12** gave a mixture of two diastereomers **13** and **14**. These two were separable by SiO_2 chromatography to give a less polar crystalline isomer, m.p. 58.5~59.5°, in 23 % yield and a more polar oily isomer in 18 % yield from **7**. The crystalline isomer was later shown to be *erythro*-**13** by its conversion to the ceramide **1b**. We were thus able to synthesize the sphingadienine part **B** of the molecule as the

protected form 13.

Synthesis of the ceramide 1b. The prerequisite to the synthesis of the ceramide 1b was to prepare a highly optically pure acylating agent 15d as shown in Fig. 3. (R)-α-Hydroxy ester 15a was synthesized as reported previously[4,5] by deaminating the corresponding (R)-α-amino acid D followed by esterification of the resulting crude α-hydroxy acid. The optical purity of (R)-15a was estimated to be 88 % by the HPLC analysis of its (R)-α-methoxy-α-trifluoromethyphenylacetate (MTPA ester).[14] Alkaline hydrolysis of (R)-15a was followed by recrystallization of the product to give (R)-15b, m.p. 92.5~93.5°, $[\alpha]_D^{22}$ -3.1°($CHCl_3$). The same compound (R)-15b, m.p. 93.3~93.5°, $[\alpha]_D^{22}$ -3.2°($CHCl_3$), was previously isolated by Horn *et al.* as a component of wool wax.[15] Our synthetic acid (R)-15b was acetylated to give (R)-15c, m.p. 61~62°, $[\alpha]_D^{22}$ +10.6° ($CHCl_3$). Activation of the CO_2H group of (R)-15c was effected by treating (R)-15c with p-nitrophenyl trifluoroacetate in C_5H_5N[16] to give a p-nitrophenyl ester (R)-15d, m.p. 32~33°, $[\alpha]_D^{21}$ +19.7° ($CHCl_3$), as the acylating agent. The optical purity of (R)-15d was shown to be 96 % e.e by the HPLC analysis of the corresponding amide 16 prepared by the treatment of (R)-15d with (R)-(+)-α-naphthylethylamine.

With the building block (R)-15d in hand, we then attempted the acylation of the sphingadienine part. Treatment of the oxazoline 13 with dil HCl afforded 1-O-benzoylsphingadienine·HCl 17. This was dissolved in C_5H_5N and acylated with (R)-15d to achieve selective N-acylation.[7,17] The resulting 1-O-benzoyl-2'-acetoxyceramide 1c, m.p. 74.0~75.0°, $[\alpha]_D^{19}$ +9.5°($CHCl_3$), was treated with NaOH to remove both the Ac and PhCO groups to give the ceramide 1b, m.p. 62~63°, $[\alpha]_D^{22}$ +7.4° ($CHCl_3$). Its identity with the natural and authentic 1b, m.p. 59~61°, $[\alpha]_D^{21}$ +7.3°±0.4°($CHCl_3$), was confirmed by the comparison of their IR, 400 MHz ^{1}H-NMR and HPTLC data. No m.p. depression was observed upon admixture of the natural and synthetic samples of 1b. The specific rotation of

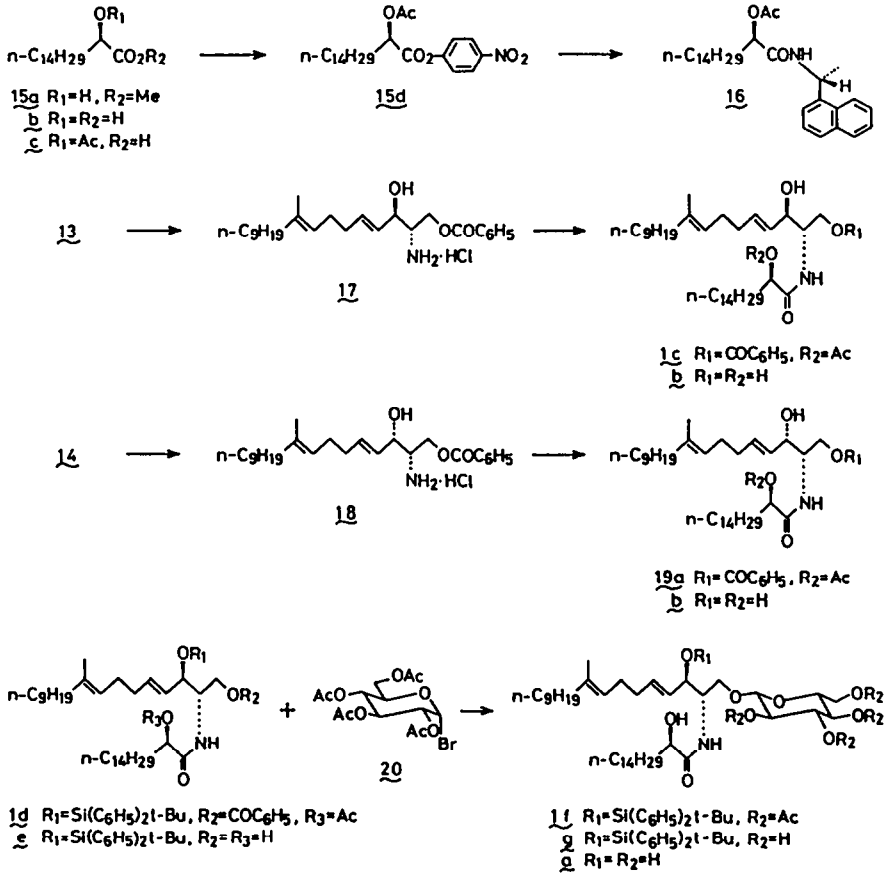

Fig. 3. Synthesis of the ceramide 1b and the cerebroside 1a.

our present **1b** was also in good accord with that of the authentic **1b** and larger than that ($[\alpha]_D^{21}$ +6.4° ($CHCl_3$)) of our previous **1b**.[4,5] Our present **1b** was therefore thought to be virtually optically pure. Since our synthesis started from (S)-serine, the absolute configuration of the ceramide **1b** was determined as (2S,3R,2'R). This derivation of **1b** from **13** enabled us to assign erythro- or anti- relative configuration of **13** implying the (R)-configuration at C-1' of **13**. In the same manner as above, threo-**14** yielded an unnatural (2S,3S,2'R)-ceramide **19b** via **18** and **19a**. The IR spectrum (KBr disc) of **19b** was distinctly different from that of **1b**.

Synthesis of the cerebroside 1a. The final stage of our synthesis was glucosidation of **1b**. Direct glucosidation of **1b** with tetra-O-acetyl-α-D-glucopyranosyl bromide **20**[18] gave an intractable mixture presumably containing two monoglucosides and a diglucoside as checked by TLC. We then tried the selective tritylation of the prim OH group of **1b** so that we might acetylate only the sec OH groups.[cf.17] If this had been possible, we might have been able to achieve glucosidation at the prim OH group after removing the Ph_3C group selectively. The tritylation, however, did not take place at all.

Finally we completed the synthesis in the following manner. The allylic sec OH group at C-3 of **1c** was protected as a t-butyldiphenylsilyl ether to give **1d**, whose alkaline hydrolysis yielded **1e**. Glucosidation of **1e** with **20** in the presence of $Hg(CN)_2$ in C_6H_6-$MeNO_2$ under the Kŏnigs-Knorr condition gave the desired glucoside **1f** in 47 % yield. This reaction was known to afford a β-D-glucoside.[7,17] Conventional deprotection of **1f** to remove Ac groups with alkali gave **1g**. The concluding step was the desilylation of **1g** with $(n\text{-}Bu)_4NF$ to give the target molecule **1a** (43 mg). Our synthetic cerebroside **1a** was identical with the natural **1a** on the basis of IR, 400 MHz ^{1}H-NMR, HPLC and HPTLC comparisons. The specific rotation of our synthetic **1a**, $[\alpha]_D^{21}$ -7.3°±0.2°(c=0.5, $CHCl_3$), was in agreement with that of the natural **1a**, $[\alpha]_D^{19}$ -7.4°±0.4°(c=0.3, $CHCl_3$). The overall yield of the cerebroside **1a** from homoprenyl acetate was 0.7 % through the 17-step synthetic operation. The synthetic cerebroside **1a** was assayed against Schizophyllum commune and found to be bioactive (10,000 units/mg).[1,2] The activity was as strong as that of the natural **1a** (10,000 units/mg), when tested simultaneously under the same condition.

In conclusion, we synthesized the naturally occurring isomer **1a** of the fruiting-inducing cerebroside in the mycelia of Schizophyllum commune. The present synthesis unambiguously established the structure and stereochemistry of the cerebroside as (4E,8E,2S,3R,2'R)-N-2'-hydroxyhexadecanoyl-1-O-β-D-glucopyranosyl-9-methyl-4,8-sphingadienine. We are currently continuing our study to clarify the structure-bioactivity relationship among closely related synthetic ceramides.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as KBr discs for solids on a Jasco IRA-102 spectrometer. ^{1}H-NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. ^{1}H-NMR spectra at 400 MHz were recorded on a Jeolco JNM FX-400 spectrometer. ^{13}C-NMR spectra were measured on a Jeolco JNM FX-100 spectrometer at 25 MHz. Optical rotations were measured on a Jasco DIP-140 polarimeter. TLC analysis was carried out with Merck pre-coated TLC plates, Kieselgel $60F_{254}$ and HPTLC analysis was with Merck pre-coated HPTLC plates Kieselgel $60F_{254}$.

(S)-Serine Me ester·HCl **2b**. HCl gas was briskly bubbled into a soln of **2a** (25 g, 238 mmol) in dry MeOH until the soln became very hot (spontaneous refluxing). Then the soln was left to stand for 16 h at room temp. MeOH was removed in vacuo. The residue was triturated with ether (50 ml). The solid **2b** was collected on a filter, washed with ether (50 ml) and dried in vacuo. Recrystallization from MeOH-ether (1:3) gave 35.9 g (97.0 %) of **2b**, m.p. 163~164°(lit.[8] m.p. 163°); $[\alpha]_D^{22}$ +3.48° (c=4.00, MeOH); νmax (nujol) 3360 (s), 1745 (s), 1250 (s), 1035 (s) cm^{-1}.

(S)-4-Methoxycarbonyl-2-phenyl-1,3-oxazolin-2-ene **3**. A soln of PhC(=NH)OEt (60 g, 0.40 mol)[19,20] in CH_2Cl_2 (100 ml) was added to a soln of **2b** (33 g, 0.21 mol) in water (20 ml). The mixture was vigorously stirred for 24 h at room temp. It was then filtered and the filtrate was diluted with CH_2Cl_2 (100 ml) and water (50 ml). The organic soln was separated, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 33.3 g (76.2 %) of **3**, b.p. 114~116°/0.03 mm (lit.[7] 109~110°/0.01 mm); $[\alpha]_D^{21}$ +120.7°(c=2.1, $CHCl_3$); νmax 1740 (s), 1640 (s), 1600 (m), 1580 (m), 1500 (m), 1360 (s), 1295 (s), 1200 (s), 1170 (s), 1085 (s), 1060 (s), 1020 (s), 970 (s), 695 (s) cm^{-1}; δ($CDCl_3$) 3.82 (3H, s), 4.60 (1H, d, J=12 Hz), 4.65 (1H, d, J=6 Hz), 5.00 (1H, dd, J=12 Hz, 6 Hz), 7.40~7.60 (3H, m), 7.90~8.15 (2H, m).

(S)-4-Formyl-2-phenyl-1,3-oxazolin-2-ene **4**. This was prepared by the method of Thornton.[7] A soln of DIBAL-H in n-hexane (1.7 M, 6.0 ml, 10.2 mmol) was added dropwise to a stirred and cooled soln of **3** (1.4 g, 6.8 mmol) in toluene (30 ml) and n-hexane (5 ml) at -70°under Ar. The mixture was stirred for 2 h at -70°. Subsequently MeOH (1 ml) was added dropwise at -

70°. After stirring for 30 min, the mixture was quenched by the addition of EtOAc (10 ml) and a sat aq soln (20 ml) of Na·K tartrate. The cooling bath was then removed and the temp was allowed to rise to room temp. The mixture was partitioned between EtOAc (500 ml) and a sat aq soln (1.5 l) of Na·K tartrate. The organic soln was dried ($MgSO_4$) and concentrated in vacuo to give 1.4 g (quantitative) of **4** as a crude yellow oil, νmax 1730 (m), 1640 (s), 1360 (s), 1080 (s), 965 (s), 695 (s) cm^{-1}; TLC ($CHCl_3$-MeOH=95:5) Rf 0.22. This was employed in the next step without further purification. **4** was very unstable. In its NMR spectrum only a weak signal was observed at δ9.77 ($CDCl_3$). Decomposition of **4** took place even within the time-span of the NMR measurement.

(E)-1-Bromo-4-methyl-3-tridecene **6**. p-TsCl (45 g, 236 mmol) was added to a stirred and ice-cooled soln of **5a** (33 g, 155 mmol) in C_5H_5N (120 ml). The mixture was stirred for 8 h. It was then poured into ice-water (500 ml) and extracted with ether (500 ml). The ether soln was washed with 2 N-HCl, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residual crude oily **5b** (58 g) was dissolved in DMF (250 ml). To this was added LiBr (40 g, 460 mmol) and the mixture was stirred for 18 h at room temp. It was then poured into ice-water (1 l) and extracted with ether (300 ml x 3). The ether soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 38.3 g (93.4 %) of **6**, b.p. 90~94°/0.08 mm; n_D^{21}1.4682; νmax 1660 (m) cm^{-1}; δ($CDCl_3$) 0.87 (3H, deformed t, J=6 Hz), 1.24 (14H, br.s), 1.60 (3H, s), 1.80~2.10 (2H, m), 2.54 (2H, q, J=7 Hz), 3.32 (2H, t, J=7 Hz), 5.15 (1H, t, J=7 Hz). (Found: C, 61.09; H, 10.01. Calc for $C_{14}H_{27}Br$: C, 61.08; H, 9.89 %).

(E)-5-Methyl-4-tetradecenenitrile **9**. A mixture of **6** (38.0 g, 138 mmol) and KCN (11.5 g, 176 mmol) in DMF (100 ml) and water (30 ml) was stirred at 70° for 24 h. It was then poured into ice-water (1 l) and extracted with ether (500 ml). The ether soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with n-hexane-ether (100:1) gave 30.0 g (98.0 %) of **9** as an oil, n_D^{21}1.4506; νmax 2250 (w), 1670 (m) cm^{-1}; δ($CDCl_3$) 0.86 (3H, deformed t, J=6 Hz), 1.25 (14H, br.s), 1.62 (3H, s), 1.80~2.20 (2H, m), 2.22~2.48 (4H, m), 5.00~5.30 (1H, m); TLC (n-hexane-ether=4:1) Rf 0.47. (Found: C, 81.43; H, 12.27; N, 6.14. Calc for $C_{15}H_{27}N$: C, 81.38; H, 12.29; N, 6.33 %).

(E)-5-Methyl-4-tetradecenal **10**. A soln of DIBAL-H in n-hexane (1.7 M, 123 ml, 209 mmol) was added dropwise to a stirred and cooled soln of **9** (30.0 g, 136 mmol) in ether (700 ml) at -60° under Ar. The mixture was stirred for 1 h at -60° and for 3 h at room temp. The excess reagent was quenched by the addition of HCO_2Et (5 ml). After stirring for 30 min, the mixture was poured into sat NH_4Cl aq (1.5 l). The mixture was stirred for 20 min, acidified with 20 % H_2SO_4 aq (1 l) and extracted with ether. The ether soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The oily residue was chromatographed over Florisil (450 g). Elution with n-hexane-ether (50:1) gave 29.0 g (95.4 %) of **10**, νmax 2720 (m), 1730 (s) cm^{-1}; δ($CDCl_3$) 0.86 (3H, deformed t, J=6 Hz), 1.23 (14H, br.s), 1.57 (3H, s), 1.73~2.15 (2H, m), 2.20~2.46 (4H, m), 4.90~5.25 (1H, m), 9.76 (1H, s); TLC (n-hexane-ether=4:1) Rf 0.51. This was employed in the next step without further purification.

(E)-1,1-Dibromo-6-methyl-1,5-pentadecadiene **11**. A soln of CBr_4 (85 g, 256 mmol) in CH_2Cl_2 (100 ml) was added dropwise to a stirred and ice-cooled soln of Ph_3P (138 g, 526 mmol) in CH_2Cl_2 (300 ml). To this was added a soln of **10** (29.0 g, 129 mmol) in CH_2Cl_2 (100 ml) with stirring and cooling at 0°. The stirring was continued for 15 min at 0°. The mixture was then quenched with ice-water (100 ml). After stirring for 20 min, the organic layer was separated. The organic soln was dried ($MgSO_4$) and concentrated in vacuo. The residue was triturated with pentane (1 l) and the insoluble Ph_3PO was filtered off. The filtrate was concentrated in vacuo. The oily residue was chromatographed over SiO_2. Elution with n-hexane gave 38.1 g (77.6 %) of oily **11**, n_D^{21}1.4976; νmax 1665 (w), 1620 (w), 775 (m) cm^{-1}; δ($CDCl_3$) 0.87 (3H, deformed t, J=6 Hz), 1.26 (14H, br.s), 1.57 (3H, s), 1.80~2.20 (6H, m), 4.90~5.20 (1H, m), 6.39 (1H, t, J=7 Hz); TLC (n-hexane) Rf 0.45. (Found: C, 50.53; H, 7.36. Calc for $C_{16}H_{28}Br_2$: C, 50.54; H, 7.42 %).

(E)-6-Methyl-5-pentadecen-1-yne **7**. A soln of n-BuLi in n-hexane (1.5 M, 150 ml, 225 mmol) was added dropwise to a stirred and cooled soln of **11** (37.0 g, 97.6 mmol) in THF (400 ml) at -70° under Ar. The mixture was stirred for 1 h at -70° and for 1.5 h at room temp. It was then poured into ice-water (1.5 l) and extracted with n-hexane. The hexane soln was washed with water, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with n-hexane gave 18.9 g (88.0 %) of **7** as an oil, n_D^{21}1.4535; νmax 3320 (s), 2120 (w), 1665 (w), 840 (w) cm^{-1}; δ($CDCl_3$) 0.87 (3H, deformed t, J=6 Hz), 1.23 (14H, br.s), 1.58 (3H, s), 1.75~2.05 (3H, m), 2.10~2.30 (4H, m), 4.95~5.25 (1H, m); TLC (n-hexane) Rf 0.52. (Found: C, 87.10; H, 12.88. Calc for $C_{16}H_{28}$: C, 87.19; H, 12.81 %).

(E)-6-Methyl-5-pentadecen-1-yne **7** and (E)-4-methyl-1,3-tridecadiene **8**. LiC≡CH was prepared by the method of Midland.[10] Gaseous HC≡CH (72 ml, 3 mmol) was slowly introduced into cold THF (5 ml) at -78°. To this was added dropwise a soln of n-BuLi in n-hexane (1.6 M, 1.6 ml, 2.6 mmol) with stirring and cooling at -78° under Ar. The stirring was continued for 10 min at -78°. Then a soln of **6** (500 mg, 1.7 mmol) in HMPA (2 ml) was added dropwise at -78°. The mixture was stirred for 20 min at -78° and for 3 h at room temp. The reaction was quenched with ice-water (50 ml) and the mixture was extracted with n-hexane (50 ml). The hexane soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with n-hexane gave 223 mg (63.4 %) of **8**, TLC (n-hexane) Rf 0.69, and 100 mg (25.0 %) of **7**, TLC (n-hexane) Rf 0.52. The present **7** was identical with **7** described above on the basis of IR and NMR comparisons. The diene **8** showed the following properties; n_D^{21}1.4642; νmax 3090 (w), 3050 (w), 1790 (m), 1650 (s), 1600 (m), 985 (s), 895 (s) cm^{-1}; δ($CDCl_3$) 0.89 (3H, t, J=6 Hz), 1.26 (14H, br.s), 1.72 (3H, s), 1.80~2.20 (2H, m), 4.91 (1H, d, J=10 Hz), 4.98 (1H, d, J=16 Hz), 5.75 (1H, d, J=10 Hz), 6.51 (1H, dt, J=16 Hz, 10 Hz). (Found: C, 86.75; H, 13.49. Calc for $C_{14}H_{26}$: C, 86.51; H, 13.49 %).

(4*S*,1'*R*)-4-(1'-Hydroxy-7'-methyl-2',6'-hexadecadienyl)-2-phenyl-1,3-oxazolin-2-ene **13** and its (1'*S*)-isomer **14**. A soln of DIBAL-H in n-hexane (1.7 M, 3.8 ml, 6.4 mmol) was added dropwise to a stirred soln of **7** (1.4 g, 6.4 mmol) in n-hexane (5 ml) under Ar. The mixture was stirred for 2 h at 50°. The resulting soln of **12** was cooled in an ice-bath. To this was added a soln of **4** (1.4 g, ca 6.8 mmol) in ether (5 ml) with stirring at 0~5°. The temp was allowed to rise to room temp and the stirring was continued for 2 h. The mixture was poured into a sat soln of Na·K tartrate (500 ml) and extracted with EtOAc (500 ml). The EtOAc soln was dried ($MgSO_4$) and concentrated in vacuo. TLC analysis (n-hexane-ether=3:7) of the residue revealed it to be a mixture of two compounds, one with Rf 0.56 and the other with Rf 0.39. These two were separated by SiO_2 chromatography. Elution with n-hexane-ether (2:1) first afforded 580 mg (23.0 % from **7**) of **13**, m.p. 58.5~59.5° (recrystallized from n-hexane); $[\alpha]_D^{21}$-10.0°(c=1.15, $CHCl_3$); νmax (KBr disc) 3200 (m), 1655 (s), 1610 (w),

1585 (m), 1505 (m), 1365 (s), 1275 (s), 1120 (s), 1110 (s), 1100 (s), 985 (s), 970 (s), 695 (s) cm^{-1}; $\delta(CDCl_3)$ 0.87 (3H, deformed t, J=6 Hz), 1.26 (14H, br.s), 1.56 (3H, s), 1.75~2.25 (6H, m), ~3.10 (1H, br), 4.25~4.65 (4H, m), 4.90~5.20 (1H, m), 5.40 (1H, dd, J=15.5 Hz, 4.5 Hz), 5.84 (1H, d, J=15.5 Hz), 7.25~7.50 (3H, m), 7.65~7.92 (2H, m). (Found: C, 78.76; H, 9.84; N, 3.46. Calc for $C_{26}H_{39}O_2N$: C, 78.54; H, 9.89; N, 3.52 %). Further elution with the same solvent gave 450 mg (17.8 % from 7) of **14**, n_D^{22} 1.5183; $[\alpha]_D^{22}$ +23.3° (c=1.02, $CHCl_3$); νmax 3300 (s), 1645 (s), 1605 (w), 1580 (m), 1500 (m), 1450 (s), 1360 (s), 1085 (s), 1025 (s), 965 (s), 695 (s) cm^{-1}; $\delta(CDCl_3)$ 0.85 (3H, deformed t, J=6 Hz), 1.22 (14H, br.s), 1.52 (3H, s), 1.70~2.20 (6H, m), ~3.00 (1H, br.), 3.80~4.40 (4H, m), 4.85~5.15 (1H, m), 5.40 (1H, dd, J=15.5 Hz, 4.5 Hz), 5.76 (1H, d, J=15.5 Hz), 7.20~7.46 (3H, m), 7.76~7.98 (2H, m). (Found: C, 78.38; H, 9.77; N, 3.47. Calc for $C_{26}H_{39}O_2N$: C, 78.54; H, 9.89; N, 3.52 %).

Methyl (R)-2-hydroxyhexadecanoate **15a**. (R)-2-Aminohexadecanoic acid (5.9 g, 21.7 mmol) was dissolved in 2 N-H_2SO_4 (40 ml) by heating at 80°. To the vigorously stirred soln was added a soln of $NaNO_2$ (3.2 g, 46.4 mmol) in water (34 ml) over 2 h at 80°. The stirring was continued for 2 h at room temp. It was then extracted with ether (300 ml x 2). The ether soln was washed with brine and concentrated in vacuo. The residue was dissolved in C_6H_6 and concentrated again in vacuo. To the residue were added C_6H_6 (60 ml), MeOH (60 ml) and conc HCl (0.1 ml). The mixture was stirred and heated under reflux for 3 h. After cooling, it was poured into ice-water (300 ml) and extracted with ether. The ether soln was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with n-hexane-ether (15:1) gave crystalline **15a**, which was recrystallized from n-hexane to give 3.8 g (61.0 %) of **15a**, m.p. 45.5°; $[\alpha]_D^{21}$ -1.35° (c=2.5, EtOH) [lit.[15] m.p. 45.5~45.7°; $[\alpha]_D^{20}$ -1.5° (c=10, EtOH), lit.[21] m.p. 45~46°; $[\alpha]_D$ -1.0° (c=5.2, EtOH)]; TLC (n-hexane-ether=2:3) Rf 0.50. (Found: C, 71.53; H, 11.86. Calc for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96 %). The IR and NMR spectra of (R)-**15a** were identical with those reported previously.[5] The optical purity of (R)-**15a** was estimated by the HPLC analysis of the corresponding (R)-MTPA ester (Column, Nucleosil®50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF-MeOH=6,000:100:1; Flow rate, 1.0 ml/min) Rt 10.7 min (94.0 %), 13.0 min (6.0 %). Our **15a** was therefore of 88 % e.e.

(R)-2-Hydroxyhexadecanoic acid **15b**. (R)-**15a** (3.5 g, 12.2 mmol) was dissolved in 95 % EtOH (100 ml) containing KOH (85 % purity, 740 mg, 12.2 mmol). The mixture was stirred and heated at 70° for 20 min. EtOH was removed in vacuo. The residue was diluted with ice-water (30 ml), acidified with 2 N-HCl and extracted with ether. The ether soln was washed with brine, and concentrated in vacuo. The residue was dissolved in C_6H_6 (5 ml) and concentrated in vacuo. The residual solid was recrystallized two times from acetone-n-hexane (1:5) to give 2.9 g (87.1 %) of **15b**, m.p. 92.5~93.5°; $[\alpha]_D^{22}$ -3.1° (c=0.5, $CHCl_3$) [lit.[15] m.p. 93.3~93.5°; $[\alpha]_D$ -3.2° ($CHCl_3$) lit.[21] m.p. 86~87°; $[\alpha]_D$ -1.0° (EtOH)]. (Found: C, 70.78; H, 11.60. Calc for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84 %). The IR and NMR spectra of (R)-**15b** were identical with those reported previously.[5]

(R)-2-Acetoxyhexadecanoic acid **15c**. Ac_2O (25 ml) was added to a soln of (R)-**15b** (2.55 g, 9.36 mmol) in C_5H_5N (50 ml). The soln was stirred for 18 h at room temp. It was then diluted with ice-water (20 ml) and C_5H_5N (20 ml). After stirring for 10 min, the soln was diluted with ether (500 ml). The ether soln was washed with 2 N-HCl (300 ml x 2) and 15 % NaCl aq (200 ml x 10) until the aq layer became neutral. The organic layer was washed with ice-water (100 ml) and concentrated in vacuo. The residue was dissolved in EtOH (5 ml) and concentrated in vacuo. The residual solid was recrystallized from n-hexane to give 2.72 g (92.4 %) of **15c**, m.p. 61.0~62.0°; $[\alpha]_D^{22}$ +10.6° (c=0.52, $CHCl_3$); νmax (nujol) 3190 (s), 1740 (s), 1690 (s), 1265 (s), 1245 (s), 1220 (s) cm^{-1}; $\delta(CDCl_3)$ 0.87 (3H, deformed t, J=6 Hz), 1.24 (24H, br.s), 1.60~2.00 (2H, m), 2.11 (3H, s), 4.96 (1H, t, J=6 Hz), 9.70 (1H, br.s, CO_2H). (Found: C, 68.52; H, 10.85. Calc for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90 %).

p-Nitrophenyl (R)-2-acetoxyhexadecanoate **15d**. A mixture of (R)-**15c** (1.26 g, 4.0 mmol) and p-nitrophenyl trifluoroacetate (4.0 g, 17.0 mmol) in C_5H_5N (5 ml) was stirred for 18 h at room temp. C_5H_5N was removed in vacuo (~5 mmHg). The residue was chromatographed over SiO_2. Elution with n-hexane-ether (20:1) gave **15d** as an oil. This was dissolved in a small amount of n-hexane and left to stand in a refrigerator to give 16.9 g (96.8 %) of **15d**, m.p. 32~33°; $[\alpha]_D^{21}$ +19.7° (c=1.00, $CHCl_3$); νmax (KBr disc) 1790 (s), 1755 (s), 1620 (m), 1600 (m), 1535 (s), 1355 (s), 1245 (s), 1210 (s) cm^{-1}; $\delta(CDCl_3)$ 0.80~1.00 (3H, m), 1.26 (24H, br.s), 1.75~2.10 (2H, m), 2.17 (3H, s), 5.16 (1H, t, J=6 Hz), 7.33 (2H, d, J=10 Hz), 8.32 (2H, d, J=10 Hz); TLC (n-hexane-ether=1:1) Rf 0.65. (Found: C, 66.10; H, 8.50; N, 3.18. Calc for $C_{24}H_{37}O_6N$: C, 66.33; H, 8.35; N, 3.22 %). The optical purity of (R)-**15d** was determined as follows. A mixture of **15d** (2 mg) and (R)-(+)-1-(1'-naphthyl)ethylamine (3 mg) in C_5H_5N (5 μl) was left to stand for 4 h at room temp. The soln was then diluted with ether (2 ml). The ether soln was washed with water, sat Na_2CO_3 aq, N-HCl and water, dried ($MgSO_4$) and concentrated in vacuo. The residual **16**, νmax (nujol) 1740 (s), 1645 (s), 1550 (s) cm^{-1}, was submitted to the HPLC analysis (Column, Nucleosil®50-5, 25 cm x 4.6 mm; Solvent, n-hexane-ether=10:1; Flow rate, 2.1 ml/min) Rt 22.7 min (2 %), 25.0 min (98 %). The optical purity of **16** was therefore 96 % e.e.

(4E,8E,2S,3R,2'R)-N-2'-Acetoxyhexadecanoyl-1-O-benzoyl-9-methyl-4,8-sphingadienine **1c**. 2 N-HCl (2 ml) was added to a soln of **13** (800 mg, 2.0 mmol) in THF (16 ml). The mixture was stirred for 20 h at room temp. It was then diluted with ice-water (40 ml) and extracted with $CHCl_3$-MeOH (87:13; 100 ml x 3). The organic soln was dried ($MgSO_4$) and concentrated in vacuo to give ca 900 mg (quantitative) of **17**. This was dissolved in C_5H_5N (4 ml). To this soln of **17** was added a soln of **15d** (1.69 g, 3.9 mmol) in C_5H_5N (4 ml). The mixture was stirred for 20 h at 45°. The solvent was removed in vacuo and the residue was chromatographed over SiO_2. Elution with n-hexane-ether (2:1) gave a yellowish oil, whose soln in a small amount of n-hexane deposited crystals of **1c**. This was recrystallized from n-hexane to give 898 mg (62.7 % from **13**) of pure **1c** as fine needles, m.p. 74.0~75.0°; $[\alpha]_D^{19}$ +9.5° (c=0.68, $CHCl_3$); νmax (KBr disc) 3120 (s), 1735 (s), 1660 (s), 1600 (w), 1550 (s), 1275 (s), 1240 (s), 705 (s) cm^{-1}; $\delta(CDCl_3)$ 0.87 (6H, deformed t, J=6 Hz), 1.23 (40H, br.s), 1.54 (3H, s), 1.70~2.20 (6H, m), 2.08 (3H, s), 2.90 (1H, br., OH), 4.10~4.70 (4H, m), 4.90~5.20 (2H, m), 5.50~5.80 (2H, m), 6.65 (1H, d, J=8 Hz, NH), 7.36~7.60 (3H, m), 7.85~8.10 (2H, m); TLC (n-hexane-ether=2:3) Rf 0.41. (Found: C, 74.32; H, 10.13; N, 2.02. Calc for $C_{44}H_{73}O_6N$: C, 74.22; H, 10.33; N, 1.97 %).

(4E,8E,2S,3R,2'R)-N-2'-Hydroxyhexadecanoyl-9-methyl-4,8-sphingadienine **1b**. A soln of NaOH in MeOH (0.3 N, 20 ml) was added to a soln of **1c** (425 mg, 0.6 mmol) in $CHCl_3$ (30 ml). The mixture was stirred for 15 min at room temp. It was then poured into ice-water (100 ml) and extracted with $CHCl_3$ (300 ml x 2). The $CHCl_3$ soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with $CHCl_3$-EtOAc (3:2) yielded a solid, which was recrystallized from n-hexane to give 248 mg (73.4 %) of **1b** as white powder-like crystals, m.p. 62.0~63.0° (natural **1b**, m.p. 59~61°); mixed m.p. with the authentic and natural **1b** 60~62° (No m.p. depression was observed.); $[\alpha]_D^{22}$ +7.4° (c=0.57,

$CHCl_3$) [natural **1b**; $[\alpha]_D^{21}$+7.3°±0.4° (c=0.25, $CHCl_3$)]; νmax (KBr disc) 3290 (s), 2960 (s), 2930 (s), 2860 (s), 1650 (s), 1630 (s), 1535 (s), 1470 (s), 1380 (w), 1330 (w), 1260 (w), 1140 (w), 1100 (m), 1070 (m), 1050 (s), 1025 (m), 960 (m), 885 (w), 720 (m) cm^{-1}; δ(400 MHz, $CDCl_3$) 0.87 (6H, t, J=7.0 Hz), 1.20~1.40 (40H, m), 1.58 (3H, s), 1.95 (2H, t, J=7.5 Hz), 2.08 (4H, br.s), 3.35 (1H, br.s), 3.73 (1H, br.s), 3.75 (1H, deformed d, J=11.0 Hz), 3.85 (1H, dd, J_1=11.0 Hz, J_2=4.0 Hz), 3.91 (1H, dt, J_1=8.0 Hz, J_2=4.0 Hz), 3.98 (1H, br.s), 4.10 (1H, deformed t, J=3.5 Hz), 4.25 (1H, br.s), 5.09 (1H, dd, J_1=6.5 Hz, J_2=5.0 Hz), 5.51 (1H, dd, J_1=15.5 Hz, J_2=6.5 Hz), 5.79 (1H, ddd, J_1=15.5 Hz, J_2=6.0 Hz, J_3=5.0 Hz); HPTLC ($CHCl_3$-MeOH=9:1) Rf 0.53. (Found: C, 74.40; H, 11.75; N, 2.39. Calc for $C_{35}H_{67}O_4N$: C, 74.28; H, 11.93; N, 2.48 %). The IR and NMR spectra of the synthetic **1b** were identical with those of the natural **1b**. The HPTLC analysis also confirmed their identity.

(4*E*,8*E*,2*S*,3*S*,2'*R*)-*N*-2'-Acetoxyhexadecanoyl-1-*O*-benzoyl-9-methyl-4,8-sphingadienine **19a**. In the same manner as described above for the synthesis of **1c**, **14** (300 mg, 0.75 mmol) gave 268 mg (49.9 %) of **19a** as a pale yellow wax, νmax (KBr disc) 3360 (s), 2940 (s), 2860 (s), 1745 (s), 1720 (s), 1645 (s), 1605 (w), 1550 (s), 1470 (m), 1450 (m), 1380 (s), 1320 (w), 1275 (s), 1240 (s), 1180 (w), 1160 (w), 1125 (s), 1110 (m), 1070 (w), 1040 (w), 970 (m), 880 (w), 800 (w), 710 (s) cm^{-1}; δ($CDCl_3$) 0.75~1.00 (6H, m), 1.23 (40H, br.s), 1.55 (3H, s), 1.70~2.20 (6H, m), 2.10 (3H, s), 4.10~4.60 (4H, m), 4.90~5.25 (2H, m), 4.90~5.25 (2H, m), 5.40~5.80 (2H, m), 6.45~6.70 (1H, m), 7.35~7.60 (3H, m), 7.90~8.12 (2H, m). This was employed in the next step without further purification.

(4*E*,8*E*,2*S*,3*S*,2'*R*)-*N*-2'-Hydroxyhexadecanoyl-9-methyl-4,8-sphingadienine **19b**. In the same manner as described above for the synthesis of **1b**, **19a** (70 mg, 0.10 mmol) yielded 43 mg (77.3 %) of **19b** as a colorless waxy solid, $[\alpha]_D^{23}$+6.6° (c=0.7, $CHCl_3$); νmax (KBr disc) 3300 (s), 2960 (s), 2930 (s), 2860 (s), 1630 (s), 1530 (s), 1460 (s), 1380 (w), 1310 (w), 1135 (w), 1080 (m), 1045 (m), 960 (m), 720 (m) cm^{-1}; δ($CDCl_3$) 0.87 (6H, deformed t, J=6 Hz), 1.24 (40H, br.s), 1.55 (3H, s), 1.70~2.20 (6H, m), 3.00~3.60 (3H, m, OH), 3.60~4.50 (5H, m), 4.90~5.20 (1H, m), 5.30~5.80 (2H, m), 7.15 (1H, m). (Found: C, 74.11; H, 11.80; N, 2.37. Calc for $C_{35}H_{67}O_4N$: C, 74.28; H, 11.93; N, 2.48 %). A small amount of **19b** was mixed with the synthetic **1b** and the mixed m.p. was measured. No sharp mixed m.p. was observable and the solid melted at 54~60°.

(4*E*,8*E*,2*S*,3*R*,2'*R*)-*N*-2'-Acetoxyhexadecanoyl-1-*O*-benzoyl-3-*O*-(t-butyldiphenylsilyl)-9-methyl-4,8-sphingadienine **1d**. A soln of **1c** (350 mg, 0.49 mmol), t-$BuPh_2SiCl$ (620 mg, 2.26 mmol) and imidazole (155 mg, 2.28 mmol) in DMF (2.0 ml) was stirred for 3 h at 70°. It was then poured into 2 N-HCl (30 ml) and extracted with ether (200 ml). The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with n-hexane-ether (10:1) gave 418 mg (89.5 %) of **1d** as an oil, n_D^{22}1.5094; $[\alpha]_D^{22}$+3.8°(c=0.6, $CHCl_3$); νmax 3440 (m), 1750 (s), 1725 (s), 1685 (s), 1600 (w), 1590 (w), 1510 (s), 1450 (s), 1270 (s), 1220 (s), 1110 (s), 705 (s) cm^{-1}; δ($CDCl_3$) 0.85 (6H, deformed t, J=6 Hz), 1.07 (9H, s), 1.22 (40H, br.s), 1.47 (3H, s), 1.60~1.95 (6H, m), 2.04 (3H, s), 4.10~4.50 (3H, m), 4.60~5.40 (5H, m), 6.50 (1H, m, NH), 7.15~8.00 (15H, m); TLC (n-hexane-ether=4:1) Rf 0.19. (Found: C, 76.23; H, 9.61; N, 1.67. Calc for $C_{60}H_{91}O_6NSi$: C, 75.82; H, 9.65; N, 1.47 %).

(4*E*,8*E*,2*S*,3*R*,2'*R*)-*N*-2'-Hydroxyhexadecanoyl-3-*O*-(t-butyldiphenylsilyl)-9-methyl-4,8-sphingadienine **1e**. A soln of NaOH in MeOH (0.2 N, 20 ml) was added to a stirred soln of **1d** (400 mg, 0.42 mmol) in $CHCl_3$ (30 ml). The mixture was stirred for 15 min at room temp, poured into ice-water (50 ml) and extracted with $CHCl_3$ (80 ml, 40 ml x 2). The $CHCl_3$ soln was dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with n-hexane-ether (1:2) gave 311 mg (91.9 %) of **1e** as an oil, n_D^{22}1.5070; $[\alpha]_D^{22}$-9.8°(c=0.7, $CHCl_3$); νmax 3400 (s), 1650 (s), 1590 (w), 1530 (s), 1460 (s), 1110 (s), 1080~1040 (s), 700 (s) cm^{-1}; δ($CDCl_3$) 0.90 (6H, deformed t, J=6 Hz), 1.09 (9H, s), 1.28 (40H, br.s), 1.52 (3H, s), 1.70~2.05 (6H, m), 2.70~3.00 (2H, m), 3.50~3.80 (2H, m), 3.80~4.40 (3H, m), 4.70~5.10 (1H, m), 5.15~5.40 (2H, m), 6.80~7.10 (1H, m, NH), 7.30~7.50 (6H, m), 7.50~7.90 (4H, m); TLC (n-hexane-ether=1:4) Rf 0.33. (Found: C, 76.42; H, 10.64; N, 1.65. Calc for $C_{51}H_{85}O_4NSi$: C, 76.15; H, 10.65; N, 1.74 %).

(4*E*,8*E*,2*S*,3*R*,2'*R*)-*N*-2'-Hydroxyhexadecanoyl-1-*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-3-*O*-(t-butyldiphenylsilyl)-9-methyl-4,8-sphingadienine **1f**. Dry C_6H_6 (8 ml) was added to a soln of **1e** (200 mg, 0.25 mmol) in $MeNO_2$ (8 ml) and the soln was stirred and heated at 100~110° to remove moisture by co-distillation with C_6H_6. The mixture was concentrated to the volume of ca 4 ml and cooled. To the soln were added **20** (154 mg, 0.37 mmol) and $Hg(CN)_2$ (94 mg, 0.37 mmol) and the mixture was stirred and heated at 80° for 3.5 h. After cooling, the mixture was diluted with ether (200 ml). The ether soln was shaken with sat H_2S aq (50 ml) and the black ppt of HgS was removed by filtration. The organic soln was washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with n-hexane-EtOAc (6:1) gave 133 mg (47.2 %) of **1f** as a viscous oil, νmax 3420 (s), 1750 (s), 1655 (s), 1590 (w), 1525 (s), 1460 (s), 1430 (s), 1370 (s), 1240~1220 (s), 1040 (s), 700 (s) cm^{-1}; δ($CDCl_3$) 0.87 (6H, deformed t, J=6 Hz), 1.05 (9H, s), 1.24 (40H, br.s), 1.48 (3H, s), 1.60~2.20 (6H, m), 2.01 (12H, br.s), 2.82 (1H, d, J=5 Hz, OH), 3.40~4.50 (9H, m), 4.70~5.50 (6H, m), 6.81 (1H, d, J=8 Hz, NH), 7.30~7.85 (10H, m); HPTLC (n-hexane-EtOAc=1:2) Rf 0.63. This was employed in the next step without further purification.

(4*E*,8*E*,2*S*,3*R*,2'*R*)-*N*-2'-Hydroxyhexadecanoyl-1-*O*-β-D-glucopyranosyl-3-*O*-(t-butyldiphenylsilyl)-9-methyl-4,8-sphingadienine **1g**. A soln of NaOH in MeOH (0.5 N, 2 ml) was added to a soln of **1f** (120 mg, 0.106 mmol) in $CHCl_3$ (6 ml). The mixture was stirred for 20 min at room temp, diluted with ice-water (5 ml), neutralized with 2 N-AcOH aq and extracted with $CHCl_3$ (20 ml x 4). The $CHCl_3$ soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with $CHCl_3$-MeOH (20:1) gave 85 mg (83.2 %) of **1g** as a gum, $[\alpha]_D^{21}$-26.5°(c=0.2, $CHCl_3$); νmax (KBr disc) 3400 (s), 1640 (s), 1530 (s), 1105 (s), 1075 (s), 700 (s) cm^{-1}; δ ($CDCl_3$) 0.70~1.00 (6H, m), 1.04 (9H, s), 1.25 (40H, br.s), 1.49 (3H, s), 1.60~2.00 (6H, m), 3.00~4.50 (13H, m), 4.80~5.50 (6H, m), 7.30~7.90 (10H, m); HPTLC ($CHCl_3$-MeOH=9:1) Rf 0.33. (Found: C, 70.20; H, 9.80; N, 1.60. Calc for $C_{57}H_{95}O_9NSi$: C, 70.83; H, 9.91; N, 1.45. Calc for $C_{57}H_{95}O_9NSi \cdot 1/2\ H_2O$: C, 70.18; H, 9.92; N, 1.44 %).

(4*E*,8*E*,2*S*,3*R*,2'*R*)-*N*-2'-Hydroxyhexadecanoyl-1-*O*-β-D-glucopyranosyl-9-methyl-4,8-sphingadienine **1a**. A soln of $(n\text{-}Bu)_4NF$ in THF (1 M, 0.8 ml, 0.8 mmol) was added to a soln of **1g** (80 mg, 0.083 mmol) in THF (0.4 ml) and the mixture was stirred for 20 h at room temp. It was then diluted with 2N-HCl (20 ml) and extracted with $CHCl_3$-MeOH (87:13; 60 ml, 30 ml x 5). The organic soln was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with $CHCl_3$-MeOH (12:1) gave 43 mg (71.4 %) of **1a** as a glassy solid, $[\alpha]_D^{21}$-7.3°±0.2°(c=0.50, $CHCl_3$) [natural **1a**: $[\alpha]_D^{19}$-7.4°±0.4° (c=0.30, $CHCl_3$)]; νmax (KBr disc) 3400 (s), 2975 (s), 2940 (s), 2870 (s), 1640 (s), 1535 (s), 1470 (s), 1380 (w), 1325 (w), 1300 (w), 1160 (w), 1080 (s), 1035 (s), 965 (m), 900 (m), 720 (m) cm^{-1}; δ(400 MHz, $CDCl_3$, recorded at 65°) 0.88 (6H,

t, J=6.3 Hz), 1.27 (38H, br.s), 1.35~1.44 (2H, m), 1.08 (3H, s), 1.65 (2H, br.s, OH), 1.95 (2H, t, J=7.5 Hz), 2.06 (4H, t, J=2.5 Hz), 3.35 (2H, q, J=8.5 Hz), 3.53 (2H, quint, J=8.5 Hz), 3.65 (1H, m, OH), 3.78~3.90 (3H, m), 3.98 (1H, dd, J_1=11.0 Hz, J_2=6.0 Hz), 4.05~4.17 (1H, m, OH), 4.34 (1H, d, J=7.8 Hz), 4.48 (2H, m, OH), 4.71 (1H, m, OH), 4.80 (1H, m, OH), 5.10 (1H, m), 5.47 (1H, dd, J_1=15.6 Hz, J_2=6.4 Hz), 5.77 (1H, deformed d, J=15.6 Hz), 7.28 (1H, d, J=8.0 Hz, NH); HPTLC: Rf 0.32 [developed with $CHCl_3$-MeOH=83:17 (v/v)]; Rf 0.47 (developed with $CHCl_3$-MeOH-99% HCO_2H=70:18:12); Rf 0.58 ($CHCl_3$-MeOH-water-28 % NH_3 aq=200:70:6:1); HPLC (Column, Senshupak® N5C_{18}, 25 cm x 4.6 mm; Solvent, MeOH; Flow rate, 1 ml/min; Detection, 220 nm) Rt 6.5 min. (Found: C, 66.80; H, 10.68; N, 1.92. Calc for $C_{41}H_{77}O_6N \cdot 1/2\ H_2O$: C, 66.81; H, 10.66; N, 1.90 %). The IR and NMR spectra of **1a** was identical with those of the natural **1a**. The HPTLC and HPLC analyses also confirmed the identity.

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