Synthesis of Sphingosine Relatives, XXI[+] Synthesis of Sphingofungin D and Its Three Diastereomers

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Keywords: Antifungal agents / *Aspergillus fumigatus* / Enzyme inhibitors / Sphingofungins / Sphingosines

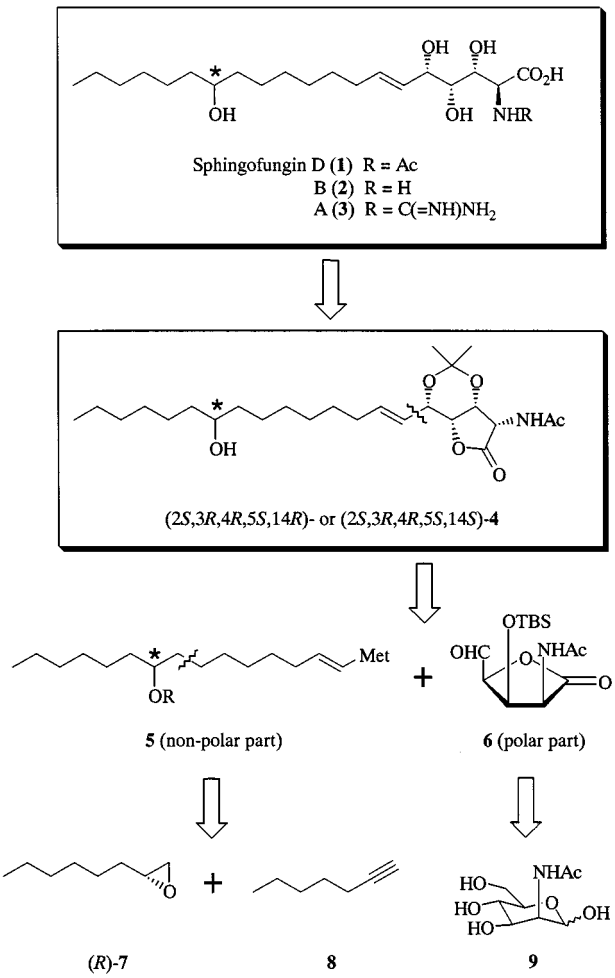
Sphingofungin D [(2*S*,3*R*,4*R*,5*S*,14*R*)-**1**] and its three diastereomers were synthesized by starting from (*R*)-1,2-epoxyoctane [(*R*)-**7**], 1-heptyne (**8**) and *N*-acetyl-D-mannosamine (**9**).

In 1992 VanMiddlesworth et al. reported the isolation[1] and structure elucidation[2] of sphingofungins, a new family of antifungal metabolites produced by *Aspergillus fumigatus* ATCC 20857. These compounds are potent and specific inhibitors of serine palmitoyl transferase. The structures **1**, **2** and **3** assigned to sphingofungins D, B and A, respectively, show their similarity to sphingolipids. Their stereochemistry at C-14 was not reported initially,[2] but in 1995, Chida et al. elucidated it to be (*R*) by examining the ozonolysis product of natural sphingofungin C (**2**, OAc instead of OH at C-5).[3]

In continuation of our synthetic studies on sphingosine relatives, we undertook a synthesis of both the (14*R*) and (14*S*) isomers of **4**. Because **4** derived from the natural sphingofungin C has been converted into sphingofungin D (**1**), B (**2**) and A (**3**),[2] the synthesis of **4** implies that of these three sphingofungins. In this paper, we will report the synthesis of four diastereomers of **4**, and their conversion into sphingofungin D and its three diastereomers.[4] In 1996, a synthesis of sphingofungin B was reported by Kobayashi et al.[5][6]

Our retrosynthetic analysis as shown in Scheme 1 suggests that **4** may be synthesized by the coupling reaction of **5** (nonpolar part) and **6** (polar part). Optically active **5** will be derived from (*R*)-1,2-epoxyoctane (**7**) and 1-heptyne (**8**). On the other hand, preparation of **6** will be possible from *N*-acetyl-D-mannosamine (**9**).

Scheme 2 summarizes the preparation of the nonpolar building block **15**. Cleavage of (*R*)-**7** (91% *ee*; purchased from Japan Energy Co.) with the acetylide from **8** yielded **10** and **11**. After separation by column chromatography, **10** was subjected to the acetylene zipper reaction[7] to give crystalline (*R*)-**12**, m.p. 42−43°C, $[\alpha]_D^{23} = -0.86$ (c = 1.7 in Et_2O). The corresponding TBS ether (*R*)-**13** was metalated with tri(*n*-butyl)tin hydride[8] to give the alkenylstannane (*R*)-**14**, which furnished the alkenyl iodide (*R*)-**15** by treatment with iodine in diethyl ether.[9] The overall yield of (*R*)-**15** based on **7** was 61% after 5 steps. Mitsunobu inversion[10] smoothly converted (*R*)-**12** into (*S*)-**12**, m.p. 41−42°C, $[\alpha]_D^{22} = +0.88$ (c = 1.7 in Et_2O). Similarly, (*S*)-**12** was converted into (*S*)-**15** in 49% overall yield based on **7** (7 steps).



Scheme 1. Structures of sphingofungins and their retrosynthetic analysis

[+] Part XX: H. Takikawa, S. Muto, K. Mori, *Tetrahedron* **1998**, *54*, 3141−3150.

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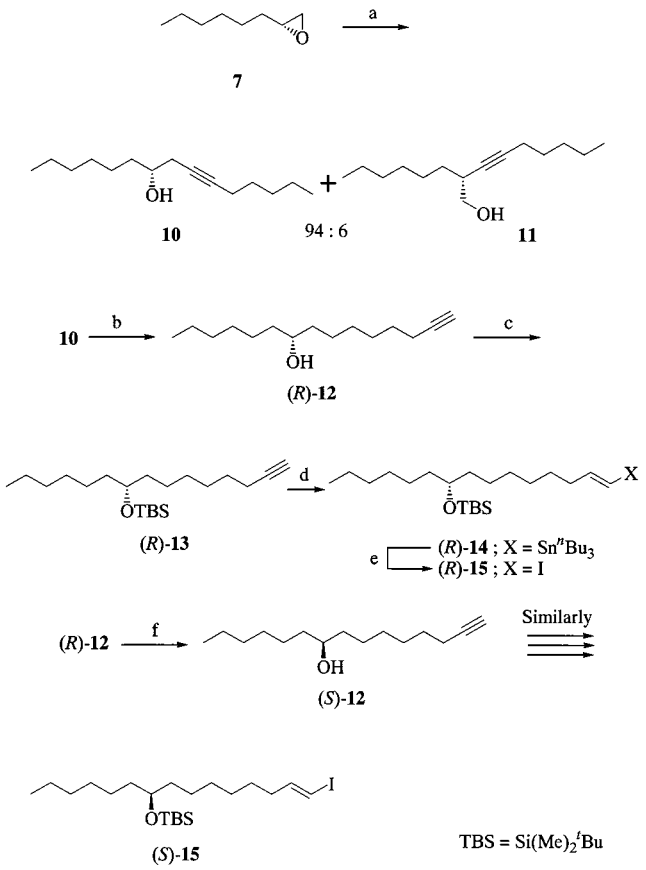
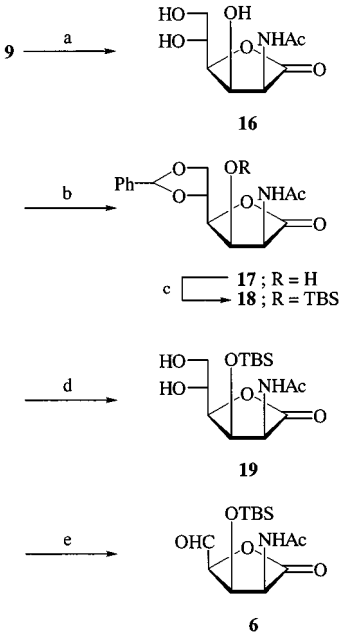


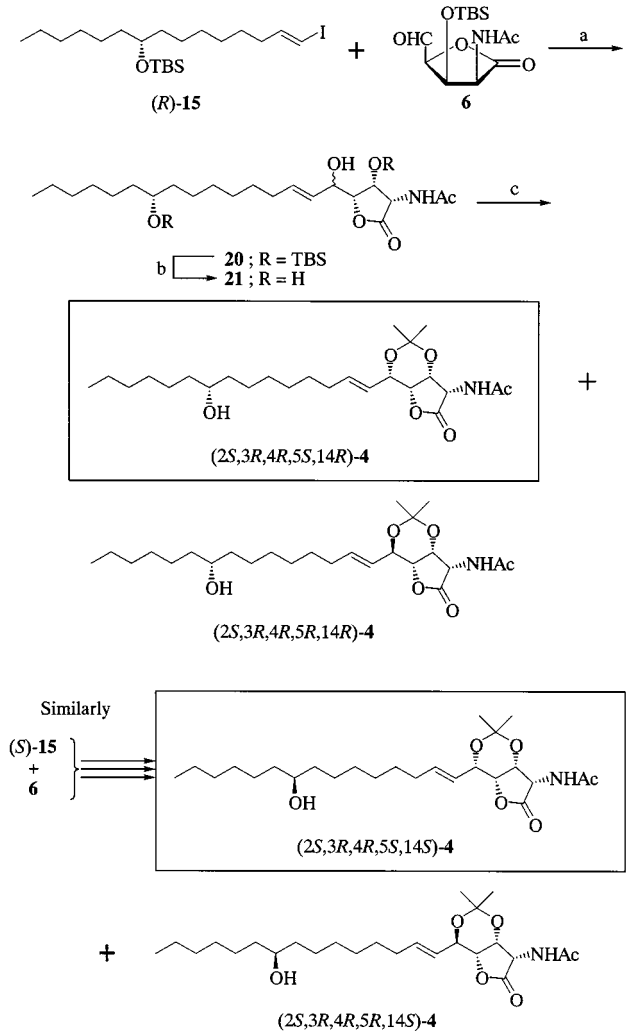
Scheme 2. Synthesis of the nonpolar building block **15**; reagents: (a) 1) 1-heptyne (**8**), *n*BuLi, BF_3·OEt_2, THF; 2) (*R*)-**7** (80%); (b) Li, *t*BuOK, $H_2N[CH_2]_3NH_2$ (88%); (c) TBSCl, imidazole, DMF (quant.); (d) $(nBu)_3SnH$, AIBN (92%); (e) I_2, Et_2O (95%); (f) 1) $EtO_2CN{=}NCO_2Et$, Ph_3P, $PhCO_2H$; 2) K_2CO_3, MeOH (80%)



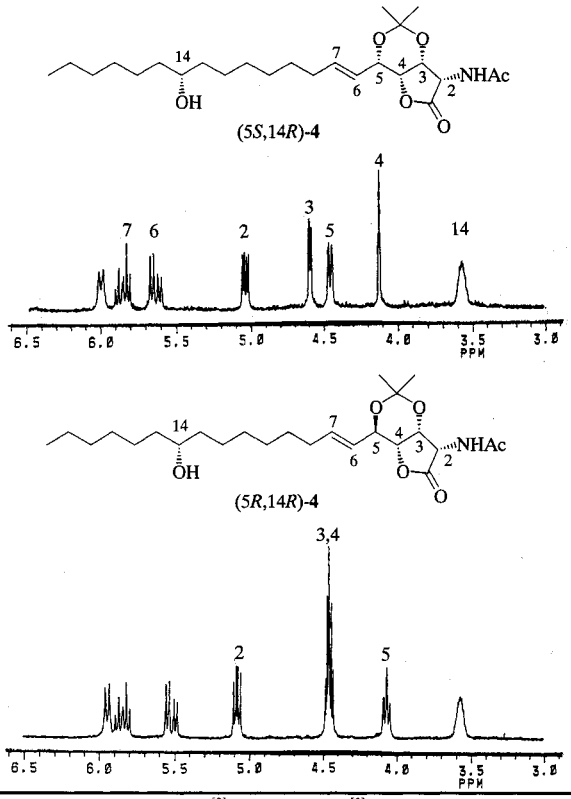
Scheme 3. Synthesis of the polar building block **6**; reagents: (a) Br_2, H_2O (41%); (b) $PhCH(OMe)_2$, HBF_4·OEt_2, DMF (98%); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2 (65%); (d) $Pd(OH)_2$, cyclohexene, EtOH (85%); (e) $NaIO_4$, H_2O, CH_2Cl_2 (crude 95%)

Synthesis of the polar building block **6** is shown in Scheme 3. *N*-Acetyl-D-mannosamine (**9**) was oxidized with bromine in water to give **16**.[11] Protection of the *vic*-diol system of **16** as benzylideneacetal **17**[12] was followed by further protection of the remaining hydroxy group of **17** as TBS ether to yield **18**.[13] Hydrogenolytic removal of the benzylidene protective group of **18** by transfer hydrogenation with cyclohexene and the Pearlman palladium[14] gave **19**. In the case of acetonide group instead of benzylidene one for the *vic*-diol protection, the selective deprotection of acetonide group did not proceed very smoothly under several conditions so far examined. The diol **19** was oxidized with sodium periodate to give the aldehyde **6** as a crude gum. The overall yield of **6** was 21% based on **9** (5 steps).

Coupling of **6** with (*R*)-**15** or its equivalent was examined under several different conditions. The best result was obtained when the coupling was carried out with chromium(II) chloride and nickel chloride in DMSO[15][16] to give in 41% yield the desired product **20** as a diastereomeric mixture as shown in Scheme 4. In the case of lithium or



Scheme 4. Synthesis of the four stereoisomers of **4**; reagents: (a) $CrCl_2$ (6.0 equiv.), $NiCl_2$ (0.04 equiv.), DMSO (41%); (b) HF aq., MeCN; (c) $Me_2C(OMe)_2$, TsOH, DMF, chromatog. sepn. [28% of (2*S*,3*R*,4*R*,5*S*,14*R*)-**4** based on **20**, 46% of (2*S*,3*R*,4*R*,5*R*,14*R*)-**4** based on **20**]



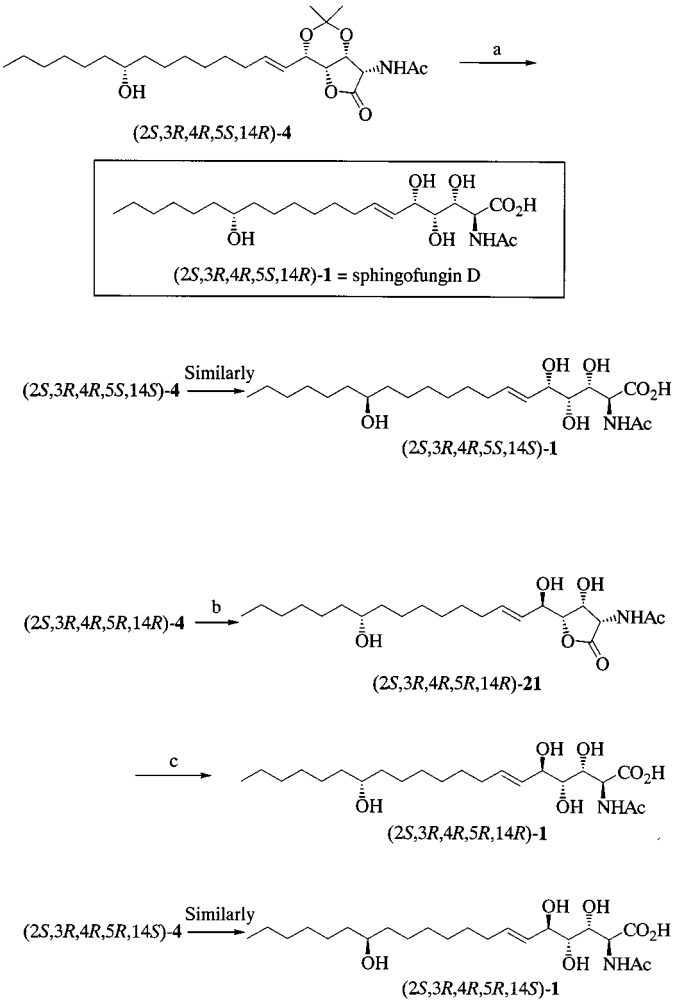
compound	protons	J (ref.[2]; calcd.)	J (ref.[2]; found)	J (this work; found)
	2 - 3	3.7 Hz	3.9 Hz	3.9 Hz
(5*S*,14*R*)-**4**	3 - 4	2.7 Hz	2.1 Hz	2.1 Hz
	4 - 5	1.6 Hz	1.6 Hz	1.7 Hz
	2 - 3	4.6 Hz	-	5.5 Hz
(5*R*,14*R*)-**4**	3 - 4	4.5 Hz	-	not determined
	4 - 5	7.5 Hz	-	6.8 Hz

Figure 1. Determination of the stereochemistry of **4** by 300-MHz ^{1}H-NMR analysis ($CDCl_3$)

aluminium as a metal of **5** (see Scheme 1), the yield of **20** was very low. Removal of the TBS protective group of **20** afforded **21**. The corresponding diastereomeric mixture of the acetonide **4** could be separated by silica gel chromatography to give a more polar compound (28% yield based on **20**) and a less polar one (46% yield based on **20**). Careful examination of their 300-MHz ^{1}H-NMR spectra (see Figure 1) revealed the spectrum of the more polar product to be identical with that of (2*S*,3*R*,4*R*,5*S*)-**4** derived from sphingofungin C.[3] Especially the magnitude of the coupling constants $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ of the more polar product were in good agreement with the values reported for (2*S*,3*R*,4*R*,5*S*)-**4**.[3]

The more polar material was therefore (2*S*,3*R*,4*R*,5*S*,14*R*)-**4**, while the less polar one must be (2*S*,3*R*,4*R*,5*R*,14*R*)-**4**. The coupling of **6** with (*S*)-**15**, followed by deprotection-protection and diastereomer separation by chromatography, yielded (2*S*,3*R*,4*R*,5*S*,14*S*)-**4** and its (5*R*) isomer. It was impossible to find out any notable differences between the ^{1}H-NMR spectrum of (2*S*,3*R*,4*R*,5*S*,14*R*)-**4** and that of the (14*S*) isomer. Their $[\alpha]_D$ values were also quite similar and did not allow the distinction between the diastereomers (see Experimental Section).

The four diastereomers of **4** were then converted into sphingofungin D (**1**) and its three diastereomers as shown in Scheme 5. The (2*S*,3*R*,4*R*,5*S*,14*R*) isomer of **4** was refluxed in aqueous acetic acid and then in aqueous methanol to give (2*S*,3*R*,4*R*,5*S*,14*R*)-**1** (sphingofungin D). Under these conditions only the (5*S*)-trihydroxylactone intermediate **21** was hydrolyzed even in the presence of a small amount of the (5*R*) isomer. In the same manner, (2*S*,3*R*,4*R*,5*S*,14*S*)-**1** was derived from the corresponding isomer of **4**. In the case of the (5*R*) isomer of **4**, the trihydroxylactone intermediate **21** could be purified by recrysrallization, which furnished (5*R*)-**1** after hydrolysis with LiOH.

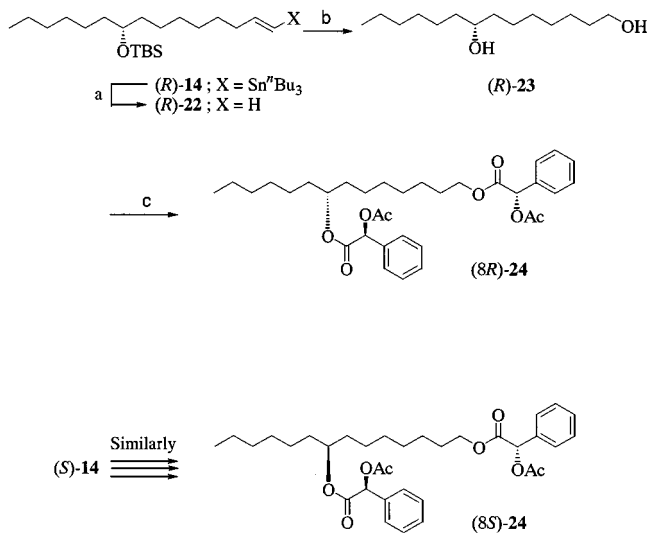


Scheme 5. Synthesis of sphingofungin D and its three stereoisomers; reagents: (a) 1) AcOH, THF, H_2O; 2) MeOH, H_2O (59%); (b) AcOH, THF, H_2O (95%); (c) LiOH, THF, H_2O (78%)

For the determination of the stereochemistry at C-14, we prepared both the enantiomers of 1,8-tetradecanediol (**23**) as shown in Scheme 6. The alkenylstannane (*R*)-**14** was hydrodestannylated to (*R*)-**22** by contact with silica gel. Reductive work up of the ozonide of (*R*)-**22**, followed by removal of the silyl protective group, gave the diol (*R*)-**23**. In the same manner (*S*)-**23** was prepared from (*S*)-**14**. Both the enantiomers of **23** were converted into bis{*O*-[(*S*)-(+)-

O-acetylmandelyl]} derivatives **24**, and their 300-MHz ^{1}H-NMR spectra were examined. As reported by Chida et al.[3] the methylene signals at C-1 were clearly different between the enantiomers, and those of the (8*R*) isomer were identical with the reported data of **24** derived from sphingofungin C.

In conclusion, we synthesized the sphingofungin D (**1**) and its three diastereomers at C-5 and C-14 by coupling reaction of the polar part **6** and the nonpolar part (*R*)-[or (*S*)-]**15** as the key step. Thanks to the previous conversion of **1** to spingofungin B (**2**) and A (**3**),[3] the present synthesis of **1** can be regarded as a formal total synthesis of **2** and **3**.



Scheme 6. Synthesis of optically active tetradecane-1,8-diol (**23**); reagents: (a) silica gel, *n*-hexane (quant.); (b) 1) O_3, MeOH then $NaBH_4$, EtOH, H_2O; 2) HF aq., MeCN (85%); (c) (*S*)-(+)-*O*-acetylmandelic acid, DCC, DMAP, CH_2Cl_2 (89%)

Experimental Section

General: IR spectra: Jasco A-102 spectrometer. − ^{1}H-NMR spectra: JNM JEOL EX 90 spectrometer (90 MHz), Bruker AC-300 spectrometer (300 MHz). − ^{13}C-NMR spectra: Bruker AC-300 spectrometer (75.5 MHz). −Optical rotations: Jasco DIP-371 polarimeter. − Refractive indices: Atago 1T. − Column chromatography: Merck Kieselgel 60, Art. Nr. 7734. − Melting points: uncorrected values.

(*R*)-9-Pentadecyn-7-ol (10): A 1.71 M solution of *n*BuLi in *n*-hexane (115 mL, 0.197 mol) was added dropwise to a solution of 1-heptyne (**8**) (19.0 g, 0.197 mol) in dry THF (300 mL) at −50 to −70°C under argon. After stirring for 1 h at −70°C, BF_3·OEt_2 (24 mL, 0.196 mol) was added and the mixture was stirred for 10 min at −70°C. To this was added dropwise a solution of (*R*)-1, 2-epoxyoctane (**7**) (91% *ee*; 21.0 g, 0.164 mol) in dry THF (40 mL) over 15 min at −60 to −70°C, and the stirring was continued at −70°C for 3 h. The mixture was then allowed to warm to room temp., and poured into a mixture of 10% aqueous ammonium chloride solution (800 mL) and diethyl ether (600 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 times). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (700 g). Elution with *n*-hexane/ethyl acetate (25:1) gave 29.5 g (80%) of **10**; n_D^{20} = 1.4595, $[\alpha]_D^{20}$ = −2.50 (*c* = 1.22 in $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3360 cm^{-1} (m, OH), 1050 (m, C−O). − ^{1}H NMR (90 MHz in $CDCl_3$): δ = 0.40−1.00 (m, 6 H), 1.00−1.80 (m, 16 H), 1.91 (br. s, 1 H, OH), 2.00−2.70 (m, 4 H, CH_2CCCH_2), 3.69 (tt, *J* = 5.7, 5.7 Hz, 1 H, 7-H). − $C_{15}H_{28}O$ (224.4): calcd. C 80.29, H 12.58; found C 80.54, H 12.74.

The less polar fractions gave 1.88 g (5%) of (*R*)-8-hydroxymethyl-6-tetradecyne (**11**). − ^{1}H NMR (90 MHz in $CDCl_3$): δ = 0.50−1.00 (m, 6 H), 1.00−1.80 (m, 16 H), 1.90−2.60 (m, 2 H, 5-H), 2.70−3.00 (m, 4 H, OCH_2, OH, 8-H).

(*R*)-14-Pentadecyn-7-ol [(*R*)-12]: Under a slightly positive pressure of argon, lithium (4.07 g, 0.586 mol, washed free of mineral oil with *n*-hexane) was added to dry 1,3-diaminopropane (300 mL). The mixture was heated and stirred at 70°C for approximately 2 h until the blue color had discharged, and a milky white suspension of the lithium salt was obtained. The mixture was cooled to 10°C and potassium *tert*-butoxide (38.1 g, 0.339 mol) was added all at once, affording a pale yellow solution. After stirring for 15 min at room temp., addition of **10** (18.6 g, 82.8 mmol) in one portion resulted in the reaction mixture turning orange with a suspended white solid. Stirring was continued for a further 5 h and the mixture was poured into a mixture of ice water (800 mL) and diethyl ether (400 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 times). The combined organic layers were washed successively with water, saturated aqueous ammonium chloride and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel [400 g, eluent: *n*-hexane/ethyl acetate (12:1)] followed by recrystallization from *n*-hexane to give 16.3 g (88%) of (*R*)-**12**; m.p. 42−43°C, $[\alpha]_D^{23}$ = −0.86 (*c* = 1.70 in Et_2O). − IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (s, OH), 2120 (w, C≡CH), 1290 (w). − ^{1}H NMR (90 MHz in $CDCl_3$): δ = 0.88 (t, *J* = 5.0 Hz, 3 H, Me), 1.00−1.85 (m, 20 H), 1.94 (t, *J* = 2.4 Hz, 1 H, C≡CH), 2.00−2.30 (m, 3 H, C≡C−CH_2, OH), 3.35−3.80 (m, 1 H, 7-H). − $C_{15}H_{28}O$ (224.4): calcd. C 80.29, H 12.58; found C 80.03, H 12.50.

(*S*)-14-Pentadecyn-7-ol [(*S*)-12]: A solution of (*R*)-**12** (6.36 g, 28.3 mmol), triphenylphosphane (11.2 g, 42.5 mmol) and benzoic acid (5.19 g, 42.5 mmol) in dry THF (200 mL) was stirred at 0°C. To this was added dropwise a solution of 7.40 g (42.5 mmol) of diethyl azodicarboxylate in 40 mL of THF over 1.5 h. The contents were stirred for 30 h at room temp. Removal of THF under reduced pressure afforded a syrupy product, which was chromatographed on silica gel (400 g). Elution with *n*-hexane/ethyl acetate (40:1−20:1) gave 8.37 g of (*S*)-1-hexyl-8-nonynyl benzoate, which was dissolved in 40 mL of MeOH. To this was added potassium carbonate (6.36 g, 46.0 mmol) at 0°C, and the mixture was stirred for 8 h at room temp. The mixture was poured into water and extracted with chloroform (4 times). The combined organic layers were washed with saturated aqueous ammonium chloride and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (100 g). Elution with *n*-hexane/ethyl acetate (20:1−9:1) gave (*S*)-**12** (5.59 g, 88%); m.p. 41−42°C, $[\alpha]_D^{23}$ = +0.88 (*c* = 1.70 in Et_2O). − The IR and ^{1}H-NMR spectra were identical with those of (*R*)-**12**. − $C_{15}H_{28}O$ (224.4): calcd. C 80.29, H 12.58; found C 80.25, H 12.66.

(*R*)-7-(*tert*-Butyldimethylsilyloxy)-14-pentadecyne [(*R*)-13]: To a solution of (*R*)-**12** (6.00 g, 26.7 mmol) and *tert*-butyldimethylchlorosilane (4.44 g, 29.5 mmol) in dry DMF (30 mL) was added imidazole (2.37 g, 34.8 mmol) in one portion at 0°C. After stirring for 10 h at 0°C to room temp., the mixture was poured into a mixture of water (100 mL) and ethyl acetate (60 mL). The organic layer was

separated, and the aqueous layer was extracted with ethyl acetate (3 times). The combined organic layers were washed with water (twice) and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (150 g). Elution with *n*-hexane, then *n*-hexane/ethyl acetate (20:1) gave 9.05 g (quant.) of (*R*)-**13**; $n_D^{19} = 1.4499$, $[\alpha]_D^{25} = -0.17$ ($c = 1.20$ in $CHCl_3$). – IR (film): $\tilde{\nu} = 3320\ cm^{-1}$ (m, C≡CH), 2120 (w, C≡CH), 1255 (s, SiMe), 1100–1020 (br. s, Si–O). – ^1H NMR (90 MHz in $CDCl_3$): δ = 0.03 (s, 6 H, SiMe), 0.88 (br. s, 12 H, *t*Bu, Me), 1.00–1.80 (m, 20 H), 1.93 (t, $J = 2.4$ Hz, 1 H, C≡CH), 2.00–2.35 (m, 2 H, C≡C–CH_2), 3.45–3.80 (m, 1 H, 7-H). – $C_{21}H_{42}SiO$ (338.6): calcd. C 74.48, H 12.50; found C 74.54, H 12.61.

(*S*)-7-(*tert*-Butyldimethylsilyloxy)-14-pentadecyne [(*S*)-13]: In the same manner as described for (*R*)-**13**, (*S*)-**12** (4.40 g, 19.6 mmol) was converted into 6.64 g (quant.) of (*S*)-**13**; $n_D^{19} = 1.4500$, $[\alpha]_D^{25} = +0.17$ ($c = 1.18$ in $CHCl_3$). – The IR and ^1H-NMR spectra were identical with those of (*R*)-**13**. – $C_{21}H_{42}SiO$ (328.6): calcd. C 74.48, H 12.50; found C 74.42, H 12.37.

(*R*)-7-(*tert*-Butyldimethylisilyloxy)-15-(tri-*n*-butylstannyl)-14-pentadecene [(*R*)-14]: A mixture of (*R*)-**13** (9.05 g, 26.7 mmol), tri-*n*-butyltin hydride (8.54 g, 29.3 mmol) and azobis(isobutyronitrile) (0.14 g, 0.85 mmol) was heated slowly to 90°C and then kept at that temp. for 40 h. The reaction mixture was cooled, a white precipitate was removed by filtration through a Celite pad, and the liquid was chromatographed on aluminium oxide 90 active neutral (Merck 1077, Activity 3, 400 g). Elution with *n*-hexane gave 16.8 g (quant.) of (*R*)-**14**; $n_D^{22} = 1.4733$, $[\alpha]_D^{20} = +0.33$ ($c = 1.17$ in $CHCl_3$). – IR (film): $\tilde{\nu} = 1250\ cm^{-1}$ (s, SiMe), 1120–1020 (br. s, Si–O). – ^1H NMR (90 MHz in $CDCl_3$): δ = 0.04 (s, 6 H, SiMe), 0.30–1.70 (m, 59 H), 1.80–2.30 (m, 2 H, 13-H), 3.45–3.75 (m, 1 H, 7-H), 5.80–6.00 (m, 2 H, vinyl). – $C_{33}H_{70}SiSnO$ (629.7): calcd. C 62.95, H 11.20; found C 63.19, H 11.33.

(*S*)-7-(*tert*-Butyldimethylsilyoxy)-15-(tri-*n*-butylstannyl)-14-pentadecene [(*S*)-14]: In the same manner as described for (*R*)-**14**, (*S*)-**13**, (6.64 g, 19.6 mmol) was converted into 11.9 g (96%) of (*S*)-**14**; $n_D^{17} = 1.4749$, $[\alpha]_D^{18} = -0.27$ ($c = 1.18$ in $CHCl_3$). – The IR and ^1H-NMR spectra were identical with those of (*R*)-**14**. – $C_{33}H_{70}SiSnO$ (629.7): calcd. C 62.95, H 11.20; found C 63.27, H 11.31.

(*R*)-7-(*tert*-Butyldimethylsilyloxy)-15-iodo-14-pentadecene [(*R*)-15]: To a solution of (*R*)-**14** (14.6 g, 23.1 mmol) in diethyl ether (54 mL) was added dropwise at 0°C a 0.2 M solution of iodine in diethyl ether (75 mL) until the color of iodine persisted. After stirring for 1 h at 0°C, a 5% aqueous sodium hydrogen sulfite solution was added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 times). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (200 g). Elution with *n*-hexane, then *n*-hexane/ethyl acetate (60:1) gave 10.6 g (98%) of (*R*)-**15**; $n_D^{17} = 1.4803$, $[\alpha]_D^{19} = -0.02$ ($c = 1.1$ in $CHCl_3$). – IR (film): $\tilde{\nu} = 1605\ cm^{-1}$ (w, C=C), 1255 (m, SiMe), 1120–1020 (br. m, Si–O), 945 (m). – ^1H NMR (90 MHz in $CDCl_3$): δ = 0.04 (s, 6H, SiMe), 0.65–1.70 (m, 32 H), 2.05 (dt, $J = 6.1$, 7.1 Hz, 2 H, 13-H), 3.45–3.70 (m, 1 H, 7-H), 5.96 (d, $J = 14.5$ Hz, 1 H, 15-H), 6.52 (dt, $J = 14.5$, 7.1 Hz, 1 H, 14-H). – $C_{21}H_{43}ISiO$ (466.6): calcd. C 54.06, H 9.29; found C 53.94, H, 9.31.

(*S*)-7-(*tert*-Butyldimethylsiliyloxy)-15-iodo-14-pentadecene [(*S*)-15]: In the same manner as described for (*R*)-**15**, (*S*)-**14** (11.4 g, 18.1 mmol) was converted into 8.16 g (97%) of (*S*)-**15**; $n_D^{17} = 1.4801$, $[\alpha]_D^{19} = +0.04$ ($c = 1.6$ in $CHCl_3$). – The IR and ^1H-NMR spectra were identical with those of (*R*)-**15**. – $C_{21}H_{43}ISiO$ (466.6): calcd. C 54.06, H 9.29; found C 54.43, H 9.35.

2-Acetamido-2-deoxy-D-mannono-1,4-lactone (16): This compound was prepared from *N*-acetyl-D-monnosamine (**9**) according to Pravdíc et al.[11] A solution of the monohydrate of **9** (50.0 g, 0.209 mol) in water (1 l) was treated with bromine (30 mL), and the mixture was kept in the dark overnight and stirred for 3 d. The excess of bromine was removed in vacuo without heating, and the solution was treated with silver carbonate (125 g). After filtration, the resulting solution was treated with hydrogen sulfide to remove silver ions, and the precipitate was removed by filtration through a layer of decolorizing carbon. The colorless filtrate was concentrated in vacuo (40°C bath), and the syrupy residue was dried in a desiccator over phosphorus pentaoxide, then the crystallization was spontaneous. The product was triturated with methanol (100 mL), and collected by filtration: 14.2 g (31%). Upon concentration, the mother liquor yielded a second crop (4.6 g), raising the total yield to 41%. After recrystallization from methanol, the pure **16** had a m.p. of 174–177°C, $[\alpha]_D^{19} = +76.5$ ($c = 1.11$ in H_2O). – IR (KBr): $\tilde{\nu} = 3500\ cm^{-1}$ (s, OH), 3400 (s, NH), 1770 (s, O–C=O), 1650 (s, HN–C=O), 1540 (s, HN–C=O). – ^1H NMR (90 MHz in [D_6]DMSO): δ = 1.93 (s, 3 H, Ac), 3.30–4.00 (m, 3 H), 4.20–4.40 (m, 2 H), 4.61 (t, $J = 5.8$ Hz, 1 H, OH), 4.83 (d, $J = 5.9$ Hz, 1 H, OH), 4.96 (dd, $J = 9.0$, 4.2 Hz, 1 H, H-2), 5.64 (d, $J = 5.9$ Hz, 1 H, OH), 8.14 (d, $J = 9.0$ Hz, 1 H, NH). – $C_8H_{13}NO_6$ (219.2); calcd. C 43.84, H 5.98, N 6.39; found C 43.72, H 5.89, N 6.39.

2-Acetamido-2-deoxy-5,6-*O*-benzylidene-D-mannono-1,4-lactone (17): To a solution of **16** (7.50 g, 34.2 mmol) in dry DMF (150 mL) were added benzaldehyde dimethylacetal (6.00 g, 39.4 mmol) and tetrafluoroboric acid–diethyl ether (85% in diethyl ether, 5.93 mL, 34.2 mmol). After stirring at room temp. for 10 h, triethylamine (48 g) was added, and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel (300 g). Elution with diethyl ether, and then diethyl ether/methanol (50:1–25:1–15:1) gave 10.3 g (98%) of **17** as a 1:1 diastereomeric mixture; m.p. 165–170°C, $[\alpha]_D^{19} = +109$ ($c = 1.09$, CH_3OH). – IR (KBr): $\tilde{\nu} = 3370\ cm^{-1}$ (s, NH, OH), 1775 (s, O–C=O), 1650 (s, HN–C=O), 1530 (s, NH–C=O), 1100 (s, C–O). – ^1H NMR (90 MHz in [D_6]DMSO): δ = 1.94 (s, 3 H, Ac), 3.80–4.70 (m, 4 H), 4.86 (dd, $J = 3.9$, 5.0 Hz, 1 H), 5.05 (dd, $J = 8.3$, 4.8 Hz, 1 H, 2-H), 5.72 and 5.87 (each s, total 1 H, benzyl), 5.99 (d, $J = 5.3$ Hz, 1 H, OH), 7.43 (br. s, 5 H, Ph), 8.25 (d, $J = 7.9$ Hz, 1 H, NH). – $C_{15}H_{17}NO_6$ (307.3): calcd. C 58.63, H 5.58, N 4.56; found C 58.35, H 5.53, N 4.57.

2-Acetamido-5,6-*O*-benzylidene-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-mannono-1,4-lactone (18): To a solution of **17** (11.3 g, 36.8 mmol) and 2,6-lutidine (11.8 g, 0.111 mol) in dry dichloromethane (70 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (24.4 g, 92.1 mmol) dropwise at 0°C under argon. After stirring at 0°C for 2.5 h, iced water (200 g) was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 times). The combined organic layers were washed successively with water (3 times) and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel (380 g). Elution with *n*-hexane/diethyl ether (1:4), diethyl ether, then diethyl ether/methanol (19:1–9:1) gave 9.36 g (60.3%) of **18** as a 1:1 diastereomeric mixture [further elution gave 0.80 g (7.1%) of the recovered **17**]; m.p. 44–46°C, $[\alpha]_D^{19} = +55.1$ ($c = 1.62$ in $CHCl_3$). – IR (KBr): $\tilde{\nu} = 3340\ cm^{-1}$ (m, NH), 1785 (s, O–C=O), 1665 (s, HN–C=O). – ^1H NMR (90 MHz in $CDCl_3$): δ = 0.04 (s, 3 H, SiMe), 0.09 and

0.10 (each s, total 3 H, SiMe), 0.89 and 0.91 (each s, total 9 H, *t*Bu), 2.05 (s, 3 H, Ac), 3.93−4.70 (m, 5 H), 4.92 and 4.97 (each dd, J = 7.5, 4.5 Hz, total 1 H, 2-H), 5.79 and 5.97 (each s, total 1 H, benzyl), 6.28 (d, J = 7.5 Hz, 1 H, NH), 7.40 (br. s, 5 H, Ph). − $C_{21}H_{31}NSiO_6$ (421.6): calcd. C 59.83, H 7.41, N 3.32; found C 59.68, H 7.46, N 3.18.

2-Acetamido-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-mannono-1,4-lactone (19): Palladium hydroxide on carbon (20%, 1.54 g) was added to a solution of **18** (2.96 g, 7.02 mmol) in ethanol (56 mL) and cyclohexene (50 mL), and the suspension was stirred under reflux for 21 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel (100 g). Elution with diethyl ether, then diethyl ether/methanol (30:1−15:1) gave 1.67 g (71%) of **19** [the less polar fractions gave 0.63 g (21%) of the recovered **18**]; m.p. 70−72°C, $[\alpha]_D^{19}$ = +78.4 (c = 1.12 in $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3390 cm^{-1} (br. s, OH), 3100 (w, NH), 1780 (s, O−C=O), 1660 (s, HN−C=O). − ^{1}H NMR (90 MHz in $CDCl_3$): δ = 0.06 (s, 3H, SiMe), 0.15 (s, 3H, SiMe), 0.90 (s, 9H, *t*Bu), 2.08 (s, 3H, Ac), 2.94 (br. s, 2H, OH), 3.60−4.10 (m, 3H, 4-H and 6-H), 4.20−4.50 (m, 1H, 5-H), 4.68 (dd, J = 2.6, 4.0 Hz, 1H, 3-H), 4.92 (dd, J = 7.4, 4.1 Hz, 1H, 2-H), 6.09 (d, J = 7.4 Hz, 1H, NH). − $C_{14}H_{27}NSiO_6$ (333.5): calcd. C 50.43, H 8.16, N 4.20; found C 49.93, H 8.01, N 4.13.

(2*S*,3*R*,4*S*)-2-Acetylamino-3-(*tert*-butyldimethylsilyloxy)-4-formyl-4-butanolide (6): To a solution of **19** (500 mg, 1.50 mmol) in dichloromethane (12 mL) and water (8 mL) was added sodium periodate (963 mg, 4.50 mmol) at room temp. After stirring for 4.5 h, the reaction mixture was poured into a mixture of dichloromethane (40 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (4 times). The combined organic layers were dried with anhydrous magnesium sulfate and concentrated in vacuo to give 452 mg (quant.) of crude **6**; $[\alpha]_D^{24}$ = +40.6 (c = 0.57 in $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3370 (m, NH), 1780 (s, O−C=O), 1745 (m, H−C=O), 1660 (s, HN−C=O), 1130 (s). − ^{1}H NMR (90 MHz in $CDCl_3$): δ = 0.01 (s, 6 H, SiMe), 0.84 (s, 9 H, *t*Bu), 2.08 (s, 3 H, Ac), 3.35−3.40 (m, 1 H), 4.60−5.10 (m, 2 H), 5.97 (br. d, J = 8.0 Hz, 1 H, NH), 9.63 (d, J = 1.8 Hz, 1 H, CHO). − This crude **6** was employed in the next step without further purification.

(2*S*,3*R*,4*R*,5*RS*,14*R*)-2-Acetylamino-3,14-bis(*tert*-butyldimethylsilyloxy)-5-hydroxyicos-6-en-4-olide [(14*R*)-20]: A mixture of anhydrous $CrCl_2$ (300 mg, 2.44 mmol) and a catalytic amount of $NiCl_2$ (2.0 mg, 0.015 mmol) in dry and oxygen-free DMSO (5 mL) was stirred at room temp. for 10 min under argon. To the reagent at room temp. was added a solution of crude **6** (122 mg, 0.405 mmol) in DMSO (3 mL) and a solution of (*R*)-**15** (567 mg, 1.22 mmol) in DMSO (2 mL) successively. After stirring at room temp. for 33 h, the reaction mixture was quenched by stirring with saturated ammonium chloride and chloroform. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (15 g). Elution with *n*-hexane/ethyl acetate (10:1−5:1) gave 107 mg (41%) of (14*R*)-**20** as a diastereomeric mixture; n_D^{19} = 1.4779, $[\alpha]_D^{19}$ = +41.7 (c = 0.60 in $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3390 cm^{-1} (br. m, OH), 1780 (s, O−C=O), 1660 (s, HN−C=O), 1250 (s, SiMe), 1190−1000 (br. s, Si−O). − ^{1}H NMR (90 MHz in $CDCl_3$): δ = 0.00−0.15 (m, 12 H, SiMe), 0.50−1.50 (m, 41 H), 1.60−2.20 (m, 3 H, 8-H, OH), 2.03 and 2.08 (each s, total 3 H, Ac), 3.45−3.75 (m, 1 H, 14-H), 4.00−5.20 (m, 4 H, 2-H, 3-H, 4-H, 5-H), 5.35−6.25 (m, 3 H, vinyl, NH). − $C_{34}H_{67}NSi_2O_6$ (642.1): calcd. C 63.60, H 10.52, N 2.18; found C 63.28, H 10.71, N 2.07.

(2*S*,3*R*,4*R*,5*RS*,14*S*)-2-Acetylamino-3,14-bis(*tert*-butyldimethylsilyloxy)-5-hydroxyicos-6-en-4-olide [(14*S*)-20]: In the same manner as described for (14*R*)-**20**, crude **6** (595 mg, 1.97 mmol) and (*S*)-**15** (2.27 g, 5.94 mmol) were converted into 381 mg (30%) of (14*S*)-**20** as a diastereomeric mixture; n_D^{19} = 1.4778, $[\alpha]_D^{19}$ = +39.4 (c = 1.03 in $CHCl_3$). There was no notable difference between the IR and ^{1}H-NMR spectra of (14*S*)-**20** and those of (14*R*)-**20**. − $C_{34}H_{67}NSi_2O_6$ (642.1): calcd. C 63.60, H 10.52, N 2.18; found C 63.32, H 10.52, N 2.15.

(2*S*,3*R*,4*R*,5*S*,14*R*)-2-Acetylamino-14-hydroxy-3,5-isopropylidenedioxyicos-6-en-4-olide [(2*S*,3*R*,4*R*,5*S*,14*R*)-4] and Its C-5 Diastereomer (2*S*,3*R*,4*R*,5*R*,14*R*)-4: To a solution of (14*R*)-**20** (390 mg, 0.607 mmol) in acetonitrile (7 mL) was added 46% aqueous hydrofluoric acid (1.32 g, 30.4 mmol) at room temp. After stirring for 20 h at this temp., 2.81 g of sodium hydrogen carbonate was added to the solution, and the mixture was stirred for 10 min. The reaction mixture was chromatographed directly on silica gel (50 g). Elution with chloroform, then chloroform/methanol (9:1−4:1) gave 239 mg of crude triol (5*RS*,14*R*)-**21**. This was then dissolved in DMF (4 mL), and 2,2-dimethoxypropane (9.0 mL, 73.2 mmol) and *p*-toluenesulfonic acid monohydrate (30 mg) were added at room temp. After stirring for 50 h at room temp., the reaction mixture was poured into a mixture of saturated aqueous sodium hydrogen carbonate (30 mL) and ethyl acetate (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 times). The combined organic layers were washed with water and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (15 g). Elution with *n*-hexane/ethyl acetate (1:1−1:2) gave 127 mg [46% based on (14*R*)-**20**] of (2*S*,3*R*,4*R*,5*R*,14*R*)-**4** (less polar) and 77 mg [28.0% based on (14*R*)-**20**] of (2*S*, 3*R*, 4*R*, 5*S*, 14*R*)-**4**.

Physical Data of (2*S*,3*R*,4*R*,5*S*,14*R*)-4: M.p. 60−62°C, $[\alpha]_D^{19}$ = +87.2 (c = 0.36 in $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3250 cm^{-1} (br. m, OH), 1780 (s, O−C=O), 1645 (s, HN−C=O), 1370 (m), 1160 (s, C−O). − ^{1}H NMR (300 MHz in $CDCl_3$): δ = 0.88 (t, J = 6.5 Hz, 3 H, 20-H), 1.15−1.75 (m, 21 H, $-CH_2-$, OH), 1.43 (s, 3 H, acetonide Me), 1.49 (s, 3 H, acetonide Me), 2.00−2.15 (m, 2 H, 8-H), 2.10 (s, 3 H, Ac), 3.50−3.65 (m, 1 H, 14-H), 4.13 (dd, J = 2.1, 1.7 Hz, 1 H, 4-H), 4.47 (dd, J = 7.3, 1.7 Hz, 1 H, 5-H), 4.61 (dd, J = 3.9, 2.1 Hz, 1 H, 3-H), 5.05 (dd, J = 8.2, 3.9 Hz, 1 H, 2-H), 5.64 (dd, J = 15.5, 7.2 Hz, 1 H, 6-H), 5.86 (dt, J = 15.5, 6.6 Hz, 1 H, 7-H), 6.00 (d, J = 8.2 Hz, 1 H, NH). −^{13}C NMR (in $CDCl_3$): δ = 14.1, 19.4, 22.6, 23.0, 25.5, 25.6, 28.6, 29.1, 29.2, 29.4, 29.5, 31.8, 32.2, 37.4, 37.5, 53.8, 67.8, 69.8, 72.0, 73.2, 98.8, 124.5, 136.7, 170.4, 173.5. − $C_{25}H_{43}NO_6$ (453.6): calcd. C 66.20, H 9.53, N 3.09; found C 66.01, H 9.47, N 2.97.

Physical Data of (2*S*,3*R*,4*R*,5*R*,14*R*)-4: M.p. 64−66°C, $[\alpha]_D^{19}$ = +48.3 (c = 0.87 in $CHCl_3$). −IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (br. m, OH), 1780 (s, O−C=O), 1645 (s, HN−C=O), 1215 (m), 1170 (s, C−O). − ^{1}H NMR (300 MHz in $CDCl_3$): δ = 0.88 (t, J = 6.6 Hz, 3 H, 20-H), 1.15−1.75 (m, 21 H, $-CH_2-$, OH), 1.39 (s, 6 H, acetonide Me), 2.00−2.20 (m, 2 H, 8-H), 2.10 (s, 3 H, Ac), 3.50−3.65 (m, 1 H, 14-H), 4.06 (dd, J = 6.8, 6.5 Hz, 1 H, 5-H), 4.40−4.55 (m, 2 H, 3-H, 4-H), 5.08 (dd, J = 8.4, 5.5 Hz, 1H, 2-H), 5.52 (dd, J = 15.4, 6.5 Hz, 1H, 6-H), 5.85 (ddt, J = 15.4, 0.8, 6.8 Hz, 1H, 7-H), 5.95 (d, J = 8.4 Hz, 1 H, NH). − ^{13}C NMR (in $CDCl_3$): δ = 14.0, 22.6, 22.9, 23.9, 24.0, 25.5, 25.6, 28.7, 29.1, 29.4, 29.5, 31.8, 32.3, 37.4, 37.5, 50.7, 66.3, 71.96, 72.02, 81.1, 101.8, 125.8, 135.6, 170.2, 173.5. −- $C_{25}H_{43}NO_6$ (453.6): calcd. C 66.20, H 9.53, N 3.09; found C 66.15, H 9.48, N 3.11.

(2*S*,3*R*,4*R*,5*S*,14*S*)-2-Acetylamino-14-hydroxy-3,5-isopropylidenedioxyicos-6-en-4-olide [(2*S*,3*R*,4*R*,5*S*,14*S*)-4] and Its C-5 Diastereomer (2*S*,3*R*,4*R*,5*R*,14*S*)-4: In the same manner as described for (2*S*,3*R*,4*R*,5*S*,14*R*)-**4** and (2*S*,3*R*,4*R*,5*R*,14*R*)-**4**, (14*S*)-**20** (360 mg, 0.561 mmol) was converted into 125 mg [49% based on (14*S*)-**20**] of (2*S*,3*R*,4*R*,5*R*,14*S*)-**4** (less polar) and 70 mg [28% based on (14*S*)-**20**] of (2*S*,3*R*,4*R*,5*S*,14*S*)-**4**.

Physical Data of (2*S*,3*R*,4*R*,5*S*,14*S*)-4: M.p. 60−62°C, $[\alpha]_D^{20}$ = +88.5 (*c* = 0.48 in $CHCl_3$). There was no notable difference between the IR, ^{1}H-NMR and ^{13}C-NMR spectra of (2*S*,3*R*,4*R*,5*S*,14*S*)-**4** and those of (2*S*,3*R*,4*R*,5*S*,14*R*)-**4**. − $C_{25}H_{43}NO_6$ (453.6): calcd. C 66.20, H 9.53, N 3.09; found C 65.98, H 9.49, N 2.99.

Physical Data of (2*S*,3*R*,4*R*,5*R*,14*S*)-4: M.p. 63−65°C, $[\alpha]_D^{24}$ = +44.8 (*c* = 1.15 in $CHCl_3$). There was no notable difference between the IR, ^{1}H-NMR and ^{13}C-NMR spectra of (2*S*,3*R*,4*R*,5*R*,14*S*)-**4** and those of (2*S*,3*R*,4*R*,5*R*,14*R*)-**4**. − $C_{25}H_{43}NO_6$ (453.6): calcd. C 66.20, H 9.53, N 3.09; found C 65.83, H 9.61, N 3.02.

(2*S*,3*R*,4*R*,5*S*,14*R*)-2-Acetylamino-3,4,5,14-tetrahydroxyicos-6-enoic Acid [(2*S*,3*R*,4*R*,5*S*,14*R*)-1]; Sphingofungin D: To a solution of (2*S*,3*R*,4*R*,5*S*,14*R*)-**4** (71.5 mg, 0.158 mmol) in THF (3 mL) and water (3 mL) was added acetic acid (3 mL) at room temp. The mixture was then heated to reflux temp. and stirred for 4 h. The reaction mixture was concentrated in vacuo, and the residue was thoroughly dried in vacuo. The resulting crude products were dissolved in methanol (2 mL) and water (2 mL), and then heated to reflux temp. After stirring for 3.5 h at this temp., the reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel (3 g). Elution with chloroform/methanol (3:1−1:1−1:2) gave 40.1 mg [59% based on (2*S*,3*R*,4*R*,5*S*,14*R*)-**4**] of sphingofungin D [(2*S*,3*R*,4*R*,5*S*,14*R*)-**1**]; m.p. 151−162°C (decomp.), $[\alpha]_D^{26}$ = +2.91 (*c* = 1.10 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3700−2900 cm^{-1} (br. s, OH), 1570 (br. s), 1410 (br. s). − ^{1}H NMR (300 MHz in CD_3OD): δ = 0.90 (t, *J* = 6.6 Hz, 3 H, 20-H), 1.25−1.55 (m, 20 H, $-CH_2-$), 1.90−2.20 (m, 2 H, 8-H), 2.02 (s, 3 H, Ac), 3.40−3.55 (m, 1 H, 4-H), 3.55−3.65 (m, 1 H, 14-H), 3.87 (bd, *J* = 4.2 Hz, 1 H, 3-H), 4.21 (br. t, *J* = 7.3 Hz, 1 H, 5-H), 4.40 (br. d, *J* = 4.2 Hz, 1 H, 2-H), 5.55 (dd, *J* = 14.9, 7.3 Hz, 1 H, 6-H), 5.79 (dt, *J* = 14.9, 7.0 Hz, 1 H, 7-H). − ^{13}C NMR (in CD_3OD): 14.4, 22.9, 23.7, 26.8 (2 ×), 30.2, 30.4, 30.6, 30.8, 33.1, 33.5, 38.5 (2 ×), 58.2, 72.5 (2 ×), 75.2, 75.7, 130.5, 135.7, 173.4, 178.2. − $C_{22}H_{41}NO_7$ (431.6): calcd. C 61.23, H 9.58, N 3.25; found C 61.16, H 9.38, N 3.22.

(2*S*,3*R*,4*R*,5*S*,14*S*)-2-Acetylamino-3,4,5,14-tetrahydroxyicos-6-enoic Acid [(2*S*,3*R*,4*R*,5*S*,14*S*)-1]: In the same manner as described for sphingofungin D [(2*S*,3*R*,4*R*,5*S*,14*R*)-**1**], (2*S*,3*R*,4*R*,5*S*,14*S*)-**4** (37.0 mg, 0.0816 mmol) was converted into 15.5 mg (44%) of (2*S*,3*R*,4*R*,5*S*,14*S*)-**1**; m.p. 151−162°C (decomp.), $[\alpha]_D^{23}$ = +2.83 (*c* = 0.73 in MeOH). − There was no notable difference between the IR, ^{1}H-NMR and ^{13}C-NMR spectra of (2*S*,3*R*,4*R*,5*S*,14*S*)-**1** and those of sphingofungin D [(2*S*,3*R*,4*R*,5*S*,14*R*)-**1**]. − $C_{22}H_{41}NO_7$ (431.6): calcd. C 61.23, H 9.58, N 3.25; found C 61.25, H 9.42, N 3.17.

(2*S*,3*R*,4*R*,5*R*,14*R*)-2-Acetylamino-3,5,14-trihydroxyicos-6-en-4-olide [(2*S*,3*R*,4*R*,5*R*,14*R*)-21]: To a solution of (2*S*,3*R*,4*R*,5*R*,14*R*)-**4** (47.0 mg, 0.104 mmol) in THF (2 mL) and water (2 mL) was added acetic acid (2 mL) at room temp. The reaction mixture was then heated to reflux temp. and stirred for 4 h. The reaction mixture was concentrated in vacuo, and the residue was chromatographed on silica gel (10 g). Elution with chloroform gave 41.0 mg (95%) of (2*S*,3*R*,4*R*,5*R*,14*R*)-**21**; m.p. 175−177°C, $[\alpha]_D^{19}$ = +67.1 (*c* = 0.32 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3540 cm^{-1} (m), 3350 (br. s, OH), 1760 (s, O−C=O), 1640 (s, HN−C=O). − ^{1}H NMR (300 MHz in CD_3OD): δ = 0.90 (t, *J* = 6.5 Hz, 3 H, Me), 1.20−1.60 (m, 20 H, $-CH_2-$), 2.00−2.20 (m, 2 H, 8-H), 2.06 (s, 3 H, Ac), 3.45−3.55 (m, 1 H, 14-H), 4.22 (dd, *J* = 8.3, 2.5 Hz, 1 H, 3-H), 4.37 (dd, *J* = 8.3, 6.8 Hz, 1 H, 5-H), 4.50−4.55 (m, 1 H, 4-H), 4.97 (d, *J* = 4.4 Hz, 1 H, 2-H), 5.59 (dd, *J* = 15.4, 6.8 Hz, 1 H, 6-H), 5.82 (dt, *J* = 15.4, 6.5 Hz, 1 H, 7-H). − ^{13}C NMR (in CD_3OD): δ = 14.4, 22.3, 23.7, 26.7, 26.8, 30.16, 30.19, 30.5, 30.7, 33.0, 33.4, 38.4 (2 ×), 55.6, 70.0, 70.1, 72.5, 84.1, 130.4, 135.1, 173.8, 176.0. − $C_{22}H_{39}NO_6$ (413.6): calcd. C 63.90, H 9.51, N 3.39; found C 64.06, H 9.47, N 3.36.

(2*S*,3*R*,4*R*,5*R*,14*S*)-2-Acetylamino-3,5,14-trihydoxyicos-6-en-4-olide [(2*S*,3*R*,4*R*,5*R*,14*S*)-21]: In the same manner as described for (2*S*,3*R*,4*R*,5*R*,14*R*)-**21**, (2*S*,3*R*,4*R*,5*R*,14*S*)-**4** (43.0 mg, 0.0948 mmol) was converted into 35.5 mg (91%) of (2*S*,3*R*,4*R*,5*R*,14*S*)-**21**; m.p. 177−179°C, $[\alpha]_D^{18}$ = +71.1 (*c* = 0.37 in MeOH). − There was no notable difference between the IR, ^{1}H-NMR and ^{13}C-NMR spectra of (2*S*,3*R*,4*R*,5*R*,14*S*)-**21** and those of (2*S*,3*R*,4*R*,5*R*,14*R*)-**21**. − $C_{22}H_{39}NO_6$ (413.6): calcd. C 63.90, H 9.51, N 3.39; found C 63.64, H 9.22, N 3.28.

(2*S*,3*R*,4*R*,5*R*,14*R*)-2-Acetylamino-3,4,5,14-tetrahydroxyicos-6-enoic Acid [(2*S*,3*R*,4*R*,5*R*,14*R*)-1]: To a solution of (2*S*,3*R*,4*R*,5*R*,14*R*)-**21** (33.0 mg, 0.0798 mmol) in a mixture of THF (2 mL) and water (2 mL) was added at 0°C lithium hydroxide monohydrate (10.0 mg, 0.238 mmol). After stirring for 30 min at this temp., water (2 mL) was added and then the mixture was neutralized with 0.5 N hydrochloric acid (pH = 7). The aqueous layer was saturated with ammonium sulfate and extracted with THF (6 times). The combined organic layers were dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (3 g). Elution with chloroform/methanol (3:1−1:1−1:2) gave 26.9 mg (78.1%) of (2*S*,3*R*,4*R*,5*R*,14*R*)-**1**; m.p. 195−205°C (decomp), $[\alpha]_D^{25}$ = +1.40 (*c* = 0.11 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (br. s, OH), 3350 (s, NH), 1660 (s), 1590 (s). − ^{1}H NMR (300 MHz in CD_3OD): δ = 0.90 (t, *J* = 6.7 Hz, 3 H, 20-H), 1.20−1.65 (m, 20 H), 1.90−2.20 (m, 2 H, 8-H), 2.01 (s, 3 H, Ac), 3.41 (dd, *J* = 7.1, 1.4 Hz, 1 H, 4-H), 3.45−3.55 (m, 1 H, 14-H), 4.02 (dd, *J* = 6.8, 1.4 Hz, 1 H, 3-H), 4.12 (dd, *J* = 7.1, 6.0 Hz, 1 H, 5-H), 4.37 (d, *J* = 6.8 Hz, 1 H, 2-H), 5.58 (dd, *J* = 15.3, 6.0 Hz, 1 H, 6-H), 5.75 (dt, *J* = 15.3, 6.2 Hz, 1 H, 7-H). − ^{13}C NMR (in CD_3OD): δ = 14.5, 22.9, 23.7, 26.8 (2 ×), 30.4 (2 ×), 30.6, 30.8, 33.1, 33.6, 38.5 (2 ×), 57.5, 71.9, 72.4 (2 ×), 74.2, 130.8, 134.5, 173.5, 178.2. − $C_{22}H_{41}NO_7$ (431.6): calcd. C 61.23, H 9.58, N 3.25; found C 60.95, H 9.39, N 3.32.

(2*S*,3*R*,4*R*,5*R*,14*S*)-2-Acetylamino-3,4,5,14-tetrahydroxyicos-6-enoic Acid [(2*S*,3*R*,4*R*,5*R*,14*S*)-1]: In the same manner as described for [(2*S*,3*R*,4*R*,5*R*,14*R*)-**1**], (2*S*,3*R*,4*R*,5*R*,14*S*)-**21** (18.9 mg, 0.0457 mmol) was converted into 15.5 mg (79%) of (2*S*,3*R*,4*R*,5*R*,14*S*)-**1**; m.p. 182−202°C (decomp.), $[\alpha]_D^{22}$ = +1.31 (*c* = 0.35 in MeOH). − There was no notable difference between the IR, ^{1}H-NMR and ^{13}C-NMR spectra of (2*S*,3*R*,4*R*,5*R*,14*S*)-**1** and those of [(2*S*,3*R*,4*R*,5*R*,14*R*)-**1**]. − $C_{22}H_{41}NO_7$ (431.6): calcd. C 61.23, H 9.58, N 3.25; found C 61.11, H 9.45, N 3.41.

(*R*)-7-(*tert*-Butyldimethylsilyloxy)-14-pentadecene [(*R*)-22]: A mixture of (*R*)-**14** (630 mg, 1.00 mmol) and silica gel (3 g) in *n*-hexane (30 mL) was stirred at room temp. for 1 h, then the whole was subjected to silica gel chromatography (15 g) directly. Elution with *n*-hexane gave 341 mg (quant.) of (*R*)-**22**; n_D^{25} = 1.4462, $[\alpha]_D^{20}$ = −0.10 (*c* = 0.46 in $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1645 cm^{-1} (w, CH=CH_2), 1255 (m, SiMe), 1160−980 (br. m, Si−O). − ^{1}H NMR (300 MHz in $CDCl_3$): δ = 0.04 (s, 6 H, SiMe), 0.85−0.95 (m, 12 H, *t*Bu, Me), 0.55−1.70 (m, 20 H, $-CH_2-$), 2.04 (dt, *J* = 6.7,

6.6 Hz, 2 H, 13-H), 3.55−3.65 (m, 1 H, 7-H), 4.85−5.05 (m, 2 H, 15-H), 5.81 (ddt, J = 17.3, 10.0, 6.7 Hz, 1 H, 14-H). − $C_{21}H_{44}SiO$ (340.7): calcd. C 74.04, H 13.02; found C 74.08, H 13.18.

(*S*)-7-(*tert*-Butyldimethylsilyloxy)-14-pentadecene [(*S*)-22]: In the same manner as described for (*R*)-**22**, (*S*)-**14** (630 mg, 1.00 mmol) was converted into 342 mg (quant.) of (*S*)-**22**; n_D^{22} = 1.4463, $[\alpha]_D^{22}$ = +0.11 (c = 0.31 in $CHCl_3$). The IR and ^{1}H NMR spectra were identical with those of (*R*)-**22**. − $C_{21}H_{44}SiO$ (340.7): calcd. C 74.04, H 13.02; found C 74.31, H 12.90.

(*R*)-Tetradecane-1,8-diol [(*R*)-23]: A 50-mL, two-necked, round-bottomed flask was fitted with a glass tube to admit ozone, a calcium chloride drying tube, and a magnetic stirring bar and was charged with 715 mg (2.10 mmol) of (*R*)-**22** and methanol (15 mL). The flask was cooled to ca. −60°C, and ozone was bubbled through the solution with stirring. When the solution turned blue, the ozone addition was stopped. Nitrogen was passed through the solution until the blue color was discharged and then the cold bath was removed. The ozone inlet was replaced with a rubber septum, and a solution of sodium tetrahydroborate (640 mg, 16.9 mmol) in ethanol (4 mL) and water (4 mL) was added. The solution was allowed to warm to room temp. and stirred for 10 h. The reaction mixture was poured into an ice-cold mixture of 1 N hydrochloric acid (30 mL) and chloroform (40 mL). The organic layer was separated and the aqueous layer was extracted with chloroform (4 times). The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate, concentrated in vacuo and dried thoroughly in vacuo. The crude products were dissolved in acetonitrile (10 mL) and stirred, followed by dropwise addition of 46% aqueous hydrofluoric acid at room temp. After stirring for 2 h at room temp., aqueous sodium hydrogen carbonate (20 mL) was added and stirring continued. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (5 times). The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (15 g). Elution with *n*-hexane/ethyl acetate (3:2−1:1) gave 409 mg (85% for 2 steps) of (*R*)-**23**; m.p. 57−58°C, $[\alpha]_D^{19}$ = −0.48 (c = 1.1 in $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3310 (br. m, OH), 1065 (m, C−O). − ^{1}H NMR (90 MHz in $CDCl_3$): δ = 0.88 (t, J = 5.6 Hz, 3 H, Me), 0.80−1.80 (m, 22 H, $-CH_2-$), 1.40 (s, 2 H, 2 OH), 3.75−3.40 (m, 3 H, 1-H, 8-H). − $C_{14}H_{30}O_2$ (230.4): calcd. C 72.99, H 13.12; found C 72.85, H 13.28.

(*S*)-Tetradecane-1,8-diol [(*S*)-23]: In the same manner as described for (*R*)-**23**, (*S*)-**22** (325 mg, 0.954 mmol) was converted into 193 mg (88% for 2 steps) of (*S*)-**23**; m.p. 57−58°C, $[\alpha]_D^{19}$ = +0.52 (c = 1.03 in $CHCl_3$). − The IR and ^{1}H-NMR spectra were identical with those of (*R*)-**23**. − $C_{14}H_{30}O_2$ (230.4): calcd. C 72.99, H 13.12; found C 72.77, H 13.31.

(8*R*)-Tetradecane-1,8-diyl Bis[(*S*)-(+)-*O*-acetylmandelate] [(8*R*)-24]: To a solution of (*R*)-**23** (50.0 mg, 0.217 mmol) and (*S*)-(+)-*O*-acetylmandelic acid (92.9 mg, 0.478 mmol) in dichloromethane (2 mL) was added 4-(dimethylamino)pyridine (46.9 mg, 0.384 mmol) at room temp. After cooling with an ice bath to 0°C, dicyclohexylcarbodiimide (103 mg, 0.499 mmol) was added and then the reaction mixture was stirred at room temp. for 24 h. The white precipitates were removed by filtration through a Celite pad, and the filtrate was washed successively with 0.5 N hydrochloric acid (twice), water and saturated aqueous sodium hydrogen carbonate, dried with anhydrous sodium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (2 g). Elution with *n*-hexane and then *n*-hexane/ethyl acetate (25:1−10:1) gave 110 mg (87%) of (8*R*)-**24**; n_D^{19} = 1.5012, $[\alpha]_D^{22}$ = +81.3 (c = 0.55 in $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1740 cm^{-1} (br. s, C=O), 1230 (br. s), 1050 (br. s). − ^{1}H NMR (300 MHz in $CDCl_3$): δ = 0.82 (t, J = 7.1 Hz, 3 H, Me), 0.95−1.60 (m, 22 H, $-CH_2-$), 2.19 (s, 3 H, Ac), 2.20 (s, 3 H, Ac), 4.11 (t, J = 6.7 Hz, 2 H, 1-H), 4.87 (tt, J = 6.2, 6.2 Hz, 1 H, 8-H), 5.86 (s, 1 H, benzyl), 5.91 (s, 1 H, benzyl), 7.25−7.50 (m, 10 H, Ph). − $C_{34}H_{46}O_8$ (582.7): calcd. C 70.08, H 7.96; found C 69.93, H 7.88.

(8*S*)-Tetradecane-1,8-diyl Bis[(*S*)-(+)-*O*-acetylmandelate] [(8*S*)-24]: In the same manner as described for (*R*)-**24**, (*S*)-**23** (45 mg, 0.195 mmol) was converted into 101 mg (89%) of (*S*)-**24**; n_D^{23} = 1.4849, $[\alpha]_D^{23}$ = +80.2 (c = 3.17 in $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1740 cm^{-1} (s, C=O), 1230 (br. s), 1050 (s). − ^{1}H NMR (300 MHz in $CDCl_3$): δ = 0.87 (t, J = 6.9 Hz, 3 H, Me), 0.95−1.65 (m, 22 H, $-CH_2-$), 2.195 (s, 3 H, Ac), 2.203 (s, 3 H, Ac), 4.08 (dt, J = 4.0, 6.7 Hz, 2 H, 1-H), 4.87 (tt, J = 6.2, 6.2 Hz, 1 H, 8-H), 5.87 (s, 1 H, benzyl), 5.91 (s, 1 H, benzyl), 7.25−7.50 (m, 10 H, Ph). − $C_{34}H_{46}O_8$ (582.7): calcd. C 70.08, H 7.96; found C 70.03, H 7.89.

Acknowledgments

We thank Dr. N. Chida (Keio University, Yokohama) for discussion. Financial support of this work by Sumitomo Chemical Co. is acknowledged with thanks.

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Received March 22, 1999
[O99170]