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A NOVEL ROUTE TO D-*erythro*-SPHINGOSINE AND RELATED COMPOUNDS FROM MONO-*O*-ISOPROPYLIDENE-D-XYLOSE OR -D-GALACTOSE

MAKOTO KISO, AKEMI NAKAMURA, YOSHIMI TOMITA, AND AKIRA HASEGAWA
Department of Agricultural Chemistry, Gifu University, Gifu 501-11 (Japan)
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ABSTRACT

An efficient synthesis of D-*erythro*-sphingosine and -ceramide from D-xylose or D-galactose is described. A mixture of 2,4-*O*-isopropylidene-D-threose and its formate, which is available in one step from 3,5-*O*-isopropylidene-D-xylofuranose or 4,6-*O*-isopropylidene-D-galactopyranose, was subjected to the Wittig alkenation with triphenylphosphonio-tetra- and -hexa-decylid. The resulting 1,3-*O*-isopropylidenated C_{18} and C_{20} alkenes were each transformed, by introduction of an azido group at C-2, and selective reduction of the azide, into the corresponding 1,3-*O*-protected sphingosines that have the 2(*S*),3(*R*)-D-*erythro* configuration, from which a variety of ceramides were prepared by the sequence of *N*-acylation with the stearoyl or lignoceroyl group, and hydrolytic removal of the isopropylidene group. Some ceramides were also obtained by direct *N*-acylations of the corresponding sphingosines.

INTRODUCTION

Glycosphingolipids[1] (such as gangliosides[2]), which are made up of a complex carbohydrate chain and a hydrophobic ceramide, play important biological roles and functions on cell surfaces. Much attention has been paid to their carbohydrate moiety, because of the possible contributions to the immunologic expression of cells, as well as the interaction with toxins, hormones, and so on. Recently, a possible role of the ceramide portion in defining the structure and function of membrane glycolipids has also been suggested[3], but little is known about the details.

In view of this situation, we have sought a facile and stereospecific preparation of a variety of ceramides. Among chemical syntheses[1b,4] of the optically active sphingosine or ceramide, several procedures that utilized the C_2-chiral unit of such carbohydrates as D-glucose[4b,f] and D-mannose[4h] seemed efficient. However, more than ten steps are required for the conversion of these sugars into the desired products. As outlined in a preceding communication[5], we have found that 2,4-*O*-isopropylidene- or 2,4-*O*-benzylidene-D-threose is a quite useful intermediate for the synthesis of the desired D-*erythro* type of compounds. Very recently, a similar pro-

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cedure employing 2,4-*O*-benzylidene-D-threose has been reported[6] by Schmidt and Zimmermann. We now describe the details of a novel, stereospecific route to a variety of sphingosines and ceramides, starting from a mono-*O*-isopropylidene-D-xylose or -D-galactose.

RESULTS AND DISCUSSION

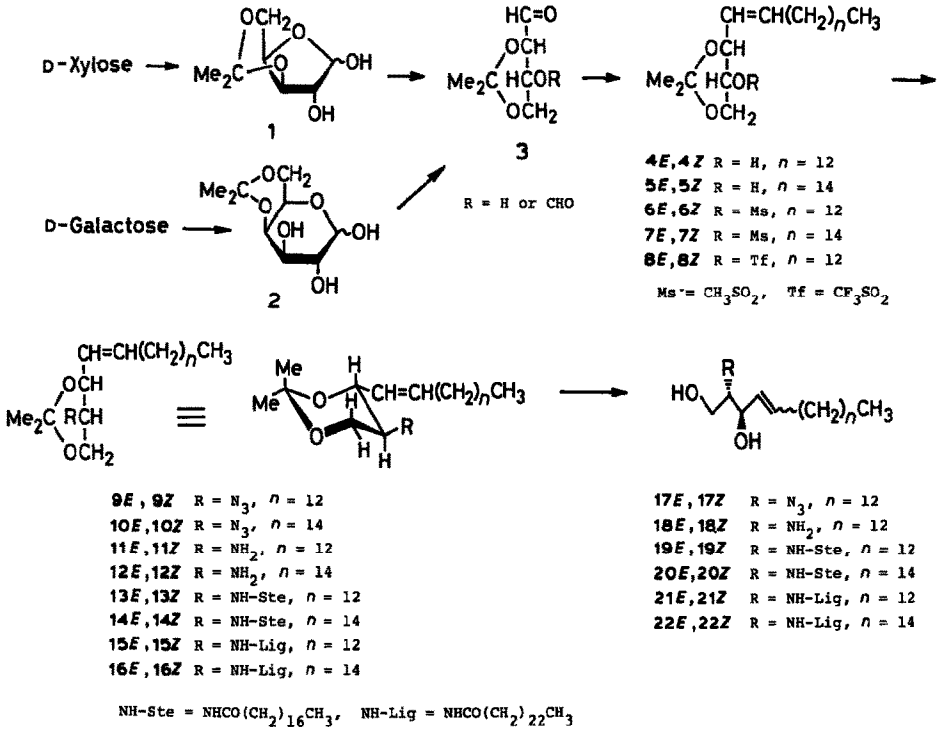
3,5-*O*-Isopropylidene-D-xylofuranose[7] (**1**), obtained in one step from D-xylose, was treated with sodium metaperiodate in methanol, to give, quantitatively, an ~1:1 mixture of 2,4-*O*-isopropylidene-D-threose (**3**) and its formate. This aldehyde intermediate **3** is also available from 4,6-*O*-isopropylidene-D-galactopyranose (**2**) by cleavage between C-2 and C-3.

The Wittig alkenation of **3** with triphenylphosphoniotetradecylid, which was prepared by treatment of tetradecyltriphenylphosphonium bromide with phenyllithium in tetrahydrofuran (THF), was achieved by a betainylid modification of Schlosser *et al.*[9], to yield, after chromatographic purification, *trans* C_{18}-olefin, *i.e.*, [2(*R*), 3(*R*), 4*E*]-1,3-*O*-isopropylidene-4-octadecene-1,2,3-triol (**4***E*; 40%), and the *cis* isomer (**4***Z*; 35%) as crystalline products. Similar treatment of **3** with triphenylphosphoniohexadecylid resulted in the formation of *trans* C_{20}-olefin (**5***E*) as the preponderant product; the *E*/*Z* ratio was ~5:2.

The 1,3-di-*O*-protected olefins (**4***E*, **4***Z*, **5***E*, and **5***Z*) were each treated with methanesulfonyl chloride in pyridine, to afford **6***E*, **6***Z*, **7***E*, and **7***Z*, respectively, which were then subjected, *in situ* or after brief purification, to an SN2 replacement reaction with sodium azide in *N*,*N*-dimethylformamide. In the ^{1}H-n.m.r. spectra of the resulting azide derivatives, the signals due to H-2 were each observed as a wide multiplet $J_{1a,2} = J_{2,3} = \sim 10$, $J_{1e,2} = 5.5$ Hz) at δ 3.29 (for **9***E* and **10***E*) and 3.33 (for **9***Z* and **10***Z*), respectively, definitely indicative of the 2(*S*),3(*R*)-D-*erythro* configuration found in natural sphingosine. When this replacement reaction was conducted with the trifluoromethanesulfonyl derivatives (**8***E* and **8***Z*), the yield of the azide was decreased to <50%, and gave two major, elimination by-products.

Selective reduction of the azide group was achieved by treament of **9***E*, **9***Z*, **10***E*, and **10***Z* with sodium borohydride in 2-propanol[10] at the reflux temperature, to yield the protected amino-olefins (**11***E*, **11***Z*, **12***E*, and **12***Z*), respectively, which were then converted, by *N*-acylation, into the corresponding 1,3-*O*-isopropylidene ceramides (*N*-stearoyl: **13***E*, **13***Z*, **14***E*, and **14***Z*, and *N*-lignoceroyl: **15***E*, **15***Z*, **16***E*, and **16***Z*) in high yields. Hydrogen sulfide[6], triphenylphosphine (with water)[4h], or hydrogenation in the presence of Lindlar catalyst[4f] may also be effective for the selective reduction of the azide to the amine.

Hydrolysis of the isopropylidene group from **9***E* and **9***Z* quantitatively afforded crystalline sphingosine precursors, **17***E* and **17***Z*, which were then transformed into the natural C_{18}-sphingosine (**18***E*; m.p. 81.5–82.5°) and the *cis* isomer (**18***Z*; m.p. 72–73°), respectively. Their C_{20} homologs can be prepared from **10***E* and **10***Z* in a similar manner.



Finally, (*a*) hydrolytic removal of the isopropylidene group from the protected ceramides (**13***E*, **13***Z*, **14***E*, **14***Z*, **15***E*, **15***Z*, **16***E*, and **16***Z*), or (*b*) *N*-acylation of a deprotected sphingosine (**18***E*), gave the desired C_{18} and C_{20} ceramides, *i.e.*, *N*-stearoyl (**19***E*, **19***Z*, **20***E*, and **20***Z*) and *N*-lignoceroyl (**21***E*, **21***Z*, **22***E*, and **22***Z*) sphingosines, respectively.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Specific rotations were determined with a Union PM-201 polarimeter, and i.r. spectra were recorded with a Jasco A-100 spectrophotometer. ^{1}H-N.m.r. spectra were recorded at 270 MHz with a JEOL JNM-GX270 spectrometer for solutions in chloroform-*d*, unless otherwise noted. T.l.c. was performed on silica gel 60 (Merck, aluminum sheets), and column chromatography on silica gel (Wako Co.; 200 or 300 mesh) was accomplished with the solvent systems (v/v) specified.

*2,4-O-Isopropylidene-*D*-threose* (**3**) *and its formate.* — To a solution of **1** (ref. 7; 5 g) in dry methanol (250 mL) was added sodium metaperiodate (7.4 g), and the mixture was stirred for 3 h at room temperature. The resulting precipitate was filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated to a residue that was chromatographed on a column of silica gel

(Wakogel C-200) with 150:1 chloroform–methanol, to give an ~1:1 mixture of 2,4-*O*-isopropylidene-D-threose and its formate (**3**; 4.2 g), $[\alpha]_D$ −50° (*c* 0.6, chloroform); i.r. data (film): ν 3700–3100 (OH), 1720 (C=O), and 850 cm^{-1} (CMe_2); ^{1}H-n.m.r. data: δ 1.49, 1.50, 1.52, 1.56 (4 s, 6 H, CMe_2), 8.06, 8.16 (2 s, 1 H, C–CHO), and 9.54 (s, 0.5 H, O–CHO). The mixture of aldehydes was, without purification, subjected to the Wittig alkenation. In the route to **3** from **2**, 2.5 mol. equiv. of sodium metaperiodate was used for cleaving the C-1–C-2 and C-2–C-3 bonds.

[2(R),3(R),4E]-1,3-O-Isopropylidene-4-octadecene-1,2,3-triol (**4E**) *and [2(R),3(R),4Z]-1,3-O-isopropylidene-4-octadecene-1,2,3-triol* (**4Z**). — Tetradecyltriphenylphosphonium bromide (18.8 g), which was prepared from tetradecyl bromide and triphenylphosphine according to the procedure reported by Gaset *et al.*[11], was dissolved in abs. THF (100 mL). To this solution was added a 2.0M solution of phenyllithium in 7:3 cyclohexane–ether (17.4 mL), and the mixture was stirred for 30 min at room temperature under a nitrogen atmosphere. The resulting, clear, red solution of ylid was cooled to −60°, and then a solution of **3** (4.7 g) in THF (19 mL) was added. After 30 min at −30°, more phenyllithium (27.7 mL) was added to the cream-colored precipitate. The resulting, dark-red solution was kept for 40 min at room temperature, and then poured into ice-cold water under vigorous stirring. The products were extracted with ether, and the extract was washed with water, dried, and evaporated. The residue was chromatographed on a column of silica gel (Wakogel C-300) with alcohol-free chloroform, to give **4E** (3.67 g; 40%) and **4Z** (3.21 g; 35%), which crystallized from aqueous ethanol.

Compound **4E** had m.p. 44.5–45.5°, $[\alpha]_D$ −26° (*c* 0.7, chloroform); ^{1}H-n.m.r. data: δ 0.88 (t, 3 H, Me), 1.15–1.5 (m, 22 H, $-CH_2-$), 1.46, 1.49 (2 s, 6 H, CMe_2), 2.06 (~q, 2 H, J ~7 Hz, H-6,6′), 3.36 (~s, 1 H, H-2), 3.84 (dd, 1 H, J_{gem} 12.1, $J_{1,2}$ 1.8 Hz, H-1*a*), 4.07 (dd, 1 H, $J_{1,2}$ 1.5 Hz, H-1*e*), 4.36 (~d, 1 H, $J_{3,4}$ 6.6 Hz, H-3), 5.6 (m, 1 H, $J_{4,5}$ 15.4, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.80 (m, 1 H, $J_{5,6}$ 6.6, $J_{5,6'}$ 5.9 Hz, H-5).

Anal. Calc. for $C_{21}H_{40}O_3$ (340.53): C, 74.06; H, 11.84. Found: C, 74.25; H, 11.78.

Compound **4Z** had m.p. 44.5–45.5°, $[\alpha]_D$ −3° (*c* 0.4, chloroform); ^{1}H-n.m.r. data: δ 0.88 (t, 3 H, Me), 1.15–1.5 (m, 22 H, $-CH_2-$), 1.45, 1.52 (2 s, 6 H, CMe_2), 2.0–2.2 (m, 2 H, H-6,6′), 2.83 (broad s, 1 H, OH), 3.33 (~s, 1 H, H-2), 3.84 (dd, 1 H, J_{gem} 12.1, $J_{1,2}$ 1.8 Hz, H-1*a*), 4.09 (dd, 1 H, $J_{1,2}$ 1.5 Hz, H-1*e*), 4.70 (~d, 1 H, $J_{2,3}$ 1.1, $J_{3,4}$ 6.2 Hz, H-3), and 5.55–5.70 (m, 2 H, H-4,5 overlapping).

Anal. Found: C, 73.91; H, 11.80.

[2(R),3(R),4E]-1,3-O-Isopropylidene-4-eicosene-1,2,3-triol (**5E**) *and [2(R),3(R),4Z]-1,3-O-isopropylidene-4-eicosene-1,2,3-triol* (**5Z**). — Aldehyde **3** was treated with triphenylphosphoniohexadecylid in THF as described for the preparation of **4E** and **4Z**, and the products were purified by chromatography on a column of silica gel, to afford **5E** (53%) and **5Z** (21%), which crystallized from cold methanol.

Compound **5E** had m.p. 50–51°, $[\alpha]_D$ −25° (*c* 0.5, chloroform); ^{1}H-n.m.r.

data: δ 0.88 (t, 3 H, Me), 1.0–1.5 (m, 26 H, $-CH_2-$), 1.46, 1.50 (2 s, 6 H, CMe_2), 2.06 (~q, 2 H, J ~7 Hz, H-6,6'), 2.62 (broad s, 1 H, OH), 3.36 (~s, 1 H, H-2), 3.84 (dd, 1 H, J_{gem} 12.1, $J_{1,2}$ 1.8 Hz, H-1*a*), 4.07 (dd, 1 H, $J_{1,2}$ 1.5 Hz, H-1*e*), 4.36 (~d, 1 H, $J_{3,4}$ 6.6 Hz, H-3), 5.6 (m, 1 H, $J_{4,5}$ 15.8, $J_{4,6(6')}$ <1.5 Hz, H-4), and 5.80 (m, 1 H, $J_{5,6(6')}$ ~6.6 Hz, H-5).

Anal. Calc. for $C_{23}H_{44}O_3$ (368.58): C, 74.94; H, 12.03. Found: C, 74.83; H, 11.86.

Compound **5***Z* had m.p. 50–51°, $[\alpha]_D$ −3° (*c* 0.5, chloroform); ^{1}H-n.m.r. data: δ 0.88 (t, 3 H, Me), 1.1–1.5 (m, 26 H, $-CH_2-$), 1.45, 1.53 (2 s, 6 H, CMe_2), 2.09 (~q, 2 H, J ~7 Hz, H-6,6'), 2.70 (broad s, 1 H, OH), 3.33 (~s, 1 H, H-2), 3.84 (dd, 1 H, J_{gem} 12.1, $J_{1,2}$ 1.8 Hz, H-1*a*), 4.10 (dd, 1 H, $J_{1,2}$ 1.5 Hz, H-1*e*), 4.70 (~d, 1 H, $J_{3,4}$ 6.6 Hz, H-3), and 5.57–5.71 (m, 2 H, H-4,5 overlapping).

Anal. Found: C, 74.72; H, 12.15.

[2(S),*3*(R),*4*E]-*2-Azido-1,3*-O-*isopropylidene-4-octadecene-1,3-diol* (**9**E). — *(a) Via mesylate* **6**E. To a stirred solution of **4***E* (1 g) in pyridine (6 mL) was added methanesulfonyl chloride (1.2–1.3 mol. equiv.) at −10°; stirring was continued at room temperature. After completion of the reaction (6 h; t.l.c., 5:1 hexane–ethyl acetate), *N,N*-dimethylformamide (DMF; 10 mL) and sodium azide (4.8 g) were added *in situ*, and the mixture was stirred overnight at 110°, cooled, and evaporated, and the residue was extracted with chloroform. The extract was washed with water, dried, and evaporated, to afford a syrup which was chromatographed on a column of silica gel with chloroform, to give **9***E* (0.918 g; 85% from **4***E*) as a syrup; $[\alpha]_D$ −35° (*c* 0.6, chloroform); i.r. data (film): ν 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data: δ 0.88 (t, 3 H, Me), 1.2–1.5 (m, 22 H, $-CH_2-$), 1.41, 1.47 (2 s, 6 H, CMe_2), 2.10 (~q, 2 H, $J_{5,6} = J_{6,7}$ = 7 Hz, H-6,6'), 3.29 (m, 1 H, $J_{1a,2}$ 10.3, $J_{2,3}$ 9.5, $J_{1e,2}$ 5.5 Hz, H-2), 3.62 (dd, 1 H, J_{gem} 11.7 Hz, H-1*a*), 3.92 (dd, 1 H, H-1*e*), 4.07 (dd, 1 H, $J_{3,4}$ 7.3 Hz, H-3), 5.46 (m, 1 H, $J_{4,5}$ 15.4, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.91 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

Anal. Calc. for $C_{21}H_{39}N_3O_2$ (365.55): C, 69.00; H, 10.75; N, 11.50. Found: C, 69.24; H, 10.68; N, 11.53.

(b) Via trifluoromesylate **8**E. To a stirred solution of **4***E* (0.4 g) in 2:1 pyridine–dichloromethane (3 mL) was added a solution of trifluoromethanesulfonic anhydride (0.3 mL) in dichloromethane (0.5 mL) at −20°; stirring was continued for 3 h at −20°. DMF (4 mL) and sodium azide (1.5 g) were added *in situ*, and the mixture was stirred overnight at −20°. After extractive processing, the title compound **9***E* (0.17 g; 40% from **4***E*) was isolated by chromatography. Two major by-products, probably resulting from elimination reactions, were also obtained as syrups.

[2(S),*3*(R),*4*Z]-*2-Azido-1,3*-O-*isopropylidene-4-octadecene-1,3-diol* (**9** Z). — Compound **9***Z* was respectively obtained in 83% yield [*(a) via mesylate* **6**Z], and in 50% yield [*(b) via trifluoromesylate* **8**Z] as a syrup, as described for the preparation of **9***E*; $[\alpha]_D$ −75° (*c* 1, chloroform); i.r. data (film): ν 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data: δ 0.88 (t, 3 H, Me), 1.2–1.5 (m, 22 H, $-CH_2-$), 1.41, 1.50 (2 s, 6 H, CMe_2),

2.18 (~q, 2 H, J ~7 Hz, H-6,6'), 3.33 (m, 1 H, $J_{1a,2} = J_{2,3} = 10$, $J_{1e,2}$ 5.5 Hz, H-2), 3.65 (dd, 1 H, J_{gem} 11.7 Hz, H-1*a*), 3.95 (dd, 1 H, H-1*e*), 4.46 (~t, 1 H, $J_{3,4}$ ~10 Hz, H-3), 5.38 (m, 1 H, $J_{4,5}$ 10.6, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.78 (m, 1 H, $J_{5,6(6')}$ 7–8 Hz, H-5).

Anal. Calc. for $C_{12}H_{39}N_3O_2$ (365.55): C, 69.00; H, 10.75; N, 11.50. Found: C, 69.32; H, 10.58; N, 11.49.

[2(S),3(R),4E]-*2-Azido-1,3-*O-*isopropylidene-4-eicosene-1,3-diol* (**10E**) *and* [2(S),3(R),4Z]-*2-azido-1,3-*O-*isopropylidene-4-eicosene-1,3-diol* (**10Z**). — Compounds **5***E* and **5***Z* were each treated with methanesulfonyl chloride in pyridine as described for **9***E*, to give **7***E*, $[\alpha]_D$ −34° (*c* 0.5, chloroform); ^{1}H-n.m.r. data: δ 3.06 (s, 3 H, $MeSO_2$) and 4.45 (~s, 1 H, H-2), and **7***Z*, $[\alpha]_D$ −38° (*c* 0.5, chloroform); ^{1}H-n.m.r. data: δ 3.08 (s, 3 H, $MeSO_2$) and 4.44 (~q, 1 H, J ~2 Hz, H-2), respectively. These were treated with sodium azide as described for the preparation of **9***E* and **9***Z*. The products were chromatographed on a column of silica gel, to yield **10***E* (79%) and the *cis* isomer **10***Z* (82%) as syrups, respectively.

Compound **10***E* had $[\alpha]_D$ −39° (*c* 0.6, chloroform); i.r. data (film): ν 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data: δ 0.88 (t, 3 H, Me), 1.0–1.6 (m, 26 H, $-CH_2-$), 1.42, 1.47 (2 s, 6 H, CMe_2), 2.09 (~q, 2 H, H-6,6'), 3.29 (m, 1 H, $J_{1a,2} = J_{2,3}$ ~10, $J_{1e,2}$ 5.7 Hz, H-2), 3.62 (dd, 1 H, J_{gem} 11 Hz, H-1*a*), 3.92 (dd, 1 H, H-1*e*), 4.07 (dd, 1 H, $J_{3,4}$ 7.5 Hz, H-3), 5.45 (m, 1 H, $J_{4,5}$ 15.4, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.92 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

Anal. Calc. for $C_{23}H_{43}N_3O_2$ (393.60): C, 70.18; H, 11.01; N, 10.68. Found: C, 69.85; H, 11.23; N, 10.46.

Compound **10***Z* had $[\alpha]_D$ −78° (*c* 0.5, chloroform); i.r. data (film): ν 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data were quite similar to those of **9***Z*, except for the number of methylene protons.

Anal. Found: C, 70.01; H, 11.20; N, 10.79.

[2(S),3(R),4E]-*2-Amino-1,3-*O-*isopropylidene-4-octadecene-1,3-diol* (**11E**). — A mixture of **9***E* (0.5 g), sodium borohydride (0.2 g) and 2-propanol (10 mL) was stirred for 48 h at the reflux temperature. The mixture was cooled, acetone was added to decompose the excess of the reagent, the solution was evaporated, the residue was suspended in ether by sonication, and the precipitate was filtered off. The filtrate was evaporated to a syrup that was chromatographed on a column of silica gel with 100:1 chloroform–methanol, to give **11***E* (0.445 g; 95%); $[\alpha]_D$ +10° (*c* 0.6, chloroform); i.r. data (film): complete loss of the peak at 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data: δ 0.88 (t, 3 H, Me), 1.0–1.5 (m, 24 H, $-CH_2-$ and NH_2), 1.42, 1.49 (2 s, 6 H, CMe_2), 2.08 (~q, 2 H, J ~7 Hz, H-6,6'), 2.69 (m, 1 H, $J_{1a,2} = J_{2,3}$ = ~10, $J_{1e,2}$ 5.1 Hz, H-2), 3.55 (~t, 1 H, J_{gem} ~11 Hz, H-1*a*), 3.85 (~t, 1 H, $J_{3,4}$ 7.7 Hz, H-3), 3.87 (dd, 1 H, H-1*e*), 5.39 (m, 1 H, $J_{4,5}$ 15.4, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.83 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

Anal. Calc. for $C_{21}H_{41}NO_2$ (339.55): C, 74.28; H, 12.17; N, 4.13. Found: C, 74.03; H, 12.36; N, 4.00.

[2(S),3(R),4Z]-*2-Amino-1,3-*O-*isopropylidene-4-octadecene-1,3-diol* (**11Z**).

— Compound **9Z** was treated with sodium borohydride as described for the preparation of **11E**, to give **11Z** in 93% yield; $[\alpha]_D$ +15° (*c* 0.9, chloroform); i.r. data (film): ν 3380, 3300 (NH), and complete loss of the peak at 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data: δ 2.72 (m, 1 H, H-2), 3.58 (~t, 1 H, H-1*a*), 3.89 (dd, 1 H, H-1*e*), 4.28 (~t, 1 H, H-3), 5.33 (m, 1 H, H-4), and 5.76 (m, 1 H, H-5); the coupling constants were quite similar to those of the azide derivative **9Z**.

Anal. Found: C, 74.14; H, 12.20; N, 3.98.

[2(S),3(R),4E]-*2-Amino-1,3-O-isopropylidene-4-eicosene-1,3-diol* (**12E**) *and* [2(S),3(R),4Z]-*2-amino-1,3-O-isopropylidene-4-eicosene-1,3-diol* (**12Z**). — The title compounds were obtained from **10E** and **10Z**, respectively, as described for the preparation of **11E** and **11Z**.

Compound **12E** (85%) had $[\alpha]_D$ +8° (*c* 0.6, chloroform); ^{1}H-n.m.r. data: δ 2.08 (~q, 2 H, H-6,6'), 2.70 (m, 1 H, $J_{1a,2} = J_{2,3} = \sim 10$, $J_{1e,2}$ 5.3 Hz, H-2), 3.55 (~t, 1 H, J_{gem} ~11 Hz, H-1*a*), 3.85 (~t, 1 H, H-3), 3.87 (dd, 1 H, H-1*e*), 5.39 (m, 1 H, $J_{4,5}$ 15.4, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.83 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

Anal. Calc. for $C_{23}H_{45}NO_2$ (367.60): C, 75.14; H, 12.34; N, 3.81. Found: C, 74.82; H, 12.50; N, 3.69.

Compound **12Z** (90%) had $[\alpha]_D$ +23° (*c* 0.4, chloroform); ^{1}H-n.m.r. data: δ 1.42, 1.52 (2 s, 6 H, CMe_2), 2.1–2.5 (m, 2 H, H-6,6'), 2.72 (m, 1 H, $J_{1a,2}$ ~11, $J_{2,3}$ 9.5, $J_{1e,2}$ 5.5 Hz, H-2), 3.58 (~t, 1 H, J_{gem} ~11 Hz, H-1*a*), 3.88 (dd, 1 H, H-1*e*), 4.28 (~t, 1 H, $J_{3,4}$ ~9 Hz, H-3), 5.34 (m, 1 H, $J_{4,5}$ ~11, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.76 (m, 1 H, $J_{5,6(6')}$ 7.3 Hz, H-5).

Anal. Found: C, 74.85; H, 12.46; N, 3.67.

[2(S),3(R),4E]-*1,3-O-Isopropylidene-2-octadecanamido-4-octadecene-1,3-diol* (**13E**). — To a solution of **11E** (0.2 g) in dichloromethane (4 mL) were added dicyclohexylcarbodiimide (DCC; 0.243 g) and octadecanoic acid (0.252 g); the mixture was stirred at room temperature. Dicyclohexylurea was filtered off, and the filtrate was evaporated to a residue which was chromatographed on a column of silica gel (Wakogel C-300) with alcohol-free chloroform, to give **13E** (0.343 g; 96%) which crystallized from ethanol, m.p. 67–67.5°, $[\alpha]_D$ −0.5° (*c* 0.4, chloroform); i.r. data (KBr): ν 3300 (NH), and 1640 and 1560 cm^{-1} (amide); ^{1}H-n.m.r. data: δ 0.88 (t, 6 H, Me), 1.0–1.7 (m, 52 H, $-CH_2-$), 1.42, 1.49 (2 s, 6 H, CMe_2), 2.03 (~q, 2 H, *J* 7–8 Hz, $-CH{=}CH-CH_2-$), 2.12 (m, 2 H, $-COCH_2-$), 3.64 (dd, 1 H, J_{gem} ~11, $J_{1,2}$ 9.2 Hz, H-1*a*), 3.77–3.89 (m, 1 H, H-2), 3.99 (dd, 1 H, $J_{1,2}$ 5.1 Hz, H-1*e*), 4.08 (~t, 1 H, $J_{2,3}$ 9.5, $J_{3,4}$ 7.7 Hz, H-3), 5.20 (d, 1 H, *J* 8.4 Hz, NH), 5.42 (dd, 1 H, $J_{4,5}$ 15.4 Hz, H-4), and 5.75 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

Anal. Calc. for $C_{39}H_{75}NO_3$ (605.99): C, 77.29; H, 12.49; N, 2.31. Found: C, 77.51; H, 12.36; N, 2.13.

[2(S),3(R),4Z]-*1,3-O-Isopropylidene-2-octadecanamido-4-octadecene-1,3-diol* (**13Z**). — Compound **11Z** was treated with octadecanoic acid and DCC as described for the preparation of **13E**, and afforded crystalline **13Z** in 94% yield; m.p. 74–74.5°, $[\alpha]_D$ −10° (*c* 0.5, chloroform); i.r. data (Nujol): ν 3360 (NH), and 1640 and 1530 cm^{-1} (amide); ^{1}H-n.m.r. data: δ 0.88 (t, 6 H, Me), 1.0–1.75 (m, 52 H, $-CH_2-$),

1.41, 1.52 (2 s, 6 H, CMe_2), 1.9–2.25 (m, 4 H, –CH=CH–CH_2– and –$COCH_2$–), 3.71 (dd, 1 H, J_{gem} 11, $J_{1,2}$ 9.2 Hz, H-1*a*), 3.8–3.96 (m, 1 H, H-2), 3.99 (dd, $J_{1,2}$ 5.1 Hz, H-1*e*), 4.50 (~t, 1 H, $J_{2,3}$ 9.5, $J_{3,4}$ 8.8 Hz, H-3), 5.23 (d, 1 H, *J* 8.1 Hz, NH), 5.39 (~t, 1 H, $J_{4,5}$ 10.7, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.69 (m, 1 H, $J_{5,6(6')}$ 7.3 Hz, H-5).

Anal. Found: C, 77.36; H, 12.44; N, 2.22.

[2(S),3(R),4E]-*1,3*-O-*Isopropylidene-2-octadecanamido-4-eicosene-1,3-diol* (**14**E) *and the* cis *isomer* (**14Z**). — To a solution of **12***E* or **12***Z* (0.7 g) in dichloromethane (12 mL) were added octadecanoic acid (0.97 g) and 3-[(dimethylamino)propyl]-1-ethylcarbodiimide hydrochloride (WSC; 0.73 g); the mixture was stirred at room temperature until the reaction was complete. After extractive processing, the product was purified by chromatography, to give, quantitatively, **14***E* or **14***Z*, which crystallized from methanol.

Compound **14***E* had m.p. 71–72°, $[\alpha]_D$ −0.5° (*c* 0.7, chloroform); i.r. data (Nujol): ν 3300 (NH), and 1640 and 1520 cm^{-1} (amide); the ^{1}H-n.m.r. data were quite similar to those of **13***E*, except for the number of methylene protons.

Anal. Calc. for $C_{41}H_{79}NO_3$ (634.05): C, 77.66; H, 12.56; N, 2.21. Found: C, 77.53; H, 12.48; N, 2.24.

Compound **14***Z* had m.p. 79.5–80.5°, $[\alpha]_D$ −10° (*c* 0.5, chloroform); i.r. data (Nujol): ν 3360 (NH), and 1640 and 1530 cm^{-1} (amide); ^{1}H-n.m.r. data: δ 0.88 (t, 6 H, Me), 1.0–1.7 (m, 56 H, –CH_2–), 1.95–2.2 (m, 4 H, –CH=CH–CH_2– and –$COCH_2$–), 3.71 (dd, 1 H, J_{gem} ~11, $J_{1,2}$ 9.2 Hz, H-1*a*), 3.86 (m, 1 H, H-2), 4.0 (dd, 1 H, $J_{1,2}$ ~5 Hz, H-1*e*), 4.50 (t, 1 H, $J_{2,3} = J_{3,4}$ = ~9 Hz, H-3), 5.18 (d, 1 H, *J* ~8 Hz, NH), 5.40 (~t, 1 H, $J_{4,5}$ ~11, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.69 (m, 1 H, $J_{5,6(6')}$ 7–8 Hz, H-5).

Anal. Found: C, 77.82; H, 12.51; N, 2.19.

[2(S),3(R),4E]-*1,3*-O-*Isopropylidene-2-tetracosanamido-4-octadecene-1,3-diol* (**15**E). — Compound **11***E* was treated with tetracosanoic acid as described for the preparation of **14***E*, to give in nearly quantitative yield, **15***E*, which crystallized from ethanol; m.p. 61.5–62°, $[\alpha]_D$ −0.4° (*c* 0.5, 50:1 chloroform–methanol); i.r. data (Nujol): ν 3310 (NH), and 1640 and 1550 cm^{-1} (amide); ^{1}H-n.m.r. data: δ 0.88 (t, 6 H, Me), 1.0–1.7 (m, 64 H, –CH_2–), 1.42, 1.49 (2 s, 6 H, CMe_2), 1.9–2.2 (m, 4 H, –CH=CH–CH_2– and –$COCH_2$–), 3.65 (dd, 1 H, J_{gem} 11, $J_{1,2}$ 9.2 Hz, H-1*a*), 3.76–3.9 (m, 1 H, H-2), 3.99 (dd, 1 H, $J_{1,2}$ 5.1 Hz, H-1*e*), 4.08 (~t, 1 H, $J_{2,3}$ 9.5, $J_{3,4}$ 7.7 Hz, H-3), 5.20 (d, 1 H, *J* 8.4 Hz, NH), 5.42 (dd, 1 H, $J_{4,5}$ 15.4 Hz, H-4), and 5.75 (m, 1 H, $J_{5,6(6')}$ 6.6 Hz, H-5).

Anal. Calc. for $C_{45}H_{87}NO_3$ (690.16): C, 78.31; H, 12.71; N, 2.03. Found: C, 78.16; H, 12.84; N, 1.99.

[2(S),3(R),4E]-*1,3*-O-*Isopropylidene-2-tetracosanamido-4-eicosene-1,3-diol* (**16***E*). — Compound **12***E* was treated with tetracosanoic acid in the presence of WSC as described previously, and the resulting **16***E* crystallized from methanol; m.p. 66.5–68°, $[\alpha]_D$ −1° (*c* 0.5, chloroform); i.r. data (Nujol): ν 3300 (NH), and 1650 and 1550 cm^{-1} (amide); the ^{1}H-n.m.r. data were quite similar to those of **13***E*, except for δ 1.0–1.6 (m, 68 H, –CH_2–), 5.13 (d, 1 H, *J* 7.7 Hz, NH), and minor differences at 1.9–2.2 (m, 4 H, –CH=CH–CH_2– and –$COCH_2$–).

[2(S),3(R),4E]-*2-Azido-4-octadecene-1,3-diol* (**17E**) *and the* cis *isomer* (**17Z**). — To a solution of **9*E*** or **9*Z*** (0.5 g) in acetic acid (10 mL) was added water (0.6 mL) and the mixture was kept at 45°. After completion of the reaction (t.l.c.; 15:1 chloroform–methanol), the mixture was evaporated to a residue that was chromatographed on a short column of silica gel (Wakogel C-200) with 400:1 chloroform–methanol in order to remove some minor contaminants. The title compounds crystallized from ether–hexane.

Compound **17*E*** had m.p. 50.5–51.5°, $[\alpha]_D$ −33° (*c* 0.4, chloroform); i.r. data (film): ν 3700–3100 (OH) and 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data: δ 0.88 (t, 3 H, Me), 1.1–1.5 (m, 22 H, $-CH_2-$), 2.06 (m, 2 H, H-6,6'), 2.48 (broad s, 2 H, OH), 3.48 (~q, 1 H, *J* 5–6 Hz, H-2), 3.78 (~d, 2 H, H-1), 4.22 (~t, 1 H, *J* ~6 Hz, H-3), 5.49 (m, $J_{3,4}$ 6.5, $J_{4,5}$ 15.4, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.82 (m, $J_{5,6(6')}$ ~6 Hz, H-5).

Anal. Calc. for $C_{18}H_{35}N_3O_2$ (325.48): C, 66.42; H, 10.84; N, 12.91. Found: C, 66.17; H, 11.02; N, 12.83.

Compound **17*Z*** had m.p. 42.5–43°, $[\alpha]_D$ −53° (*c* 0.6, chloroform); ^{1}H-n.m.r. data: δ 2.11 (m, 2 H, H-6,6'), 2.27 (broad s, 2 H, OH), 3.49 (~q, 1 H, *J* 5–6 Hz, H-2), 3.79 (~d, 2 H, H-1), 4.58 (dd, 1 H, $J_{2,3}$ ~6, $J_{3,4}$ ~8 Hz, H-3), 5.45 (m, 1 H, $J_{4,5}$ ~11, $J_{4,6(6')}$ ~1 Hz, H-4), and 5.67 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

Anal. Found: C, 66.25; H, 10.77; N, 13.12.

[2(S),3(R),4E]-*2-Amino-4-octadecene-1,3-diol* (*sphingosine;* **18E**) *and* [2(S),3(R),4Z]-*2-amino-4-octadecene-1,3-diol* (cis-*sphingosine;* **18Z**). — Compound **17*E*** and **17*Z*** were each treated with sodium borohydride in 2-propanol as described previously. Chromatographic purification on a column of silica gel (Wakogel C-200, 20:1 dichloromethane–methanol) gave **18*E*** (92%) and **18*Z*** (91%), respectively; crystallized from ether–petroleum ether (for **18*E***) or ethyl acetate (for **18*Z***).

Sphingosine (**18*E***) had m.p. 81.5–82.5° (lit.[12] 82.5°; lit.[4b] 80–84°); ^{1}H-n.m.r. data: δ 5.43 (m, 1 H, $J_{3,4}$ 6.6, $J_{4,5}$ 15.4, $J_{4,6}$ 1.5 Hz, H-4) and 5.75 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

cis-Sphingosine (**18*Z***) had m.p. 72–73° (lit.[13] 72–73°; lit.[4b] 73–74°); ^{1}H-n.m.r. data: δ 0.88 (t, 3 H, Me), 1.0–1.43 (m, 22 H, $-CH_2-$), 1.9–2.2 (m, 2 H, H-6,6'), 2.84 (broad m, 1 H, H-2), 2.9–3.25 (broad m, 4 H, NH and OH), 3.5–3.8 (broad m, 2 H, H-1,1'), 4.41 (m, 1 H, H-2), 5.43 (~t, 1 H, $J_{3,4}$ 9–10, $J_{4,5}$ 10.6 Hz, H-4), and 5.6 (m, 1 H, $J_{5,6(6')}$ 7.3 Hz, H-5).

[2(S),3(R),4E]-*2-Octadecanamido-4-octadecene-1,3-diol* (**19E**). — *(a) From* **13E**. A solution of **13*E*** (1.2 g) in acetic acid (60 mL) plus a little water was kept at 45°. After completion of the reaction (t.l.c.; 10:1 chloroform–methanol), the mixture was evaporated to a residue that was chromatographed on a column of silica gel (Wakogel C-200) with chloroform. The **19*E*** (1.06 g; 95%) crystallized from ethanol; m.p. 97–98° (lit.[14] 89–91°; lit.[4b] 91–93°), $[\alpha]_D$ −5° (*c* 0.5, chloroform); ^{1}H-n.m.r. data ($CDCl_3$ + CD_3OD): δ 0.88 (t, 6 H, Me), 1.0–1.4 and 1.5–1.7 (m, 50 H + 2 H, $-CH_2-$), 2.04 (~q, 2 H, $J_{5,6} = J_{6,7}$ = ~7 Hz, $-CH{=}CH-CH_2-$), 2.21 (t, 2 H, *J* 7–8 Hz, $-COCH_2-$), 3.64 (m, 1 H, H-1), 3.75–3.90 (m, 2 H, H-1',2), 4.19 (~t, 1

H, $J_{2,3}$ ~5, $J_{3,4}$ 6.6 Hz, H-3), 5.49 (~dd, 1 H, $J_{4,5}$ 15.4 Hz, H-4), and 5.75 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

Anal. Calc. for $C_{36}H_{71}NO_3$ (565.94): C, 76.40; H, 12.65; N, 2.48. Found: C, 76.55; H, 12.48; N, 2.51.

(b) From sphingosine (**18**E). *N*-Acylation of sphingosine, as described for the preparation of **14***E* or **14***Z*, gave **19***E* in nearly quantitative yield.

[*2*(S),*3*(R),*4*Z]-*2-Octadecanamido-4-octadecene-1,3-diol* (**19**Z). — Compound **13***Z* was treated with aqueous acetic acid as already described, to give **19***Z* (~100%), which crystallized from ethanol; m.p. 94–95°, $[\alpha]_D$ −7° (*c* 0.5, chloroform); ^{1}H-n.m.r. data ($CDCl_3$ + CD_3OD): δ 0.88 (t, 6 H, Me), 1.0–1.4 and 1.5–1.7 (m, 50 H + 2 H, $-CH_2-$), 1.95–2.3 (m, 4 H, $-CH=CH-CH_2-$ and $-COCH_2-$), 3.6–3.9 (m, 3 H, H-1,1′ and H-2), 4.52 (dd, 1 H, $J_{2,3}$ 5.1, $J_{3,4}$ 8–9 Hz, H-3), 5.43 (~t, 1 H, $J_{4,5}$ ~11 Hz, H-4), and 5.57 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

Anal. Found: C, 76.24; H, 12.53; N, 2.38.

[*2*(S),*3*(R),*4*E]-*2-Octadecanamido-4-eicosene-1,3-diol* (**20**E) *and the* cis *isomer* (**20**Z). — The title compounds were prepared from **14***E* and **14***Z*, respectively, as described for **19***E* and **19***Z*. The ^{1}H-n.m.r. data for **20***E* and **20***Z* were similar to those of **19***E* and **19***Z*, respectively, except for the number of methylene protons.

Compound **20***E* crystallized from ethanol; m.p. 101.5–102°, $[\alpha]_D$ −3° (*c* 0.9, 10:1 chloroform–methanol).

Anal. Calc. for $C_{38}H_{75}NO_3$ (593.99): C, 76.83; H, 12.73; N, 2.36. Found: C, 76.63; H, 12.87; N, 2.31.

Compound **20***Z* crystallized from methanol; m.p. 99.5–100°, $[\alpha]_D$ −8° (*c* 0.4, 10:1 chloroform–methanol).

Anal. Found: C, 76.65; H, 12.92; N, 2.44.

[*2*(S),*3*(R),*4*E]-*2-Tetracosanamido-4-octadecene-1,3-diol* (**21**E) *and the* cis *isomer* (**21**Z). — Hydrolysis of the isopropylidene group from **15***E*, as described for the preparation of **19***E*, afforded **21***E*, which crystallized from methanol–ethanol; m.p. 92–94°, $[\alpha]_D$ −2° (*c* 1, 50:1 chloroform–methanol) (lit.[4f] m.p. 91–92° and $[\alpha]_D$ −2.0°; lit.[15] m.p. 93–95°); i.r. data (Nujol): ν 3600–3100 (OH, NH), and 1650 and 1550 cm^{-1} (amide); ^{1}H-n.m.r. data ($CDCl_3$ + CD_3OD): δ 0.89 (t, 6 H, 2 Me), 1.01–1.4 and 1.45–1.7 (m, 62 H + 2 H, $-CH_2-$), 2.04 (~q, 2 H, $J_{5,6} = J_{6,7}$ = ~7 Hz, $-CH=CH-CH_2-$), 2.21 (t, 2 H, *J* 7.8 Hz, $-COCH_2-$), 3.65 (dd, 1 H, J_{gem} ~11, $J_{1,2}$ 3–4 Hz, H-1), 3.81 (dd, 1 H, $J_{1,2}$ 4.8 Hz, H-1′), 3.8–3.9 (m, 1 H, H-2), 4.14 (~t, 1 H, *J* 6–7 Hz, H-3), 5.48 (~dd, 1 H, $J_{3,4}$ 7, $J_{4,5}$ 15.4 Hz, H-4), and 5.73 (m, 1 H, $J_{5,6(6')}$ 7 Hz, H-5).

Anal. Calc. for $C_{42}H_{83}NO_3$ (650.09): C, 77.59; H, 12.87; N, 2.15. Found: C, 77.85; H, 12.76; N, 2.08.

Treatment of **11***Z* with tetracosanoic acid as described for **14***Z* gave crude **15***Z* containing a small proportion of WSC-urea, which without purification, was converted into **21***Z* as described for **21***E*.

Compound **21***Z* had m.p. 90.5–91.5°, $[\alpha]_D$ −8° (*c* 0.4, 10:1 chloroform–methanol); i.r. data (Nujol): ν 3300 (OH, NH), and 1660 and 1560 cm^{-1} (amide);

^{1}H-n.m.r. data ($CDCl_3$ + CD_3OD): δ 2.0–2.25 (m, 4 H, –CH=CH–CH_2–), 3.68 (dd, 1 H, J_{gem} 11.4, $J_{1,2}$ 4 Hz, H-1), 3.81 (dd, 1 H, $J_{1,2}$ ~5 Hz, H-1'), 3.8–3.92 (m, 1 H, H-2), 4.50 (dd, 1 H, $J_{2,3}$ 6.6, $J_{3,4}$ 8.8 Hz, H-3), 5.42 (m, 1 H, $J_{4,5}$ ~11, $J_{4,6(6')}$ 1.5 Hz, H-4), and 5.56 (m, 1 H, $J_{5,6(6')}$ ~7 Hz, H-5).

Anal. Found: C, 77.68; H, 12.94; N, 2.11.

[2(S),3(R),4E]-*2-Tetracosanamido-4-eicosene-1,3-diol* (**22E**) *and the* cis *isomer* (**22Z**). — Hydrolytic removal of the isopropylidene group from **16***E*, as described for **19***E*, gave **22***E*, quantitatively; this crystallized from ethanol; m.p. 95.5–96.5°, $[\alpha]_D$ −2° (*c* 0.7, 10:1 chloroform–methanol).

Anal. Calc. for $C_{44}H_{87}NO_3$ (678.14): C, 77.92; H, 12.93; N, 2.07. Found: C, 78.05; H, 12.81; N, 1.99.

The *N*-acylation of **12***Z* with tetracosanoic acid, to give **16***Z*, and the mild hydrolysis of the isopropylidene group as described for **22***E*, afforded crystalline **22***Z* in nearly quantitative yield; m.p. 94–95°, $[\alpha]_D$ −5° (*c* 1, 10:1 chloroform–methanol).

Anal. Found: C, 77.67; H, 13.10; N, 2.12.

The i.r. and ^{1}H-n.m.r. data for **22***E* and **22***Z* were similar to those of **21***E* and **21***Z*, respectively, except for the number of methylene protons.

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