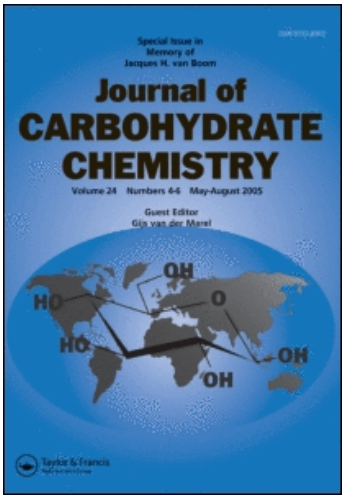

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Communication

A CONVENIENT SYNTHESIS OF SPHINGOSINE AND CERAMIDE FROM D-XYLOSE OR D-GALACTOSE

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Ceramide, i.e., N-fatty acylated sphingosine and its homolog, is a highly heterogeneous and hydrophobic component of the glycosphingolipids[1] such as gangliosides,[2] which may play important roles in the surface region of the biological membranes.

In the chemical synthesis[1b,3] of the optically active sphingosine and ceramide, some carbohydrates such as D-glucose[3b,3f] and D-mannose[3h] have been utilized as the chiral templates. However, more than ten steps are required for the conversion of these sugars to the natural product. We here describe a more convenient route to sphingosine and ceramide, including their homologs, from D-xylose or D-galactose.

3,5-O-Isopropylidene-D-xylofuranose (1), which can be easily prepared in one step from D-xylose,[4] was treated with sodium metaperiodate in methanol to give a ca. 1:1 mixture of 2,4-O-isopropylidene-D-threose and its formate (2) in a quantitative yield (Scheme 1). This aldehyde intermediate is also available from 4,6-O-isopropylidene-D-galactopyranose (13)[5] by a similar manner.

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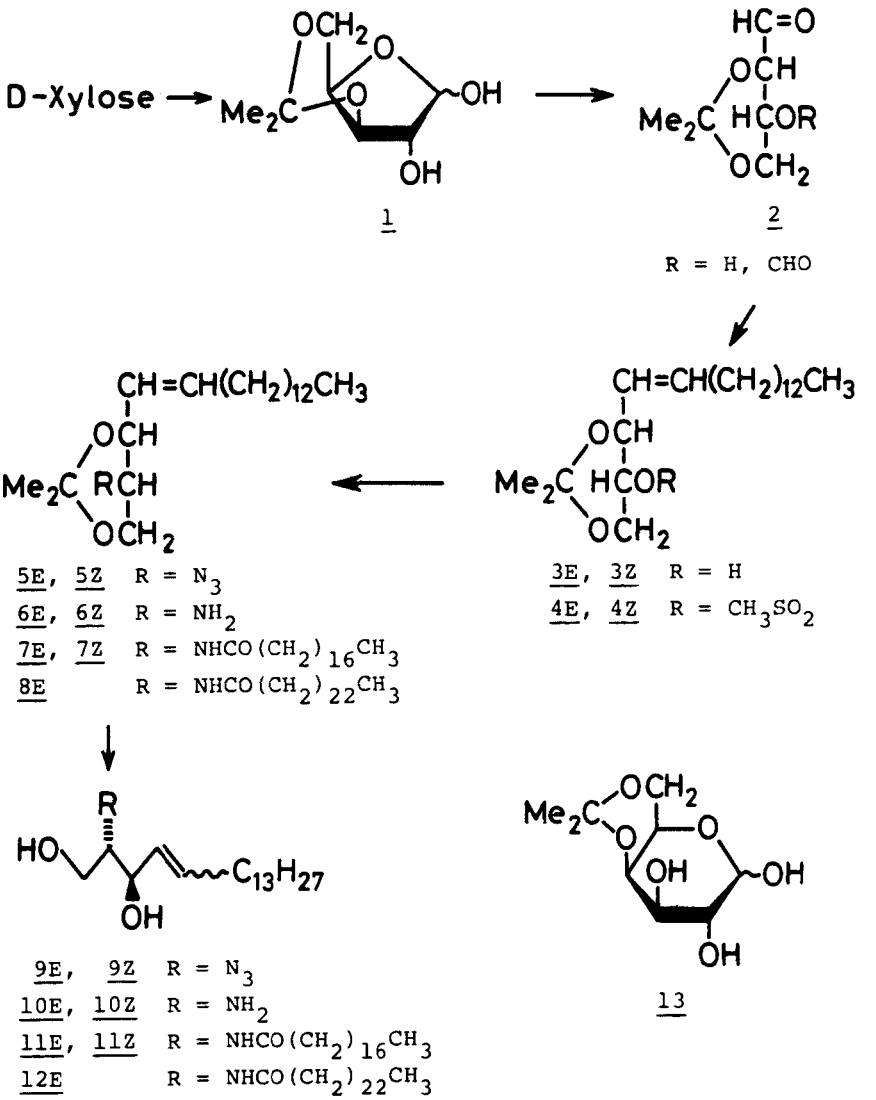


Scheme 1

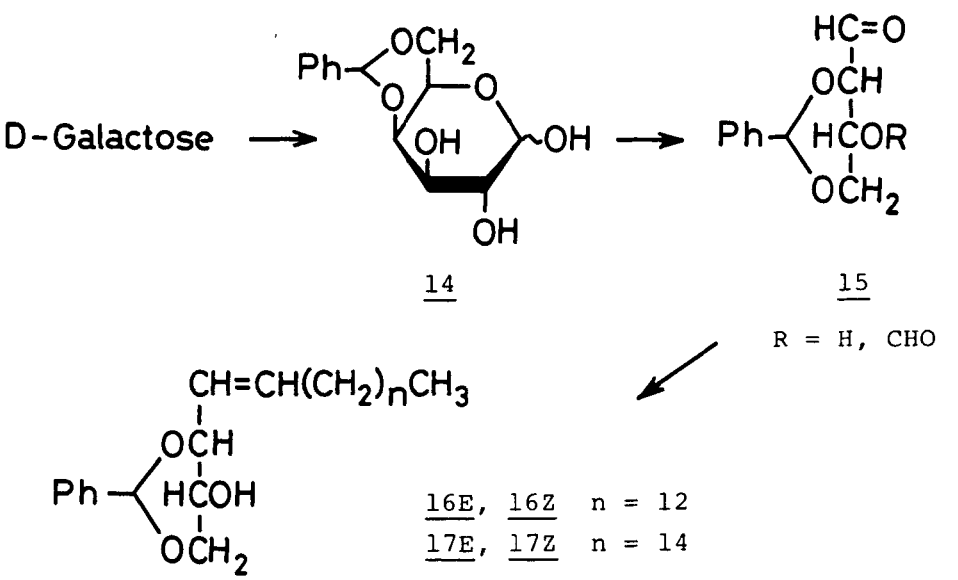
The Wittig condensation of the aldehyde mixture 2 with tetradecyl-triphenylphosphonium bromide in tetrahydrofuran was accomplished by the betain-ylid procedure of Schlosser et al.[6] to afford a mixture of trans-olefin, (2R, 3R, 4E)-1,3-O-isopropylidene-4-octadecene-1,2,3-triol (3E)[7] {mp 44.5-45.5°, $[\alpha]_D$ -26.4° (c 0.69, $CHCl_3$)} in 40% yield, and the cis-isomer 3Z {mp 44.5-45.5°, $[\alpha]_D$ -3.2° (c 0.37, $CHCl_3$)} in 35% yield.

The olefins 3E and 3Z were each treated with methanesulfonyl chloride in pyridine, to give 4E or 4Z, respectively, which was successively treated in situ with sodium azide in a 3:5 (v/v) mixture of pyridine and N,N-dimethylformamide at 110°. The main product was purified on a silica gel column, respectively, to yield (2S, 3R, 4E)-2-azido-1,3-O-isopropylidene-4-octadecene-1,3-diol (5E) {85%, $[\alpha]_D$ -35.3° (c 0.567, $CHCl_3$)} and the cis-isomer 5Z[8] {83%, $[\alpha]_D$ -74.7° (c 0.91, $CHCl_3$)}. In their ^1H NMR spectra (270 MHz, $CDCl_3$), the signals due to H-2 were each observed as a wide multiplet showing $J_{1ax,2} \simeq J_{2,3} = \sim 10$, $J_{1eq,2} = 5.5$ Hz at δ 3.29 (for 5E) and 3.33 (for 5Z) ppm, obviously indicative of the 2S; 3R (D-erythro) configuration found in the natural sphingosine.

Reduction of the azido group was achieved by treatment of 5E and 5Z with sodium borohydride in 2-propanol[9] at the reflux temperature, to afford (2S, 3R, 4E)-2-amino-1,3-O-isopropylidene-4-octadecene-1,3-diol (6E) {93%, $[\alpha]_D$ +9.7° (c 0.559, $CHCl_3$)} and the cis-isomer 6Z {91%, $[\alpha]_D$ +14.8° (c 0.864, $CHCl_3$)}, respectively.

The N-acylation of 6E and 6Z was conducted with stearic acid and dicyclohexylcarbodiimide in 1:1 (v/v) dichloromethane-1,4-dioxane to give (2S, 3R, 4E)-1,3-O-isopropylidene-2-octadecanamido-4-octadecene-1,3-diol (7E) {mp 67-67.5°, $[\alpha]_D$ -0.5° (c 0.4, $CHCl_3$)} in 84% yield, and the cis-isomer 7Z {mp 74-74.5°, $[\alpha]_D$ -9.9° (c 0.485, $CHCl_3$)} in 87% yield, respectively.[10] The lignoceroyl homolog 8E {mp 61.5-62°, $[\alpha]_D$ -0.4° (c 0.507, 50:1 $CHCl_3$-MeOH)} was also prepared from 6E in a similar manner.

The isopropylidene group of 5E and 5Z was removed quantitatively by acid hydrolysis to give (2S, 3R, 4E)-2-azido-4-octadecene-1,3-diol 9E {mp 50.5-51.5°, $[\alpha]_D$ -33.3° (c 0.441, $CHCl_3$)} and the cis-isomer 9Z {mp 42.5-43°, $[\alpha]_D$ -53.1° (c 0.557, $CHCl_3$) , which were then



14

15

R = H, CHO

16E, 16Z n = 12

17E, 17Z n = 14

Scheme 2

converted, by treatment with sodium borohydride in 2-propanol, into the natural sphingosine 10E (mp 81.5-82.5°; lit.[11] 82.5°, lit.[3b] 80-84°), and cis-sphingosine 10Z (mp 72-73°; lit.[12] 72-73°, lit.[3b] 73-74°) in high yields, respectively.

Finally, the N-acylation of 10E and 10Z as described for the preparation of 7E and 7Z, or the de-O-isopropylidenation of 7E and 7Z afforded a ceramide 11E {mp 97-98° (lit.[13a] 89-91°, lit.[13b] 91-93°), $[\alpha]_D$ -4.8° (c 0.5, $CHCl_3$)} and the corresponding cis-isomer 11Z {mp 94-95°, $[\alpha]_D$ -7° (c 0.5, $CHCl_3$)} in almost quantitative yields. Similarly, the lignoceroyl homolog 12E {mp 92-94°, $[\alpha]_D$ -1.5° (c 1.165, 50:1 $CHCl_3$-MeOH); lit.[3f] mp 91-92°, $[\alpha]_D$ -2.0°} was prepared from 8E.

When this procedure was employed for the benzylidene aldehyde 15 which was prepared from 4,6-O-benzylidene-D-galactopyranose (14) {mp 180-182°, $[\alpha]_D$ +126.5° (c 0.51, MeOH)}, as expected, (2R, 3R, 4E)-1,3-O-benzylidene-4-octadecene-1,2,3-triol (16E) {mp 53.5°, $[\alpha]_D$ -0.6° (c 0.506, $CHCl_3$)} and the cis-isomer 16Z {syrup, $[\alpha]_D$ +30.5° (c 0.485, $CHCl_3$)} were obtained. If hexadecyl-triphenylphosphonium bromide is used as the Wittig reagent, (2R, 3R, 4E)-1,3-O-benzyl-

idene-4-icosene-1,2,3-triol (17E) {mp 63-63.5°, $[\alpha]_D$ -1.9° (c 0.537, $CHCl_3$)} and the cis-olefin 17Z {mp 47-48°, $[\alpha]_D$ +42.3° (c 0.40, $CHCl_3$)} can be obtained. The E/Z ratio of the Wittig olefination was about 4:1 to indicate the favored formation of the trans-olefin.

In conclusion, sphingosine and ceramide could be synthesized in 6-7 steps from D-xylose or D-galactose, and a possibility of the more stereo-controled route was proposed. All new compounds were characterized by IR and NMR spectra, and had elemental compositions in satisfactory accord with theory.

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7. ^1H NMR (270 MHz, $CDCl_3$): δ 5.60 (m, 1 H, $J_{3,4}$=6.6, $J_{4,5}$=15.4, $J_{4,6(6')}$=1.5 Hz, H-4) and 5.80 (m, 1 H, $J_{4,5}$=15.4, $J_{5,6}\simeq J_{5,6'}$ =6~7 Hz, H-5).

8. ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.38 (m, 1 H, $J_{3,4}$=9, $J_{4,5}$=10.6, $J_{4,6(6')}$=1.5 Hz, H-4) and 5.78 (m, 1 H, $J_{4,5}$=10.6, $J_{5,6(6')}$= 7~8 Hz, H-5).

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10. In the routine work, the crude 7E and 7Z were successively converted to the corresponding ceramides, 11E and 11Z, which were then purified.

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