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TOTAL SYNTHESIS AND DETERMINATION OF ABSOLUTE CONFIGURATION OF CEREBROSIDE B_{1b} AND ITS STEREOISOMERS

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Summary: First total synthesis of (+)-cerebroside B_{1b}, **1b**, was described, the absolute configuration of which was determined to be (2S,3R)-1-O-ß-D-glucopyranosyl-2-N-(2'R)-2'-hydroxypalmitoyl-sphinga-4E,8Z-dienine.

There have been a number of synthesis reported of biologically important cerebrosides.[1] Recently, cerebroside B_{1a}, **1a**, and B_{1b}, **1b** (tentative name) were isolated from Tetragonia tetragonoides as a principle with anti-ulcerogenic activity and the structures were determined to be geometrical isomers of 1-O-ß-D-glucopyranosyl-2-N-2'-hydroxypalmitoyl-sphinga-4,8-dienine.[2] However the stereochemistry of C-2' and the absolute configuration of 1 were not determined yet, although the configuration of the C-2 and C-3 has been suggested to be D-*erythro* form without experimental evidence. In this communication, We report the first total synthesis of (+)-cerebroside B_{1b} and determined the absolute configuration of **1b**. One of crucial steps in the synthesis of **1b** consists in a regio- and stereoselective formation of the unsaturated aminodiols moiety. we have recently explored a simple method to *erythro*-sphingosine and ceramides employing 1,2-addition reaction of 2-nitroethanol to α,ß-unsaturated aldehyde.[3]

For the synthesis of **1b**, 2E,6Z-hexadecadienal, **4**, was requried as the key intermediate, which was prepared as follows: The 4Z-tetradecenol **2**[4], prepared by Wittig reaction of δ-butyrolactol with n-decyl triphenyl-phosphonium bromide[5] in 76% yield, was oxidized to the aldehyde **3** (76%)[6] with PDC (1.5 equiv) in refluxing CH_2Cl_2 followed by Wittig reaction with formylmethylenetriphenylphosphorane[7] in refluxing toluene to give the dienoaldehyde **4** (62%). According to our developed procedure described in the previous paper[3], the reaction of **4** with 2-nitroethanol was carried out (Et_3N , 0°C, 5days) to give 1,2-adduct **5** (72%) accompanied with a small amount of 1,4-adduct.[8] The diastereoisomeric mixture **5** was treated with 2,2-dimethoxypropane (PPTS, acetone) to give the acetonides which were readily separated by silica gel chromatogrphy to the *erythro*- (**7**) and *threo*-(**6**) isomers. The *threo*-isomer **6** was readily converted to the desired *erythro*-isomer **7** by refluxing in Et_3N, giving a total yield of 58% of **7** from **4**.

Reduction of the nitro group of 7 (aluminium amalgam or $LiAlH_4$, THF) gave the amine 8 in 79% yield. Condensation of 8 with D(R)-α-acetoxypalmitic acid 9[9] (DCC, 1-hydroxybenzotriazole, CH_2Cl_2) gave the diastereomeric mixture of the protected ceramides 11 (98%). Deacetonization (PPTS, MeOH) and tritylation (Ph_3CCl, DMAP, Et_3N, CH_2Cl_2) of 11 followed by silica gel chromatography gave 13 (31%, $[\alpha]_D$ + 3.5°) and 14 (27%, $[\alpha]_D$ + 5.7°). Benzoylation of 13 (benzoyl chloride, pyridine) followed by detritylation (CH_2Cl_2-MeOH(1:1), p-TsOH) gave the 1-O-unprotected ceramide 15 (80%, $[\alpha]_D$ + 36.4°).

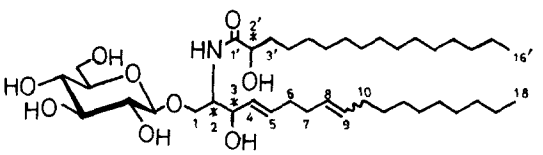
Glycosylation of 15 with O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-trichloroacetimidate 21 in CH_2Cl_2 in the presence of BF_3-etherate and molecular sieves 4A[12] gave the protected cerebroside, which was treated with NaOMe in MeOH to give a 57% yield (two steps) of 22 (mp 183°C, $[\alpha]_D$ + 4.6°). Likewise, 14 was converted to the corresponding cerebroside 23 (55%, mp 149°C, $[\alpha]_D$ + 1.7°) via the benzoyl derivative 16 (80%, $[\alpha]_D$ -16.1°).

In a similar fashion, the condensation of the erythro-amine 8 with L(S)-10[9] gave the diastereomeric mixture of 12 (99%). Deacetonization and tritylation followed by chromatography gave 17 (25%, $[\alpha]_D$ -5.4°) and 18 (31%, $[\alpha]_D$ -3.8°), which were benzoylated and detritylated to give 19 (81%, $[\alpha]_D$ + 16.2°) and 20 (84%, $[\alpha]_D$ -35.9°), respectively. Subsequent glycosylation followed by deprotection of 19 and 20 gave cerebrosides 24 (57%, mp 151°C, $[\alpha]_D$ -14.7°) and 25 (57%, mp 178°C, $[\alpha]_D$ - 18.7°), respectively.

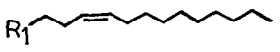
The cerebroside 22 out of four diastereomers was completely identical with the natural cerebroside 1b in all respects (mp, IR, Mass, and ^{1}H-NMR spectra, chromatographic mobility).[13]

In order to determine the absolute configuration of 22, the intermediate 13 was hydrogenated (PtO_2, MeOH) followed by detritylation (p-TsOH, CH_2Cl_2-MeOH) to give the tetrahydro derivative 26 (82%, $[\alpha]_D$ + 11.3°). Deacetylation of 26 (K_2CO_3, MeOH) gave the ceramide 27 (86%, mp 121.5-124°C, $[\alpha]_D$ + 19.6°).

On the other hand, the hydrogenation of the natural sphingosine 28[14] followed by treatment with 2,2-dimethoxypropane in the presence of (+)-camphor-10-sulphonic acid gave 29 (68%). Condensation of 29 with D(R)-9 in a similar manner as above and deacetonization with p-TsOH in MeOH-CH_2Cl_2 gave 26 (81%, $[\alpha]_D$ + 11.9°). Deacetylation of 26 gave 27 (92%, $[\alpha]_D$ + 19.6°). Ceramides 26 and 27 thus obtained were completely identical with the synthetic specimens obtained as above, demonstrating that the cerebroside B_{1b} has the same absolute configuration with sphingosine. The application of the present method to the synthesis of 1a is under investigation.

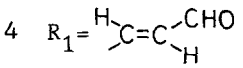


1 a: 8-E cerebroside B_{1a}
b: 8-Z cerebroside B_{1b}

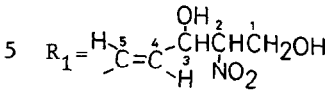


2 $R_1=CH_2OH$

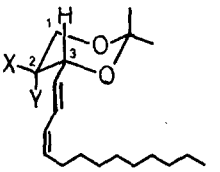
3 $R_1=CHO$



4 $R_1=$



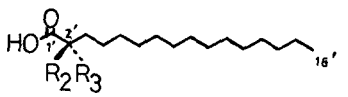
5 $R_1=$



6 X=H, $Y=NO_2$

7 $X=NO_2$, Y=H

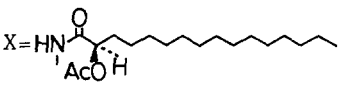
8 $X=NH_2$, Y=H



9 $R_2=OAc$, $R_3=H$

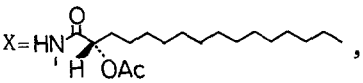
10 $R_2=H$, $R_3=OAc$

11 X=

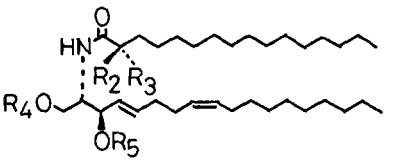


, Y=H

12 X=



, Y=H

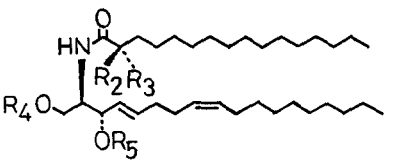


13 $R_2=OAc$, $R_3=H$, $R_4=Tr$, $R_5=H$

15 $R_2=OAc$, $R_3=H$, $R_4=H$, $R_5=Bz$

17 $R_2=H$, $R_3=OAc$, $R_4=Tr$, $R_5=H$

19 $R_2=H$, $R_3=OAc$, $R_4=H$, $R_5=Bz$

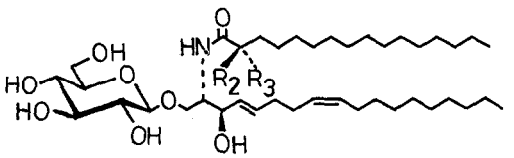


14 $R_2=OAc$, $R_3=H$, $R_4=Tr$, $R_5=H$

16 $R_2=OAc$, $R_3=H$, $R_4=H$, $R_5=Bz$

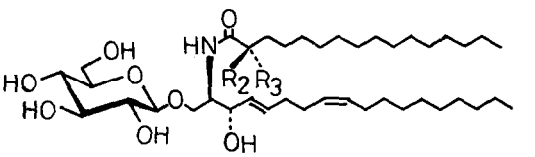
18 $R_2=H$, $R_3=OAc$, $R_4=Tr$, $R_5=H$

20 $R_2=H$, $R_3=OAc$, $R_4=H$, $R_5=Bz$



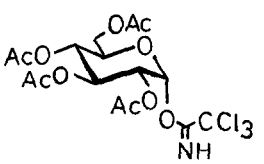
22 $R_2=OH$, $R_3=H$

24 $R_2=H$, $R_3=OH$

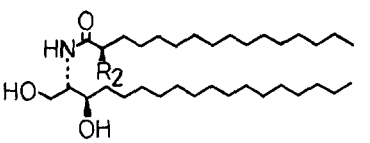


23 $R_2=OH$, $R_3=H$

25 $R_2=H$, $R_3=OH$

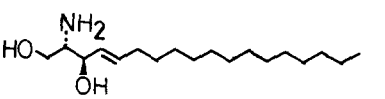


21

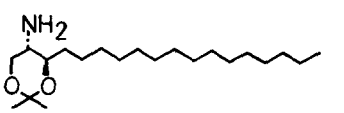


26 $R_2=OAc$

27 $R_2=OH$



28



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References and Notes

1. For some recent reviews, see: a) S. Hakomori, ''Handbook of Lipid Research'', Vol 3, ''Sphingolipid Biochemistry'', J.N. Kanfer and S. Hakomori, Ed., Plenum Press, New York, 1983, p 137; b) ''New Comprehensive Biochemistry'', Vol 10, ''Glycolipids'', H. Wiegandt, Ed., Elsevier, Amsterdam, 1985; c) K. Koike, M. Sugimoto, Y. Nakahara, and T. Ogawa, Glycoconjugate J., 2, 105 (1985).
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4. All new compounds gave satisfactory spectral data. ^{1}H-NMR spectroscopy was performed either at 270 MHz or 400 MHz with a JEOL GX-270 or GSX-400 spectrometer. Crystalline compounds gave satisfactory microanalysis. Optical rotations were measured either in $CHCl_3$ or in $CHCl_3$-MeOH (1:1) at 20°C.
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6. The obtained 3 contained the E-isomer. The Z:E ratio of 3 was determined by 400 MHz ^{1}H-NMR spectrum to be approximately 7:1 by comparing the ratio of C-6 protons as well as CHO protons.
7. S. Tripett and D.M. Walker, J.Chem.Soc., 1266 (1961).
8. The reaction of an α,ß-unsaturated aldehyde such as hexadec-2-enal with $THPOCH_2CH_2NO_2$ using a stong base (BuLi, THF-HMPA, -78°C) gave only a low yield of the nitrodiols (erythro, 9.7%; threo, 14.7%).
9. D(R)-**9**: mp 59-61°C; $[\alpha]_D$ + 11.8° (c 1.60, $CHCl_3$). L(S)-**10**: mp 59-61°C; $[\alpha]_D$ - 12.3° (c 1.52, $CHCl_3$). The optically active **9** and **10** were prepared by acetylation of (Ac_2O-pyridine) of the corresponding hydroxy acids,[10] respectively, which were obtained by optical resolution according to Karlsson's method.[11]
10. a) D.H.S. Horn, F.W. Hougen, E. von Rudloff, and D.A. Sutton, J.Chem.Soc., 177 (1954); b) D.H.S. Horn and M.Y.Y. Pretonus, ibid, 1460 (1954).
11. K.A. Karlsson and I. Pascher, Chem.Phys.Lipids, 12, 65 (1974).
12. R.R. Schmidt and J. Michael, Angew.Chem.Int.Ed.Engl., 19, 731 (1980).
13. The value of $[\alpha]_D$ for cerebroside B_{1b}, **1b**, is not described.[2] However, 1b was estimated to have a positive optical rotation since the natural cerebroside B_{1a}, **1a**, gave a positive specific rotation.
14. Natural sphingosine was purchased from Sigma Chemical Co.

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