Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 1992, **2(3)**, 108–110
Mendeleev Communications

Synthesis of C_{21}-(2*R*,3*S*,6*R*,4*E*)-2-*N*-Hexadecanoyl-6-hydroxysphingenine Dibenzoate

Aleksander G. Tolstikov,* Radik Kh. Yamilov, Leonid V. Spirikhin and Genrikh A. Tolstikov

Institute of Organic Chemistry, Ural Branch of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. Fax: +7 347 234 2914

Based on (2*R*,3*S*)-methyl-2-hydroxy-3,4-*O*-isopropylidenebutanoate, C_{21}-(2*R*,3*S*,6*R*,4*E*)-2-*N*-hexadecanoyl-6-hydroxysphingenine has been synthesized as its dibenzoate.

A good deal of information on the isolation of cerebrosides from natural material and on the synthetic preparation thereof is available from recent publications. As compared to conventional glycosphingolipids,[1] the cerebrosides have a different basic sphingosine structure[2,3] and differently constructed *N*-acyl and glycoside fragments.[4–6] The synthesis of structural analogues of the cerebrosides is a field of increasing interest at present, owing to their attractive properties that are similar to those of natural cerebrosides.[7,8]

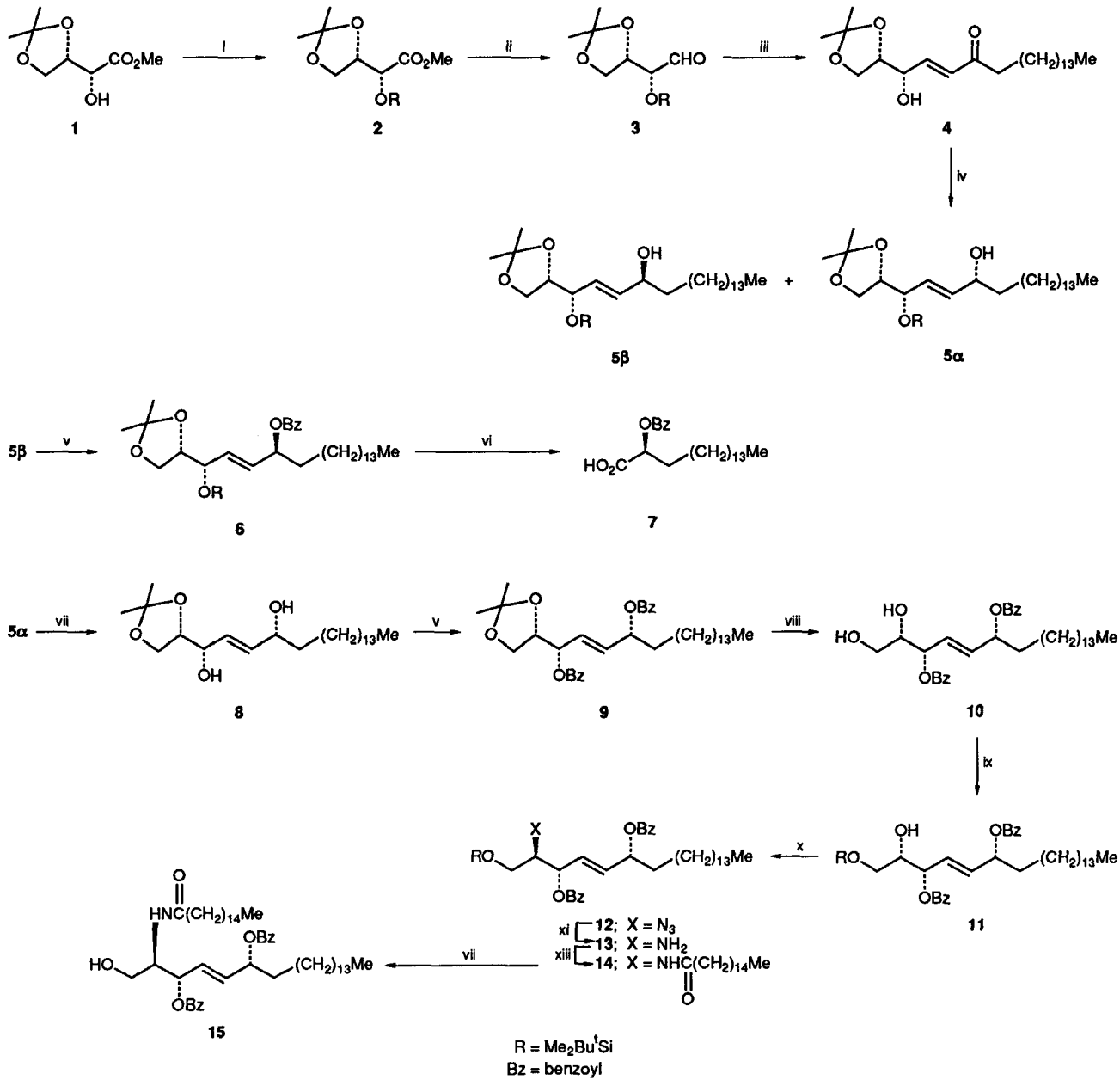
In this Communication we describe a synthetic procedure for the preparation of (2*R*,3*S*,6*R*,4*E*)-2-*N*-hexadecanoyl-6-hydroxysphingenine **15**, from the available L-methylthreonate acetonide **1**.[9]

According to the synthetic plan, the starting threonate **1** was treated with Me_2Bu^tSiCl to yield silyl ether **2** (98%). The latter was then reduced by diisobutylaluminium hydride (DIBAH) in hexane, which led to a 72% yield of aldehyde **3**. Coupling of **3** with dimethyl-2-oxoheptadecylphosphonate gave a 72% yield of enone **4** that was further treated with $NaBH_4$ in methanol to give a mixture of C-6 epimeric alcohols **5α** and **5β** in a 1:1 ratio, isolated by HPLC.† The individual epimers were identified by ^1H and ^{13}C NMR spectroscopy,‡ and a full coincidence of the signals was found, so we were unable to use these as a true criterion for assigning the configuration of the C-6 chiral centre. The stereochemical problem was solved using a chemical transition, whereby benzoate **6**, prepared from alcohol **5β**, was ozonolysed with treatment of the peroxide products, by 30% H_2O_2 in the presence of SeO_2. The optically active 2-benzoyloxyheptadecanoic acid **7** ($[\alpha]_D^{20}+1.49$) resulted (32%), the *S*-configuration of which was confirmed by correlation with the known (2*S*)-benzoyloxydocosanoic acid ($[\alpha]_D^{20}+1.39$).[10] Based on the correlation obtained, an *S*-configuration was ascribed to the asymmetric centre C-6 in

† The epimers **5α** and **5β** were separated on a Du Pont 8800 instrument, Zorbax Sil, R-401 refractometer, hexane–propan-2-ol (100:1).

‡ *Spectroscopic assignments for the isomers* **5α**: $[\alpha]_D^{20}$ −24.3 (*c* 4.7, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ −4.86, −4.54 [$(CH_3)_2Si$], 14.11 (C-21), 18.23 [$SiC(CH_3)_3$], 22.70 (C-20), 25.05 (C-8), 25.42, 25.83 [$C(CH_3)_2$], 26.35 (C-18), 29.38, 29.64, 29.72 [C-9–C-17, $SiC(CH_3)_3$], 31.95 (C-19), 37.24 (C-7), 65.11 (C-1), 72.14 (C-6), 73.02 (C-3), 78.65 (C-2), 109.37 [$C(CH_3)_2$], 128.46 (C-4), 135.62 (C-5).

5β: $[\alpha]_D^{20}$ −6.1 (*c* 8.6, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ −4.86, −4.56 [$(CH_3)_2Si$], 14.14 (C-21), 18.27 [$SiC(CH_3)_3$], 22.73 (C-20), 25.16 (C-8), 25.44, 25.88 [$C(CH_3)_2$], 26.41 (C-18), 29.41, 29.66, 29.74 [C-9–C-17, $SiC(CH_3)_3$], 31.98 (C-19), 37.34 (C-7), 65.24 (C-1), 72.17 (C-6), 73.25 (C-3), 78.73 (C-2), 109.43 $C(CH_3)_2$], 128.55 (C-4), 135.57 (C-5).



Scheme 1 *Reagents and conditions*: i, Me_2Bu^tSiCl, imidazole, DMF, 25°C, 4 h; ii, DIBAH, C_6H_{14}, −60°C, 1 h; iii, $(MeO)_2P(O)CH_2(CO)C_{15}H_{31}$, KOH, CH_2Cl_2, 25°C, 0.5 h; iv, $NaBH_4$, MeOH, 0°C, 1 h; v, BzCl, Py, PhMe, 25°C, 4 h; vi, O_3/O_2, CH_2Cl_2, −78°C, 5 min, then AcOH, 30% H_2O_2, SeO_2, 50°C, 6 h; vii, Bu^n_4NF, THF, 0→25°C, 1.5 h; viii, HCl, MeCN, 25°C, 3 h; ix, Me_2Bu^tSiCl, Py, 0°C, 2 h; x, Tf_2O, Py, CH_2Cl_2, −10°C, 10 min, then NaN_3, DMF, −10→20°C, 0.5 h; xi, Ph_3P, PhH, 50°C, 45 min, then H_2O, 50°C, 4 h; xii, $ClCO(CH_2)_{14}Me$, Et_3N, cat. DMAP, CH_2Cl_2, 20 min

compound **5β**, and an *R*-configuration to that in **5α**, respectively.

Enantiomerically pure enol **5α** was used for further transformations. Treatment of **5α** with Bu^n_4NF, followed by reaction of the resultant diol **8** with benzoyl chloride, gave an 85% yield of henicosene **9**. Acidic hydrolysis of the latter gave a 72% yield of the related 1,2-diol **10**, which was further transformed into its monosilyl ether **11** in quantitative yield. Compound **11** was treated with trifluoromethanesulfonic anhydride (Tf_2O) in pyridine, followed by one-pot reaction of the resultant product with NaN_3 in the presence of *N*,*N*-dimethylformamide (DMF), which inverted the configuration of the C-2 centre to produce a 63% yield of azide **12**. The latter was reduced with Ph_3P to give the key amine **13** (82%), which was subsequently acylated with hexadecanoyl chloride in the presence of Et_3N and a catalytic amount of 4-dimethylaminopyridine (DMAP) to give amide **14**. Amide **14** was then treated with Bu^n_4NF to lead finally to the target product (2*R*,3*S*,6*R*,4*E*)-3,6-di-*O*-benzoyl-1-hydroxy-2-*N*-hexadecanoylhenicos-4-ene **15**.§

Thus, (2*R*,3*S*)-methyl-2-hydroxy-3,4-*O*-isopropylidenebut-

§ *Spectroscopic assignments* for **15**: $[\alpha]_D^{20}$ +2.8 (*c* 0.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.83, 0.87 (2t, 6H, 21-H, 16′-H, *J* 6.8, 7.0 Hz), 1.12–1.42 (m, 52H, 8-H–20-H, 3′-H–15′-H), 1.72–1.95 (m, 3H, 7-H, OH), 2.09 (t, 2H, 2′-H, *J* 7.3 Hz), 3.65 (dd, 1H, 1-H_a, J_{gem} 10.0, $J_{1a,2}$ 5.3 Hz), 3.84 (dd, 1H, 1-H_b, J_{gem} 10.0, $J_{1b,2}$ 3.5 Hz), 4.46 (m, 1H, 2-H), 5.38 (q, 1H, 6-H, *J* 6.5 Hz), 5.68 (m, 1H, NH), 5.73 (dd, 1H, 3-H, $J_{3,2}$ 4.9, $J_{3,4}$ 8.7 Hz), 5.88 (dd, 1H, 4-H, $J_{4,5}$ 15.8, $J_{4,3}$ 8.7 Hz), 5.92 (dd, 1H, 5-H, $J_{5,4}$ 15.8, $J_{5,6}$ 6.5 Hz), 7.62–8.02 (m, 10H, 2 Ph); ^{13}C NMR ($CDCl_3$) δ 14.10, 14.18 (C-21, C-16′), 22.76 (C-20, C-15′), 25.17 (C-3′), 25.84, (C-8), 29.32, 29.44, 29.56, 29.72 (C-9–C18, C-4′–C-13′), 31.91, 32.01 (C-19, C-14′), 34.42 (C-7), 36.89 (C-2′), 52.36 (C-2), 62.50 (C-1), 72.80, 75.40 (C-3, C-6), 127.04 (C-4), 128.07, 129.67, 130.18, 132.55, 133.04 (2 Ph), 134.12 (C-5), 164.03, 166.18 (2 CO), 174.76 (C-1′).

anoate is a convenient structural unit from which to synthesize optically active sphingosine species and derivatives thereof.

References

1 R. R. Schmidt and P. Zimmermann, *Angew. Chem.*, 1986, **98**, 722.
2 R. Kraus and G. Spiteller, *Liebigs Ann. Chem.*, 1991, 125.
3 T. Bar and R. R. Schmidt, *Liebigs Ann. Chem.*, 1988, 669.
4 K. C. Nicolaou, T. J. Coulfield and H. Katoaka, *Carbohydr. Res.*, 1990, **202**, 177.
5 T. Nakano, Y. Yto and T. Ogawa, *Tetrahedron Lett.*, 1990, **31**, 1597.
6 R. Higuchi, J. X. Jhou, K. Jnukai and T. Komori, *Liebigs Ann. Chem.*, 1991, 745.
7 T. Bar and R. R. Schmidt, *Liebigs Ann. Chem.*, 1991, 185.
8 V. V. Bessonov, A. S. Bushnev and E. N. Zvonkova, *Bioorg. Khim.*, 1991, **17**, 403 [*Sov. J. Bioorg. Khim. (Engl. Transl.)*, 1991, **17**, 220].
9 C. C. Wei, S. Bernardo, J. P. Tendi, J. Borgese and M. Weigele, *J. Org. Chem.*, 1985, **50**, 3462.
10 K. Yamagata, Y. Yamagiva and T. Kamikawa, *J. Chem. Soc., Perkin Trans. 1*, 1990, **12**, 3355.

Received: Moscow, 26th December 1991
Cambridge, 20th February 1992; Com. 2/00270A