Synthesis of Dihydrosphingosine

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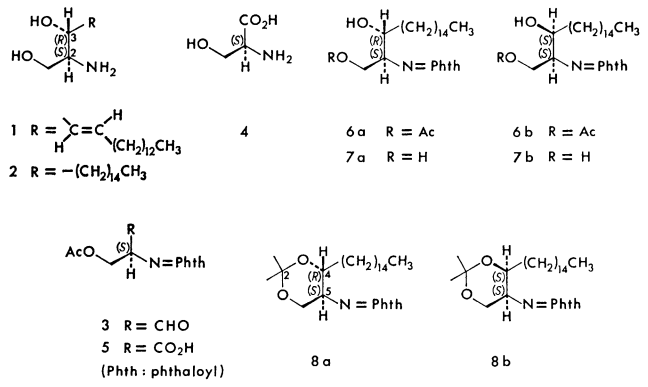
Synopsis. A conversion of (*S*)-3-acetoxy-2-phthalimidopropanal into dihydrosphingosine is described.

A number of syntheses of sphingosine (**1**), dihydrosphingosine (**2**), and related compounds have been reported.[1-3] This paper deals with a convenient synthesis of dihydrosphingosine [**2**; (2*S*,3*R*)-*erythro*-2-aminooctadecane-1,3-diol] from (*S*)-3-acetoxy-2-phthalimidopropanal (**3**).

The chiral aldehyde (**3**) was prepared from L-serine (**4**) *via* (*S*)-3-acetoxy-2-phthalimidopropanoic acid (**5**) by the known procedure.[2] The Grignard reaction of **3** with pentadecylmagnesium bromide in ether at a temperature between −88 and −45 °C gave a mixture of diol monoacetates (**6a** and **6b**). This mixture was subjected to acid hydrolysis and the product mixture was separated by column and thin-layer chromatography to afford (2*S*,3*R*)-*erythro*-2-phthalimidooctadecane-1,3-diol (**7a**) and (2*S*,3*S*)-*threo*-2-phthalimidooctadecane-1,3-diol (**7b**) in 13% and 1% yields from **3**, respectively.

The *erythro* and *threo* configurations were shown for **7a** and **7b**, respectively, on the basis of the following evidence. Treatment of **7a** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid gave an acetonide (**8a**) in an almost quantitative yield. Acetalization of **7b** gave the corresponding acetonide (**8b**) in 55% yield. The coupling constant between a C-4 proton and a C-5 proton was determined to be 10 Hz and 5 Hz for **8a** and **8b**, respectively; the two protons should be in a *trans* relationship for **8a** and in *cis* one for **8b**. Acid hydrolysis of these acetonides (**8a** and **8b**) gave the diols (**7a** and **7b**), respectively.



These results suggest that a stereoselective attack[2] of the Grignard reagent to the aldehyde (**3**) was effected preferentially from the less hindered side of **3** to give predominantly the desired *erythro* derivative (**6a**).

Finally, hydrazinolysis of **7a** afforded dihydrosphingosine (**2**) in 81% yield.

Experimental

IR spectra were measured with a Hitachi EPI-G2 spectrometer, ^{1}H-NMR spectra with a JEOL PS-100 (100 MHz), a Varian EM-390 (90 MHz), or a Hitachi R-20B (60 MHz) spectrometer in deuteriochloroform solution containing tetramethylsilane as an internal standard, high resolution and chemical ionization (CI-MS) mass spectra with a JEOL JMS-D300 mass spectrometer. Measurements of optical rotation were carried out with a JASCO polarimeter DIP-SL, and high performance liquid chromatography (HPLC) analyses with a Waters liquid chromatograph model ALC-GPS 202-401. For column chromatography Wakogel C-200 (Wako Pure Chemical Industries) was used. Thin-layer chromatography (TLC) was carried out on Kieselgel GF_{254} (E. Merck, Darmstadt) in 0.25 mm thickness.

Grignard Reaction of (S)-3-Acetoxy-2-phthalimidopropanal (3) with Pentadecylmagnesium Bromide. A solution of pentadecylmagnesium bromide (3.6 mmol) in ether (60 ml) was added dropwise to a solution of the aldehyde (**3**; 0.94 g, 3.6 mmol) in ether (3.6 ml) with stirring under an argon atmosphere at a temperature between −88 and −80 °C. After the mixture had been stirred at −78 °C for 2 h and then at −45 °C for 30 min, a saturated aqueous solution (10 ml) of ammonium chloride was added at −45 °C. The reaction mixture was treated in the usual way to give a residue (1.90 g) which was chromatographed on a column of silica gel (60 g). Elution with hexane–ethyl acetate (17: 3) gave a mixture (410 mg) of crude diol monoacetates (**6a** and **6b**). This mixture was purified by preparative TLC to give a sample for spectral measurements; this sample showing one spot on TLC gave two peaks at R_t=28.4 min (major product; **6a**) and R_t=27.7 min (minor product; **6b**) on HPLC examination [column: μ-PORASIL, 1/4(inch) × 1(foot); solvent system: 30% ether–hexane; flow rate: 1 ml/min]. However, separation of each of two diastereomers (**6a** and **6b**) was unsuccessful due to proximity of their retention times. Mixture of **6a** and **6b**: mp 60 °C (crystallized from acetone): IR (KBr) 3400, 2920, 2850, 1780, 1750, 1710, 1560, 1380, 1370, 1250, 1240, and 720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, t-like; $-CH_2C\underline{H}_3$), 1.97 (3H, s; CH_3-CO–), 3.77 (1H, br. s; disappeared on addition of D_2O; –OH), 4.10 (1H, br. s; $-C\underline{H}$–OH), 4.35 (1H, m; $-C\underline{H}$–N–), 4.60 (2H, m; $-C\underline{H}_2OAc$), and 7.85 (4H, m; aromatic H's).

In the column chromatography described above, successive elution with hexane–ethyl acetate (4: 1) gave a residue (*ca.* 450 mg) showing ^{1}H-NMR signals at δ 6.58 (2H, s; $-C(=CH_2)$–), 7.75 (4H, m; aromatic H's), and 9.63 (1H, s; –CHO). This suggested that the unchanged starting material (**3**) suffered elimination of acetic acid to give 2-phthalimido-2-propenal. Further purification of the residue was not carried out.

Treatment of **3** with the Grignard reagent at room temperature resulted in a formation of a complex mixture probably due to an attack of the reagent to the phthaloyl grouping. Further examination of the mixture was not effected. In the reaction at a temperature between −88 and −45 °C, this kind of product mixture was not formed.

*Acid Hydrolysis of the Mixture of Diol Monoacetates (**6a** and **6b**).* The mixture of crude diol monoacetates (**6a** and **6b**; 410 mg) was added to a solution (30 ml) prepared from 1 M hydrochloric acid and methanol (1: 9 v/v), and the whole mixture was refluxed for 3 h. The reaction mixture was neutralized with aqueous sodium hydrogencarbonate solution and extracted thrice with chloroform. The combined chloroform solution (total 30 ml) was treated in the usual way to give a solid (380 mg), which was chromatographed on a column of silica gel (12 g). Elution with hexane–ethyl acetate (7: 3) gave a mixture of **7a** and **7b**, and then pure **7a** (125 mg). This mixture was subjected to separation by TLC to afford **7a** (71 mg) and **7b** (16.4 mg; 1% yield from **3**). The *erythro*-diol (**7a**; total 196 mg) was obtained in 13% yield from **3**. (2*S*,3*R*)-*erythro*-2-Phthalimidooctadecane-1,3-diol (**7a**), mp 69—70 °C (crystallized from hexane–ethyl acetate), $[\alpha]_D^{24}$ −6° (*c* 0.18; EtOH); IR (Nujol) 3400, 1780, and 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, t-like; $-CH_2C\underline{H}_3$), 3.1—3.6 (2H, broad signal; 2×OH), 4.18 [4H, m; HO–C<u>H</u>–C<u>H</u>($C\underline{H}_2OH$)–N–], and 7.81 (4H, m; aromatic H's); CI-MS (using methane as reactant gas) *m/e* 432 $(M+1)^+$. Found: *m/e* 431.3033. Calcd for $C_{26}H_{41}NO_4$: M, 431.3034. (2*S*,3*S*)-*threo*-2-Phthalimidooctadecane-1,3-diol (**7b**), mp 46—48 °C (crystallized from hexane–ethyl acetate), $[\alpha]_D^{23}$ +3° (*c* 0.24; $CHCl_3$); IR (KBr) 3450, 2920, 2850, 1780, 1710, 1470, 1400, 1380, and 720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, t-like; $-CH_2C\underline{H}_3$), 3.3—3.6 (2H, broad signal; 2×OH), 4.05 (3H, m; $-C\underline{H}_2OH$ and –C<u>H</u>OH), 4.35 (1H, m; –C<u>H</u>–N–), and 7.81 (4H, m; aromatic H's); CI-MS *m/e* 432 $(M+1)^+$. Found: *m/e* 431.3034. Calcd for $C_{26}H_{41}NO_4$: M, 431.3034.

Acetalization of the erythro-*Diol (**7a**).* A solution of the *erythro*-diol (**7a**; 50 mg) in 2,2-dimethoxypropane (1.5 ml) containing a trace of *p*-toluenesulfonic acid was stirred at room temperature for 10 h. The reaction mixture was treated in the usual way to give a residue, which was subjected to purification by preparative TLC giving an acetonide (**8a**; 53.9 mg) in an almost quantitative yield. (4*R*,5*S*)-2,2-Dimethyl-4-pentadecyl-5-phthalimido-1,3-dioxane (**8a**), mp 65—65.5 °C (crystallized from ethanol), $[\alpha]_D^{30}$ +18° (*c* 0.21; EtOH); IR (Nujol) 1780, 1720, 1260, 1200, 1160, 1120, 1105, 1090, 1075, and 800 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, t-like; $-CH_2C\underline{H}_3$), 1.48 and 1.67 (each 3H, s; *t*-CH_3), 3.73 [1H, dd, J=10 and J=5 Hz, $C_{(6\alpha)}$–H], 4.28 [1H, td, J=10 and J=5 Hz; $C_{(5\alpha)}$–H], 4.53 [1H, t, J=10 Hz; $C_{(6\beta)}$–H], 4.65 [1H, m; $C_{(4\beta)}$–H], and 7.86 (4H, m; aromatic H's); CI-MS *m/e* 472 $(M+1)^+$; MS *m/e* 456.3114 $(M-15)^+$. Found: C, 74.12; H, 9.64; N, 3.17%. Calcd for $C_{29}H_{45}NO_4$: C, 73.84; H, 9.62; N, 2.97%.

Acetalization of the threo-*Diol (**7b**).* The *threo*-diol (**7b**; 28 mg) was dissolved in 2,2-dimethoxypyropane (1.5 ml) containing a trace of *p*-toluenesulfonic acid, and the solution was stirred at room temperature for 12 d. The reaction mixture was treated in the usual way to give a residue. This was subjected to separation by preparative TLC to afford the corresponding acetonide (**8b**; 16.7 mg) in 55% yield, besides unchanged **7b** (11.1 mg). When the reaction was carried out for 12 h, almost all the starting material (**7b**) was found to be unchanged. (4*S*,5*S*)-2,2-Dimethyl-4-pentadecyl-5-phthalimido-1,3-dioxane (**8b**), mp 59—60 °C (crystallized from ethanol), $[\alpha]_D^{25}$ −20° (*c* 0.15; $CHCl_3$); IR (Nujol) 1780, 1710, 1230, 1170, 1140, 1120, and 880 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, t-like; $-CH_2C\underline{H}_3$), 1.45 and 1.61 (each 3H, s; *t*-CH_3), 3.96 [1H, dd, J=11 and J=7 Hz; $C_{(6)}$–H], 4.16 [1H, m; $C_{(4\alpha)}$–H], 4.41 [1H, dd, J=11 and J=7 Hz; $C_{(6)}$–H], 4.70 [1H, td, J=7 and J=5 Hz; $C_{(5\alpha)}$–H], and 7.90 (4H, m; aromatic H's); CI-MS *m/e* 472 $(M+1)^+$; MS *m/e* 456.3106 $(M-15)^+$.

*Acid Hydrolysis of the Acetonides (**8a** and **8b**).* The (4*R*,5*S*)-acetonide (**8a**; 38 mg) was added to a solution (5 ml) prepared from 1 M hydrochloric acid and methanol (1: 9 v/v), and the mixture was refluxed for 2 h. The reaction mixture was neutralized with aqueous sodium hydrogencarbonate solution and extracted with chloroform. The chloroform solution was treated in the usual way to give the *erythro*-diol (**7a**; 20.9 mg). The *threo*-diol (**7b**) was obtained from the (4*S*,5*S*)-acetonide (**8b**) by the same acid hydrolysis.

Hydrazinolysis of the erythro-*Diol Phthalimide (**7a**).* Hydrazine hydrate (80%; 0.2 ml) was added to a solution of the *erythro*-diol phthalimide (**7a**; 70.5 mg) in ethanol (1.3 ml), and the mixture was refluxed for 1.5 h. The reaction mixture was extracted with dichloromethane (5 ml) after addition of water (1 ml) and potassium hydroxide (0.2 g). The organic layer was treated in the usual way to give a residue, which crystallized from chloroform to afford an *erythro*-amine (**2**; 39.8 mg) in 81% yield. (2*S*,3*R*)-*erythro*-2-Aminooctadecane-1,3-diol (**2**; dihydrosphingosine), mp 76.5—77.5 °C (lit,[4] 78.5—79 °C), $[\alpha]_D^{21}$ +5° [*c* 0.40; $CHCl_3$–EtOH (9: 1)] (lit[4] +6°); IR (Nujol) 3350, 3300, 1620, 1580, 1070, and 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t-like; $-CH_2C\underline{H}_3$), 2.87 [5H, broad signal; <u>H</u>O–CH_2–C<u>H</u>($N\underline{H}_2$)–C<u>H</u>(O<u>H</u>)–], and 3.70 (3H, broad signal; $-C\underline{H}_2OH$ and –C<u>H</u>OH). Found: *m/e* 301.2964. Calcd for $C_{18}H_{39}NO_2$: M, 301.2979.

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