A Convenient Stereoselective Synthesis of D-*erythro*-C_{18}-Sphingosine from Galactal[1]

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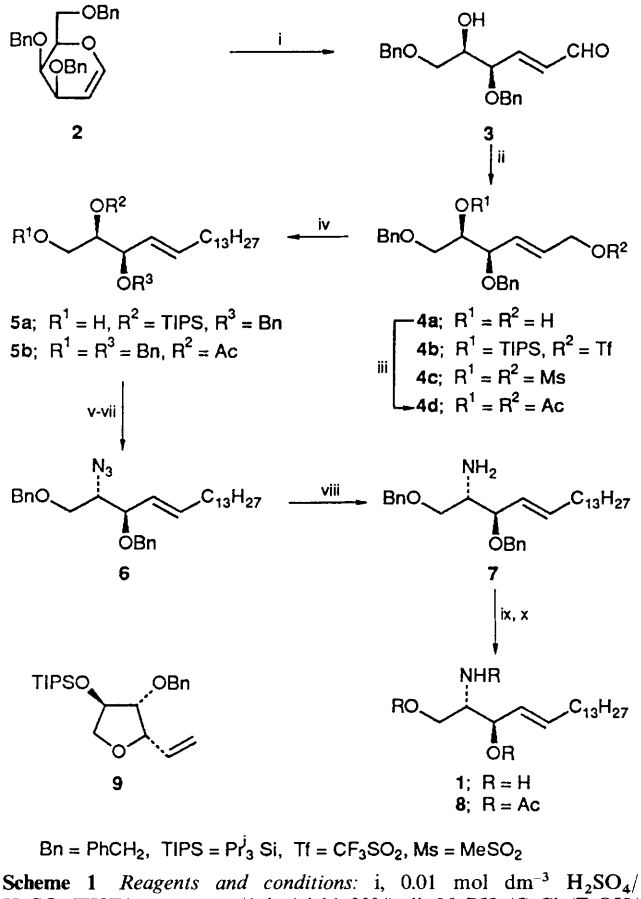
The highly efficient stereoselective synthesis of D-*erythro*-C_{18}-sphingosine from 3,4,6-tribenzyloxygalactal *via* 4,6-tribenzyloxy-5-hydroxyhexenal is described.

Recently, many glycosphingolipids have been isolated from the membrane of animal cells. Although their biological functions are still not clear, these compounds are assumed to participate in various processes associated with recognition phenomena.[2] The syntheses of these compounds, which have received increasing attention, have been reported either starting from natural chiral sources or by using stereoselective transformations.[3]

The strategy for the present synthesis of sphingosine follows the findings by Pedersen[4] that mercuric ion-assisted acid hydrolysis of glycals yielded *trans* enals. Thus, extension of the carbon chain of the enal and conversion of the C-5 oxygen function into amino group was expected to offer an efficient method for synthesizing D-*erythro*-C_{18}-sphingosine **1**.

3,4,6-Tribenzyloxy-D-galactal, prepared from 3,4,6-tri-*O*-acetyl-D-galactal in the conventional way, was treated with 0.01 mol dm^{-3} sulphuric acid in the presence of mercuric sulphate to give the hydroxy-*trans*-enal **3**† (95%). Reduction of **3** with sodium borohydride in the presence of cerium(III) chloride gave the diol **4a**. An initial attempt to extend the carbon chain of **4a** involved its conversion into the triisopropylsilyoxy triflate **4b** followed by coupling with dodecylmagnesium bromide and dilithium tetrachlorocuprate. The coupling, however, gave **5a** in only poor yield (39%), the major product being the tetrahydrofuran **9** (54%). The coupling with the dimesylate **4c** also proved troublesome. More successful, however, was the coupling of the allylic acetate **4d** with the cuprate to give the desired α-substitution product **5b** in 60% yield. The reaction was regioselective and no γ-substitution product was detected. Displacement of the acetyl group in **5b** to obtain the azide **6** with complete inversion of the stereochemistry was carried out in three steps (methanolysis, mesylation and azidation) in 82% yield. Reduction of the azide **6** followed by deprotection gave **1** as a pure colourless powder in 56% yield, m.p. 72–74 °C (lit.[5] m.p. 72–75 °C). The triacetylated derivative of this material was identical with an authentic specimen of **8**.‡



Bn = $PhCH_2$, TIPS = Pr^i_3 Si, Tf = CF_3SO_2, Ms = $MeSO_2$

Scheme 1 *Reagents and conditions:* i, 0.01 mol dm^{-3} H_2SO_4/$HgSO_4$/THF/room temp./1 h (yield 99%); ii, $NaBH_4/CeCl_3$/EtOH/room temp./1 h (yield 96%); iii, Ac_2O/Py/DMAP/0 °C – room temp./0.5 h (yield 100%); iv, $C_{12}H_{25}MgBr/Li_2CuCl_4$/THF/ – 18 °C/1 h (yield 60%); v, NaOMe/MeOH/room temp./2 h (yield 100%); vi, MsCl/Py/CH_2Cl_2/room temp./20 h (yield 99%); vii, LiN_3/DMF/90 °C/24 h (yield 82%); viii, Ph_3P/THF/H_2O/room temp./2 days (yield 79%); ix, Li/liq. NH_3/THF/ – 33 °C/1 h (yield 73%); x, Ac_2O/Py/DMAP/room temp./0.5 h (yield 100%)

In summary, we have completed an economic synthesis of *erythro*-C_{18}-sphingosine **1** in nine steps in 26% overall yield from **2**.

Experimental§

A typical procedure is exemplified by the following reaction sequence. To a solution of **2** (1.484 g, 3.56 mmol) in tetrahydrofuran (THF) (22 cm^3) was added sulphuric acid (0.01 mol dm^{-3}; 6 cm^3) and mercuric sulphate (0.01 g, 0.0356 mmol). The mixture was stirred overnight at room temperature after which

† Physical data for **3**: $[\alpha]_D^{20}$ –13.5 (*c* 1, in $CHCl_3$); ν_{max}(liquid film)/cm^{-1} 3400, 1675 and 1630; δ_H(270 MHz, $CDCl_3$) 1.71 (br, 1 H, exchangeable with D_2O), 3.50 (dd, *J* 9.7 and 5.4, 1 H), 3.59 (dd, *J* 9.7 and 4.9, 1 H), 3.86 (m, 1 H), 4.29 (ddd, *J* 5.9, 5.1 and 1.4, 1 H), 4.43 (A part of ABq, *J* 10.8, 1 H), 4.48 (A part of ABq, *J* 10.8, 1 H), 4.53 (B part of ABq, *J* 10.8, 1 H), 4.63 (B part of ABq, *J* 10.8, 1 H), 6.33 (ddd, *J* 15.9, 7.8 and 1.4, 1 H), 6.78 (dd, *J* 15.9 and 5.9, 1 H), 7.25–7.39 (m, 10 H) and 9.55 (d, *J* 7.8, 1 H).

‡ Physical data for synthetic **8**: m.p. 101.5–102.5 °C (from hexane–AcOEt); $[\alpha]_D^{20}$ –13.0° (*c* 1, in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3280, 1730, 1655 and 1550; δ_H(500 MHz, $CDCl_3$) 0.88 (t, *J* 6.8, 3 H), 1.20–1.40 (m, 22 H), 1.98 (s, 3 H), 2.30 (m, 2 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 4.04 (dd, *J* 11.5 and 4.0, 1 H), 4.30 (dd, *J* 11.5 and 6.0, 1 H), 4.43 (m, 1 H), 5.28 (dd, *J* 7.3 and 6.8, 1 H), 5.39 (ddt, *J* 15.5, 7.3 and 1.3, 1 H), 5.67 (d, *J* 9.0, 1 H) and 5.79 (dt, *J* 15.5 and 6.8, 1 H) [lit. m.p. 101–102 °C (from ether–light petroleum); $[\alpha]_D^{24}$ –11.4° (*c* 1, in $CHCl_3$)]; Y. Ito, M. Sawamura and T. Hayashi, *Tetrahedron Lett.*, 1988, **29**, 239; P. Herold, *Helv. Chim. Acta*, 1988, **71**, 354; H. Shibuya, K. Kawashima, M. Ikeda and I. Kitagawa, *Tetrahedron Lett.*, 1989, **30**, 7205.

§ *J* values in Hz and [α] in 10^{-1} deg cm^2 g^{-1}.

work-up and purification of the crude product [SiO_2, elution with C_6H_6–AcOEt (85:15)] gave **3** (1.102 g, 95%) as an oil.

The mixture of **3** (0.770 g, 2.36 mmol), $NaBH_4$ (0.045 g, 1.18 mmol) and $CeCl_3 \cdot 7H_2O$ (0.879 g, 2.36 mmol) in ethanol (7 cm^3) was stirred for 1 h at room temperature after which work-up and purification [SiO_2, elution with $CHCl_3$–MeOH (98:2)] gave **4a** (0.742 g, 96%) as an oil.

Acetylation of **4a** gave **4d** as an oil in quantitative yield.

To a solution of dodecylmagnesium bromide [prepared from dodecyl bromide (1.32 cm^3, 5.40 mmol) and magnesium (0.13 g, 5.40 mmol)] in THF (15 cm^3) was added a solution (0.1 mol dm^{-3}) of Li_2CuCl_4 in THF (0.36 cm^3, 0.0360 mmol) at −18 °C followed by a solution of **4d** (0.741 g, 1.8 mmol) in THF (5 cm^3). The reaction mixture was stirred for an hour at the same temperature and then quenched with saturated NH_4Cl (aq). Work-up and purification [SiO_2, elution with C_6H_6–AcOEt (95:5)] gave **5b** as an oil (0.567 g, 60%).

For a procedure of the conversion of **5b** into **8**, see ref. 3.

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