Stereoselective syntheses of D-*ribo*- and L-*lyxo*-phytosphingosine

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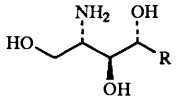
D-*ribo*-Phytosphingosine has been synthesized from D-galactose *via* the key intermediate **5**, itself prepared by stereoselective prop-2-ynylation with prop-2-ynyl bromide and zinc, and L-*lyxo*-phytosphingosine has been synthesized from D-xylose *via* the key intermediate **18**, itself prepared by a CBr_4–Ph_3P–Zn Wittig reaction and debromination. These key chiral intermediates, **5** and **18**, have potential as intermediates for the synthesis of other phytosphigosine derivatives.

Phytosphingosines, a group comprised of the long-chain bases of various glycosphingolipids, together with sphingosine are important membrane components and appear to function as endogenous media for cell recognition and cell regulation.[1] Thus, there is a great deal of interest in studies directed towards their synthesis.[2] Recently, many new glycosphingolipids have been isolated from marine biological sources which exhibit significant antitumour, immunostimulatory, neuritogenic and growth-inhibitory activity *etc.*[3] The structure of the phytosphingosine component incorporated in the ceramide of these glycosphingolipids is quite complex, as shown below.



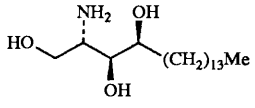
R = $C_{14}H_{29}$ D-*-ribo*-phytosphyngosine **1**

cis -$(CH_2)_xCH{=}CH(CH_2)_yMe$ $x + y = 15$ See Lit.. 3*a*

trans - $MeCH{=}CHC_{11}H_{23}$ See Lit. 3*b*

$(CH_2)_{11}CHMe_2$ *etc.* See Lit. 3*c*

Earlier we described a chiral synthesis of D-*erythro*-sphingosine starting from D-mannitol[4] and a chiron approach to the precursors of all four sphingosine stereoisomers.[5] Here, we report the stereoselective synthesis of D-*ribo*- **1** and L-*lyxo*-phytosphingosine **2**, work directed towards probing the difference in biologically activity caused by changing the configuration of the 4-hydroxy group.

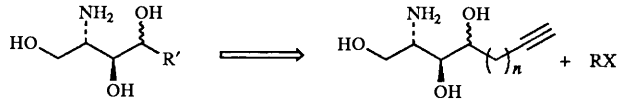


L-*lyxo*-phytosphingosine **2**

Any synthesis of phytosphingosine has to take into consideration the establishment of chiral centres and chain elongation. Since differences in the various phytosphingosines occur mainly in the aliphatic substituent, we wished to find a common chiral intermediate which, by chain elongation *via* an acetylenic intermediate (see Scheme 1) could lead to a general synthesis.

Synthesis of D-*ribo*-phytosphingosine 1 from D-galactose

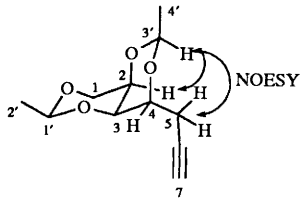
We recently reported that prop-2-ynylation of α-alkoxy aldehydes with prop-2-ynyl bromide and zinc provided mainly the *erythro* product.[6] We exploited this stereoselectivity in the synthesis of **1**. Thus, 2,4-*O*-ethylidene-D-threose **4**, prepared



n = 0 or 1

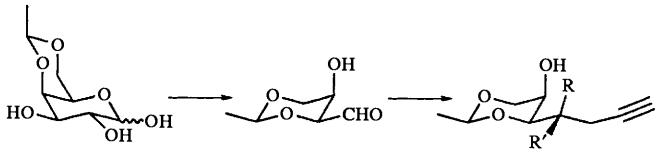
Scheme 1

from D-galactose,[7] was treated with prop-2-ynyl bromide in the presence of zinc to give compound **5** in 85% yield (*erythro*:*threo*, 11.7:1, total yield 89%) after separation by chromatography (Scheme 2). The *erythro* configuration of **5** was confirmed by a 2D NMR spectroscopic study of its acetal **7**.



7

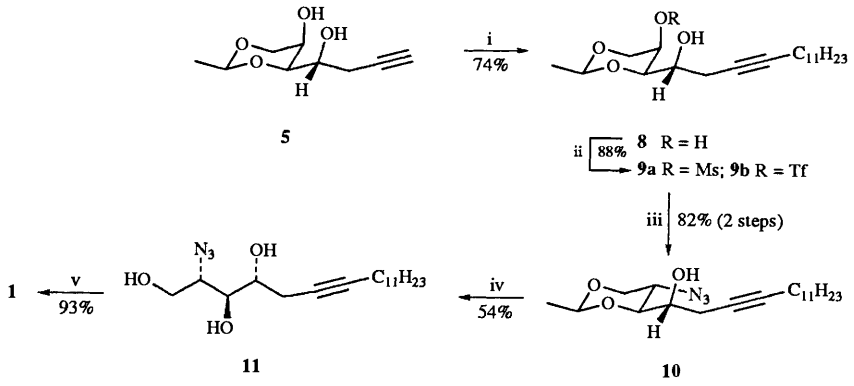
Schmidt *et al.*[8] have reported that in the synthesis of D-*ribo*-phytosphingosine, reaction of 2,4-*O*-benzylidene-D-threose with tetradecylmagnesium bromide gave a 1:1 mixture of the *erythro* product, D-*arabino*-octadecanetetrol and the *threo* product, L-*xylo*-octadecanetetrol.



3 **4** **5** R = OH, R′ = H; **6** R = H, R′ = OH

Scheme 2 *Reagents and conditions:* i, ref. 7; ii, prop-2-ynyl bromide, zinc, DMF–ether, 85% (**5** : **6** = 11.7 : 1)

Substitution at the terminal alkyne of **5** with 1-bromoundecane yielded compound **8** in 74% yield. The regioselective mesylation of the 2-OH was achieved as in the literature[8] in 88% yield, although a 5.5% yield of bis-mesylated product was also isolated. However, treatment of **9a** with sodium azide in DMF afforded compound **10** only in very low yield, probably because of steric effects arising from the prop-2-ynyl chain. Triflation of compound **8** with triflic anhydride at −78 °C occurred with the same regioselectivity and the resulting crude reaction mixture was treated directly with



Scheme 3 *Reagents and conditions:* i, $C_{11}H_{23}Br$, BuLi, THF–HMPA, 74%; ii, for **9a**: MsCl, pyr., −30 °C; for **9b**: Tf_2O, pyr., CH_2Cl_2, −78 °C to 0 °C; iii, NaN_3, DMF, room temp.; iv, 90% CF_3CO_2H; v, 10% Pd–C, MeOH

sodium azide in DMF at room temperature to form the 2-azide **10** and the 2,4-diazide in a ratio of *ca.* 5:1. Deprotection of the azide **10** by treatment with acid and subsequent reduction of the azide and alkyne groups in the presence of Pd–C furnished the natural D-*ribo*-phytosphingosine **1**.

Synthesis of L-*lyxo*-phytosphingosine 2 from D-xylose

For the synthesis of L-*lyxo*-phytosphingosine, 2,3:4,5-di-*O*-isopropylidene-D-xylose[9] **13** was converted into the alkyne **15** by Wittig reaction and debromination with BuLi.[10] Compound **15** was then treated with Grignard reagent to transform[11] regioselectively the terminal acetonide into the *tert*-butyl hydroxyalkyl ether **16** in 52% yield. The free 2-OH of compound **16** was then subjected to mesylation and S_N2 displacement using sodium azide to give compound **18**, which was subsequently treated with 1-bromododecane to afford the terminal alkyne substituted product **19**. Deprotection by acidic treatment and subsequent reduction of both the azide and alkyne groups in the presence of Pd–C furnished L-*lyxo*-phytosphingosine **2**.

Experimental

Melting points are uncorrected. Optical rotations, recorded in units of 10^{-1} deg cm^2 g^{-1}, were measured on a Perkin-Elmer 241 MC Autopol polarimeter. IR spectra were obtained on an IR-440 or Perkin-Elmer 983 spectrophotometer. ^1H NMR spectra were taken at a Varian EM-390, AMX-300 or AMX-600 spectrometer; *J* values given in Hz. Mass spectra were obtained on a HP 5989A spectrometer. Microanalyses were carried out by the Microanalytic Laboratory at the Institute. Flash column chromatography was performed on silica gel (10–40 μm).

(2*R*,3*R*,4*R*)-1,3-*O*-Ethylidenehept-6-yne-1,2,3,4-tetrol 5 and (2*R*,3*R*,4*S*)-1,3-*O*-ethylidenehept-6-yne-1,2,3,4-tetrol 6

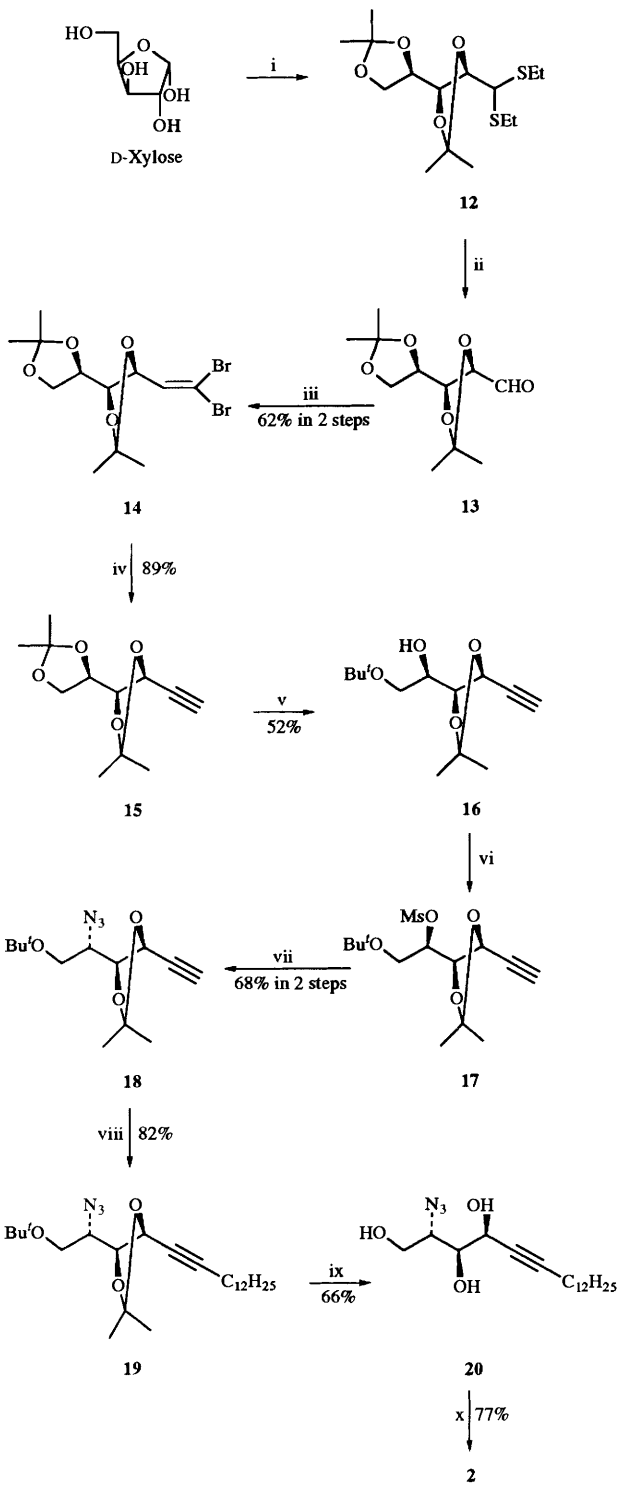
To a stirred mixture of the aldehyde dimer **4** (1.46 g, 10 mmol) and prop-2-ynyl bromide (2.23 cm^3, 25 mmol) in DMF–Et_2O (1:1; 20 cm^3) was slowly added zinc dust (1.97 g, 30 mmol). An exothermic reaction started within a few minutes and brought the mixture to reflux; this was allowed to continue until most of compound **4** had been consumed. The reaction mixture was then poured into saturated aq. NH_4Cl. Work-up followed by chromatography yielded the title compound **5** (1.52 g, 85%) and the corresponding *threo* product **6** (0.13 g). Physical data for compound **5**: mp 128–130 °C; $[\alpha]_D^{20}$ −6.8 (*c* 0.9, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3350, 3290, 2100, 1405, 1170, 1130, 1060 and 910; δ_H($CDCl_3$, 300 MHz) 1.35 (3 H, d, *J* 5.1), 2.05 (1 H, t, *J* 2.6), 2.49 (1 H, ddd, *J* 2.6, 6.3 and 16.7), 2.59–2.66 (3 H, m), 3.62 (1 H, dd, *J* 1.3 and 8.0), 3.80 (1 H, m), 3.86 (1 H, dd, *J* 1.6 and 12.0), 3.97 (1 H, dt, *J* 6.3 and 8.0), 4.09 (1 H, dd, *J* 1.6 and 12.0) and 4.75 (1 H, t, *J* 5.1); *m/z* 186 (M^+), 185 (M^+ − 1), 171 (M^+ − CH_3), 150 (M^+ − $2H_2O$), 125 (M^+ + 1 − H_2O − CH_3CHO), 99, 73 and 42 (100%) (Found: C, 57.7; H, 7.9. Calc. for $C_9H_{14}O_4$: C, 58.05; H, 7.58). Physical data for the *threo* product **6**: mp 127–129 °C; $[\alpha]_D^{20}$ +9.2 (*c* 0.5, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3300, 3250, 2100, 1440, 1250, 1150, 1110 and 1095; δ_H($CDCl_3$, 300 MHz) 1.40 (3 H, d, *J* 5.1), 2.04 (1 H, t, *J* 2.6), 2.50 (1 H, ddd, *J* 2.6, 5.3 and 17.0), 2.61 (1 H, ddd, *J* 2.6, 5.3 and 17.0), 2.86 (2 H, br s), 3.65 (1 H, m), 3.78 (1 H, m), 3.86 (1 H, dd, *J* 0.9 and 12.1), 4.02 (2 H, m) and 4.81 (1 H, q, *J* 5.1); *m/z* 185 (M^+ − 1), 171 (M^+ − CH_3), 125 (M^+ + 1 − H_2O − CH_3CHO), 103, 100, 99, 88 and 73 (100%) (Found: C, 58.2; H, 7.8. Calc for $C_9H_{14}O_4$: C, 58.05; H, 7.58%).

(2*R*,3*R*,4*R*)-1,3:2,4-Di-*O*-ethylidenehept-6-yne-1,2,3,4-tetrol 7

A solution of the alcohol **5** (62 mg, 0.33 mmol), diethyl acetal (0.095 cm^3, 0.66 mmol) and toluene-*p*-sulfonic acid monohydrate (5 mg) in DMF (2 cm^3) was stirred at 40 °C under N_2 for 6 h after which it was diluted with Et_2O and washed successively with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed to give pure title compound **7** (43 mg, 61%); ν_{max}(KBr)/cm^{-1} 3290, 2100, 1420, 1380, 1130, 1100, 940, 890 and 640; δ_H($CDCl_3$, 600 MHz) 1.37 (3 H, d, *J* 5.0, 4′-H), 1.40 (3 H, d, *J* 5.0, 2′-H), 2.07 (1 H, t, *J* 2.7, 7-H), 2.58 (1 H, ddd, J_{57} 2.7, J_{45} = 6.7, J_{55} 17.2, 5-H), 2.71 (1 H, ddd, J_{57} 2.7, J_{45} 2.9, J_{55} 17.2, 5-H), 3.65 (1 H, d, J_{12} 1.9, 2-H), 3.69 (1 H, d, J_{34} 0.9, 3-H), 3.84 (1 H, dd, J_{12} 1.9, J_{11} 12.6, 1-H), 4.10 (1 H, ddd, J_{34} 0.9, J_{45} 2.9, J_{45} 6.7, 4-H), 4.13 (1 H, d, J_{11} 12.6, 1-H), 4.78 (1 H, q, *J* 5.0, 1′-H) and 4.99 (1 H, q, *J* 5.0, 3′-H); irradiation of the resonance at δ 4.12 resulted in collapse of the multiplets at δ 3.84, 3.69, 3.65, 2.71 and 2.58, giving essentially a singlet, singlet, singlet, double doublet (J_{55} 17.2, J_{57} 2.7), and double doublet (J_{57} 2.7, J_{55} 17.2), respectively; irradiation of the resonance at δ 3.84 resulted in collapse of the multiplets at δ 4.12, giving essentially a singlet ^1H-^1H NOESY ($CDCl_3$, 600 MHz). There are correlations between the resonance at δ 4.99 (3′-H) and that at δ 2.71 (5-H) and 3.65 (2-H); there are correlations between the resonance at δ 4.13 (1-H) and that at δ 3.84 (1-H); there are correlations between the resonance at δ 4.78 (1′-H) and that at δ 3.69 (3-H) and 3.84 (1-H); *m/z* 213 (M^+ + 1, 5.4), 212 (M^+, 1.4), 211 (M^+ − 1, 9.3), 197 (M^+ − CH_3, 33.2), 173 (M^+ − C_3H_3, 9.8), 151 (12.0), 129 (19.3) and 87 (100).

(2*R*,3*R*,4*R*)-1,3-*O*-Ethylideneoctadec-6-yne-1,2,3,4-tetrol 8

To a stirred solution of compound **5** (0.85 g, 4.57 mmol) in dry THF (25 cm^3) was added BuLi (2.5 mol dm^{-3} in hexane; 14.98 mmol) dropwise at −40 °C followed after 30 min, by a solution of $BrC_{11}H_{23}$ (1.52 cm^3, 6.81 mmol) in HMPA (4 cm^3). Stirring was continued for 1 h at the same temperature and then



Scheme 4 *Reagents and conditions:* i, 2 steps according to known method[9]; ii. HgO–BF_3·OEt, THF–H_2O; iii, CBr_4, PPh_3, Zn, CH_2Cl_2; iv, BuLi, THF; v, MeMgI, Et_2O–PhMe, reflux; vi, MsCl, pyridine, DMAP, CH_2Cl_2; vii, NaN_3, DMF, Bu_4NI, 110 °C; viii, $C_{12}H_{25}Br$, LDA, THF HMPA; ix, CF_3CO_2H; x, 10% Pd–C, MeOH

overnight at room temperature. After this the reaction mixture was diluted with Et_2O and saturated aq. NH_4Cl and the organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue gave the title compound **8** as a solid (1.15 g, 74%), mp 61–62 °C; $[\alpha]_D^{20}$ +2.8 (*c* 1.1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3300, 1470, 1420, 1340, 1140, 1100, 1060 and 980; δ_H($CDCl_3$, 300 MHz) 0.88 (3 H, t, *J* 6.9), 1.34 (3 H, d, *J* 5.0), 1.49–1.26 (18 H, m), 2.17 (2 H, m, 8-H), 2.49 (4 H, m, 5-H, 2 OH), 3.60 (1 H, m, 2-H), 3.81 (1 H, dd, *J* 1.5 and 3.0, 3-H), 3.85 (1 H, dd, *J* 0.9 and 11.8, 1′-H), 3.92 (1 H, m, 4-H), 4.09 (1 H, dd, *J* 2.0 and 11.9, 1-H) and 4.75 (1 H, q, *J* 5.0, CH_3CH); *m/z* 339 (M^+ − 1, 2.6), 325 (M^+ − CH_3, 2.5), 279 (3.3), 253 (9.3), 235 (22.4), 147 (32.5) and 103 (100) (Found: C, 70.6; H, 10.7. Calc. for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66%).

(2*R*,3*R*,4*R*)-2-*O*-Methylsulfonyl-1,3-*O*-ethylideneoctadec-6-yne-1,2,3,4-tetrol 9a and (2*R*,3*R*,4*R*)-2,4-di-*O*-methylsulfonyl-1,3-*O*-ethylideneoctadec-6-yne-1,2,3,4-tetrol

To a solution of **8** (100 mg, 0.29 mmol) in dry pyridine (4 cm^3) at −30 °C was added methanesulfonyl chloride (0.025 cm^3, 0.29 mmol). The mixture was stirred for 12 h at −30 °C and then warmed to room temperature. The pyridine was removed by evaporation with toluene and the residue was purified by flash column chromatography to give title compound **9a** (108 mg, 88%) and 2,4-dimethylated product (8 mg). Physical data for compound **9a**: $[\alpha]_D^{20}$ −22.9 (*c* 1.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3500, 1420, 1375, 1180, 1085, 1060, 920 and 760; δ_H($CDCl_3$, 300 MHz) 0.88 (3 H, t, *J* 6.4), 1.26–1.50 (18 H, m), 1.37 (3 H, d, *J* 5.1, CH_3CH), 2.17 (2 H, m, 8-H), 2.49 (1 H, m, 5-H), 2.64 (1 H, m, 5′-H), 3.17 (3 H, s, CH_3SO_2), 3.71 (1 H, dd, *J* 1.3 and 9.1, 3-H), 3.82 (1 H, m, 4-H), 3.93 (1 H, dd, *J* 0.9 and 13.2, 1-H), 4.38 (1 H, dd, *J* 1.5 and 13.3, 1′-H), 4.76 (1 H, q, *J* 5.1, CH_3CH) and 4.81 (1 H, d, *J* 1.3, 2-H); *m/z* 419 (M^+ − 1, 4.8), 401 (M^+ − H_2O + 1, 1.7), 309 (5.5), 279 (9.7), 223 (23.4), 181 (37.2), 100 (100) and 85 (71.6). Physical data for the 2,4-dimethylated product: mp 110–112 °C; $[\alpha]_D^{20}$ −43.4 (*c* 0.4, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1340, 1180, 1090, 1010 and 970; δ_H($CDCl_3$, 300 MHz) 0.88 (3 H, t, *J* 6.8), 1.26–1.52 (18 H, m), 1.40 (3 H, d, *J* 5.1, CH_3CH), 2.17 (2 H, m, 8-H), 2.72 (1 H, m, 5-H), 2.92 (1 H, m, 5′-H), 3.16 (3 H, s, CH_3SO_2), 3.21 (3 H, s, CH_3SO_2), 3.90 (1 H, dd, *J* 0.9 and 13.5, 1-H), 4.10 (1 H, dd, *J* 1.5 and 8.4, 3-H), 4.56 (1 H, dd, *J* 1.7 and 13.5, 1′-H), 4.73 (1 H, d, *J* 1.2, 2-H) and 4.81 (2 H, m, CH_3CH, 4-H); *m/z* 495 (M^+ − 1, 3.3), 417 (M^+ − CH_3SO_2, 3.9), 401 (48.1), 387 (2.9), 341 (M^+ − $C_{11}H_{23}$, 4.1), 305 (11.6), 277 (25.5) and 69 (100).

(2*S*,3*S*,4*R*)-2-Azido-1,3-*O*-ethylideneoctadec-6-yne-1,3,4-triol 10 and (2*S*,3*R*,4*S*)-2,4-diazido-1,3-*O*-ethylideneoctadec-6-yne-1,3-diol

A solution of compound **8** (700 mg, 2.06 mmol) in dry CH_2Cl_2 (20 cm^3) was cooled to −78 °C and diluted with dry pyridine (1 cm^3). A solution of trifluoromethanesulfonic anhydride (0.36 cm^3, 2.16 mmol) in anhydrous CH_2Cl_2 (10 cm^3) was added to the mixture over 40 min under N_2 after which the mixture was warmed to 0 °C and stirred at that temperature for an additional 1 h. It was then neutralized at 0 °C with sat. aq. $NaHCO_3$. The organic layer was processed in the usual way and after co-evaporation with toluene, the residue was used directly in the next step.

To a solution of the crude compound **9b** in dry DMF (10 cm^3) was added sodium azide (1.62 g, 24.91 mmol). The mixture was stirred at room temperature overnight after which it was diluted with Et_2O, washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography to yield title compound **10** (616 mg, 82% in 2 steps) and the 2,4-diazide (123 mg). Physical data for compound **10**: $[\alpha]_D^{20}$ +15.7 (*c* 2.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3400, 2100, 1460, 1405, 1280, 1135, 1090 and 1030; δ_H($CDCl_3$, 300 MHz) 0.88 (3 H, t, *J* 6.4), 1.26–1.52 (18 H, m), 1.33 (3 H, d, *J* 5.2, CH_3CH), 2.17 (2 H, m, 8-H), 2.36 (1 H, br s, OH), 2.56 (2 H, m, 5-H), 3.47 (1 H, dd, *J* 10.6 and 10.6), 3.53 (1 H, dd, *J* 4.0 and 9.5), 3.62 (1 H, dd, *J* 4.9 and 10.1), 3.92 (1 H, ddd, *J* 4.0, 6.4 and 10.4), 4.22 (1 H, dd, *J* 5.0 and 10.8) and 4.66 (1 H, q, *J* 5.2); *m/z* 366 (M^+ + 1, 6.4), 365 (M^+, 5.1), 350 (M^+ − CH_3, 0.9), 336 (M^+ − N_2 − 1, 2.1), 322 (M^+ − CH_3CHO + 1, 3.0), 294 (6.5), 264 (17.7) and 224 (61.4) (Found: C, 66.1; H, 9.8;

N, 11.4. Calc. for $C_{20}H_{35}N_3O_3$: C, 65.72; H, 9.65; N, 11.50%). Physical data for the 2,4-diazide: $[\alpha]_D^{20}$ +8.3 (*c* 0.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 2100, 1460, 1410, 1380, 1250, 1160, 1105 and 1040; δ_H($CDCl_3$, 300 MHz) 0.88 (3 H, t, *J* 6.8), 1.27–1.46 (18 H, m), 1.35 (3 H, d, *J* 5.0, CH_3CH), 2.18 (2 H, m, 8-H), 2.61 (2 H, m, 5-H), 3.49 (1 H, dd, *J* 10.7 and 10.8), 3.60 (1 H, dd, *J* 9.8 and 10.2), 3.71 (1 H, m), 3.91 (1 H, dd, *J* 5.4 and 5.4), 4.25 (1 H, ddd, *J* 5.6, 10.6 and 16.2) and 4.66 (1 H, q, *J* 5.0); *m*/*z* 391 (M^+ + 1, 1.3), 348 ($M^+ - N_2 - CH_3$ + 1, 13.1), 320 ($M^+ - 2N_2 - CH_3$ + 1, 10.1), 304 (4.7), 276 (9.9), 263 (11.0), 149 (17.1) and 55 (100).

(2*S*,3*S*,4*R*)-2-Azidooctadec-6-yne-1,3,4-triol 11

The acetal **10** (70 mg, 0.19 mmol) was treated with 90% CF_3CO_2H (5 cm^3) at room temperature for 3 h after which the mixture was evaporated to dryness. The residue was purified by column chromatography on silica gel to give title compound **11** (35 mg, 54%); $[\alpha]_D^{20}$ +17.2 (*c* 0.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3400, 2100, 1470, 1380, 1200, 1130, 1080 and 900; δ_H($CDCl_3$, 300 MHz) 0.88 (3 H, t, *J* 6.2), 1.45–1.27 (18 H, m), 2.15 (2 H, m, 8-H), 2.59 (2 H, m, 5-H) and 3.75–4.20 (8 H, m); after addition of D_2O, the multiplet at δ 3.75–4.20 ppm collapsed to 5 H; *m*/*z* 295 ($M^+ - N_2 - CH_3$ − 1, 0.9), 253 ($M^+ - HOCH_2N_3$, 1.1), 235 ($M^+ - HOCH_2N_3 - H_2O$, 1.8), 223 (18.9), 183 (9.1), 149 (71.5), 129 (56.6) and 43 (100).

(2*S*,3*S*,4*R*)-2-Aminooctadecane-1,3,4-triol 1

10% Pd–C (5 mg) was added to a solution of the azide **11** (30 mg, 0.088 mmol) in MeOH (5 cm^3). After the reaction vessel had been purged with hydrogen, the mixture was stirred at room temperature overnight, filtered, and the filtrate concentrated. Purification of the residue on a silica gel column eluted with $CHCl_3$ – MeOH – 2 mol dm^{-3} aq. NH_3 (100:10:0.5) yield D-*ribo*-phytosphingosine **1** (26 mg, 93%), mp 98–100 °C; $[\alpha]_D^{20}$ +8.9 (*c* 0.6, pyridine) [lit.,[8] mp 95 °C; $[\alpha]_D^{20}$ +8.5 (*c* 1, pyridine); lit.,[2a] mp 98–101 °C; $[\alpha]_D^{20}$ +8.7 (*c* 0.8, pyridine)]; ν_{max}(KBr)/cm^{-1} (FT IR) 3400, 1466, 1384, 1205, 1131 and 1072; δ_H([$^2H_6$]-DMSO, 300 MHz) 0.85 (3 H, *J* 6.8), 1.24 (24 H, m), 1.58 (2 H, m), 3.05 (2 H, m), 3.39 (6 H, m) and 3.54 (2 H, m); *m*/*z* (FAB MS) 340 ($M^+ + Na^+$), 318 (M^+ + 1) and 300 ($M^+ - CH_3$).

(2*R*,3*R*,4*S*)-6,6-Dibromo-1,2:3,4-di-*O*-isopropylidenehex-5-ene-1,2,3,4-tetrol 14

Red mercury(II) oxide (2.57 g, 11.9 mmol), boron trifluoride–diethyl ether (1.43 cm^3, 11.9 mmol) and 85% aq. THF (10 cm^3) were stirred vigorously in a flask. A solution of the dithioacetal **12** (2.0 g, 5.95 mmol) in THF (6 cm^3) was added over the course of 30 min under nitrogen to the mixture which was then stirred for 1 h after the addition was complete. During this period the red mercury(II) oxide gradually dissolved. Diethyl ether (60 cm^3) was added to the reaction mixture which was then neutralized with anhydrous sodium carbonate (4.2 g). The salt was filtered off, and the filtrate concentrated to give compound **13** as a syrup. This material was immediately used in the next step.

Triphenylphosphine (6.24 g, 23.8 mmol) was added at 0 °C to a solution of carbon tetrabromide (3.94 g, 11.9 mmol) and zinc dust (0.39 g, 5.95 mmol) in CH_2Cl_2 (35 cm^3). The reaction mixture was stirred at 0 °C for 1 h after which the crude aldehyde was added at 0 °C to it with vigorous stirring. After being stirred for 2 h at 0 °C, the mixture was poured into stirred light petroleum (400 cm^3), and the resulting precipitate was filtered off through a cotton plug and the filtrate concentrated under reduced pressure. The residue was chromatographed on silica gel to afford the title compound **14** (1.43 g, 62% in 2 steps); $[\alpha]_D^{20}$ −25.50 (*c* 0.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3400, 1630, 1450 and 1380; δ_H($CDCl_3$, 90 MHz) 1.50 (12 H, s), 3.80 (2 H, m), 4.12 (2 H, m), 4.56 (1 H, t, *J* 8.9) and 6.48 (1 H, d, *J* 8.8); *m*/*z* 369 ($M^+ - CH_3$, 4.8), 313 (9.3), 285 (3.1), 256 (19.8), 227 (9.9), 175 (18.2), 101 (80.9) and 43 (100) (Found: C, 37.6; H, 4.7. Calc. for $C_{12}H_{18}Br_2O_4$: C, 37.33; H, 4.70%).

(2*R*,3*R*,4*S*)-1,2:3,4-Di-*O*-isopropylidenehex-5-yne-1,2,3,4-tetrol 15

A butyllithium solution (2.5 mol dm^{-3}; 6.6 mol) was added dropwise at −78 °C to a solution of compound **14** (1.05 g, 3.0 mmol) in THF (20 cm^3). The mixture was stirred at the same temperature for 2 h and then allowed to warm to room temperature. The mixture was poured into cold brine to which ether was then added. After the mixture had been partitioned, the aqueous layer was again extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated and the residue was chromatographed to give compound **15** as a white solid (0.547 g, 89%); mp 48 °C; $[\alpha]_D^{20}$ −28.1 (*c* 0.22, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3250, 2100, 1460, 1380 and 1070; δ_H($CDCl_3$, 90 MHz) 1.40, 1.49 (12 H, 3 s), 2.56 (1 H, d, *J* 1.8), 4.03 (4 H, m) and 4.46 (1 H, dd, *J* 1.8 and 7.7); *m*/*z* 212 (M^+, 5.2), 211 ($M^+ - 1$, 44.0), 153 (17.8), 125 (13.3), 101 (46.5) and 43 (100) (Found: C, 63.6; H, 8.2. Calc. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02%).

(2*R*,3*R*,4*S*)-1-*tert*-Butyl-3,4-*O*-isopropylidenehex-5-yne-1,2,3,4-tetrol 16

Several drops of a solution of MeI (1.26 g, 8.85 mmol) in ether (5 cm^3) was added to magnesium (0.22 g, 8.85 mmol) in ether (5 cm^3). Once the reaction had been initiated by gentle heating, the mixture was cooled with a cold-water bath and the remaining MeI in ether was slowly added to it. A solution of the acetonide **15** (0.40 g, 1.77 mol) in toluene (10 cm^3) was added to the reaction mixture which was then stirred at 60 °C for 12 h before being poured into saturated aqueous NH_4Cl. Work-up followed by chromatography gave title compound **16** as a colourless oil (0.23 g, 52%); $[\alpha]_D^{20}$ −16.4 (*c* 0.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3450, 3300, 2100, 1460, 1380 and 1060; δ_H($CDCl_3$, 300 MHz) 1.02 (9 H, s), 1.35 (3 H, s), 1.45 (3 H, s), 2.07 (1 H, d, *J* 2.1), 3.31 (1 H, dd, *J* 6.0 and 8.7), 3.48 (1 H, dd, *J* 6.5 and 8.7), 3.80 (1 H, dt, *J* 3.4 and 6.2), 4.31 (1 H, dd, *J* 3.3 and 7.2) and 4.95 (1 H, dd, *J* 2.1 and 7.2); *m*/*z* 243 (M^+ + 1, 6.8), 227 ($M^+ - CH_3$, 5.9), 187 (100), 171 (26.1) and 129 (32.9) (Found: C, 64.6; H, 9.2. Calc. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15%).

(2*R*,3*R*,4*S*)-1-*tert*-Butyl-2-*O*-methylsulfonyl-3,4-*O*-isopropylidenehex-5-yne-1,2,3,4-tetrol 17

To a solution of compound **16** (160 mg, 0.66 mmol) in dry CH_2Cl_2 (10 cm^3) was added pyridine (0.13 cm^3, 1.58 mmol) and MsCl (0.064 cm^3, 0.825 mmol). The mixture was stirred at room temperature overnight after which work-up furnished the crude mesylate **17**. An analytical sample was obtained by flash chromatography; ν_{max}(film)/cm^{-1} 3250, 2950, 2100, 1460, 1360 and 1070; δ_H($CDCl_3$, 300 MHz) 1.22 (9 H, s), 1.46, 1.50 (6 H, 2 s), 2.56 (1 H, d, *J* 2.2), 3.14 (3 H, s), 3.60 (1 H, dd, *J* 4.3 and 10.2), 3.70 (1 H, dd, *J* 7.5 and 10.2), 4.15 (1 H, m), 4.24 (1 H, dd, *J* 4.1 and 7.2) and 4.73 (1 H, dd, *J* 2.2 and 7.1); *m*/*z* 281 (27.6), 255 (8.2), 233 (12.5), 225 ($M^+ - CH_3SO_3$, 8.4), 199 (94.8), 183 (25.2), 113 (100) and 95 (35.9).

(2*S*,3*S*,4*S*)-2-Azido-1-*tert*-butyl-3,4-*O*-isopropylidenehex-5-yne-1,3,4-triol 18

To a solution of crude compound **17** in DMF (20 cm^3) were added sodium azide (0.12 g, 1.98 mmol) and Bu_4NI (40 mg). After being stirred at 110 °C for 40 h, the mixture was diluted with ether and successively washed with water and brine, dried ($MgSO_4$) and concentrated. Purification of the residue on a silica gel column yielded the azide **18** (120 mg, 68% in 2 steps); $[\alpha]_D^{20}$ −20.6 (*c* 0.33, $CHCl_3$); ν_{max}(film)/cm^{-1} 3300, 2100, 1460, 1380 and 1050; δ_H($CDCl_3$, 300 MHz) 1.22 (9 H, s), 1.46, 1.50 (6

H, 2 s), 2.55 (1 H, d, *J* 2.0), 3.50 (1 H, m), 3.63 (2 H, d, *J* 4.0), 4.20 (1 H, dd, *J* 5.5 and 6.3) and 4.68 (1 H, dd, *J* 2.1 and 6.4); *m/z* 251 ($M^+ - CH_3 - 1$, 0.7), 239 ($M^+ - N_2$, 5.6), 224 (0.9), 196 (5.3), 183 (14.7), 108 (40.3) and 125 (100) (Found: C, 58.1; H, 7.7; N, 15.7. Calc. for $C_{13}H_{21}N_3O_3$: C, 58.41; H, 7.92; N, 15.72).

(2*S*,3*S*,4*S*)-2-Azido-1-*tert*-butyl-3,4-*O*-isopropylideneoctadec-5-yne-1,3,4-triol 19

To a solution of Pr^i_2NH (0.12 cm^3, 0.84 mmol) in THF (10 cm^3), was added BuLi (2.5 mol dm^{-3}; 0.84 mmol) at −20 °C under N_2, and the resulting solution was stirred for 30 min at the same temperature. To this LDA solution at −78 °C, a solution of compound **18** (160 mg, 0.60 mmol) in THF (5 cm^3) was added dropwise. After the mixture had been stirred for 30 min, a solution of 1-bromododecane (0.22 cm^3, 0.90 mmol) in HMPA (2 cm^3) was added to it and stirring was continued first at −78 °C for 2 h and then at −78 °C to room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl after which the aqueous layer was extracted with ether. The combined extracts were washed with brine, dried and evaporated and the residue was chromatographed to give title compound **19** (214 mg, 82%); $[\alpha]_D^{20}$ −30.8 (*c* 0.17, $CHCl_3$); ν_{max}(film)/cm^{-1} 2100, 1465, 1380, 1200 and 1060; δ_H($CDCl_3$, 300 MHz) 0.88 (3 H, t, *J* 6.7), 1.23 (29 H, m), 1.44, 1.48 (6 H, 2 s), 2.19 (2 H, m), 3.56 (1 H, dd, *J* 7.3 and 9.5), 3.59 (2 H, d, *J* 3.8), 4.08 (1 H, dd, *J* 5.3 and 6.8) and 4.65 (1 H, m); *m/z* 292 ($M^+ - Bu^tOCH_2CHN_3$, 67.5), 277 (61.3), 263 (8.4), 230 (7.1), 201 (10.1), 137 (22.6), 121 (18.4) and 43 (100).

(2*S*,3*S*,4*S*)-2-Azidooctadec-5-yne-1,3,4-triol 20

Compound **19** (200 mg, 0.46 mmol) was treated with CF_3CO_2H (5 cm^3) at room temperature after which for 3 h the mixture was evaporated to dryness. The residue was purified by column chromatography on silica gel to give compound **20** (103 mg, 66%); $[\alpha]_D^{20}$ +50.95 (*c* 0.12, $CHCl_3$); ν_{max}(film)/cm^{-1} 3350, 2200, 2100, 1460 and 1170; δ_H($CDCl_3$, 300 MHz) 0.88 (3 H, t, *J* 6.5), 1.27 (20 H, m), 2.23 (2 H, m), 3.72 (2 H, m), 3.95 (2 H, m) and 4.52 (1 H, dt, *J* 1.9 and 3.6); *m/z* 340 ($M^+ + 1$, 75.5), 338 ($M^+ - 1$, 4.8), 312 ($M^+ - N_2 + 1$, 7.6), 294 (12.6), 279 (9.7), 264 (11.7), 172 (34.6) and 70 (100) (Found: *m/z* 338.2480. Calc. for $C_{18}H_{32}N_3O_3$: *m/z* 338.2444).

(2*S*,3*S*,4*S*)-2-Aminooctadecane-1,3,4-triol 2

Compound **20** (18 mg, 0.053 mmol) was hydrogenated by the procedure described for compound **11** to give L-*lyxo*-phytosphingosine **2** (13 mg, 77%), mp 96–98 °C; $[\alpha]_D^{20}$ −7.1 (*c* 0.4, pyridine) [lit.,[8] mp 95 °C; $[\alpha]_D^{20}$ −6.20 (*c* 1, pyridine)]; ν_{max}(KBr)/cm^{-1} (FT IR) 3332, 1465 and 1072; δ_H([$^2H_6$]-DMSO, 300 MHz) 0.86 (3 H, *J* 6.9), 1.24 (24 H, m), 1.39 (2 H, m), 3.08 (2 H, m), 3.36 (6 H, m) and 3.68 (2 H, m); *m/z* (FAB MS) 318 ($M^+ + 1$), 316 ($M^+ - 1$) and 300 ($M^+ - H_2O + 1$).

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