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SYNTHESIS OF D-*ribo*- AND L-*lyxo*-PHYTOSPHINGOSINE: TRANSFORMATION INTO THE CORRESPONDING LACTOSYL-CERAMIDES*,†

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ABSTRACT

2,4-*O*-Benzylidene-D-threose (**2**) reacted with tetradecylmagnesium bromide to give the D-*arabino*- and the L-*xylo*-octadecanetetrol derivatives **3a** and **3x** as a readily separable mixture. Each of these compounds was transformed, *via* regioselective mesylation, azide displacement, benzylidene cleavage, and azide reduction, into D-*ribo*- (**1r**) and L-*lyxo*-phytosphingosine (**1l**), respectively. 3,4-*O*-Isopropylidenation of the intermediate azido derivatives **7r** and **7l** afforded the 1-*O*-glycosyl acceptors 2-azido-3,4-*O*-isopropylidene-D-*ribo*-1,3,4-octadecanetriol (**8r**) and 2-azido-3,4-*O*-isopropylidene-L-*lyxo*-1,3,4-octadecanetriol (**8l**), respectively. With the trichloroacetimidate-activated lactosyl donor **9**, the expected glycosides 2-azido-1-*O*-(2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-lactosyl)-3,4-*O*-isopropylidene-D-*ribo*- and -L-*lyxo*-1,3,4-octadecanetriol (**10r** and **10l**) were obtained, which were conveniently transformed into the corresponding unprotected glycosphingolipids **14r** and **14l**

INTRODUCTION

D-*ribo*-Phytosphingosine (**1r**), a constituent of glycosphingolipids, is widespread in Nature[1]. After its first isolation[2] and structural elucidation[3], it was demonstrated to be present not only in the membranes of plants but also in mammalian tissues[4]. Several syntheses of the racemate have been published[5,6]. Starting from natural D-*erythro*-sphingosine, a stereoselective synthesis of the D-*ribo* isomer was claimed[7], which was later shown to also give other isomers[8]. The *N*-benzoyl derivative of the D-*ribo* isomer was obtained from 2-amino-2-deoxy-D-glucose and D-galactose *via* lengthy routes[9]. A recently reported synthesis starting from D-glyceraldehyde required several diastereospecific manipulations of functional groups[10].

We have developed[11] an efficient methodology for the synthesis of sphingos-

*Dedicated to Professor Hans Paulsen.
†Glycosylimidates, Part 32. For Part 31, see ref. 14; Synthesis of Sphingosines, Part 3. For Part 2, see ref. 11.

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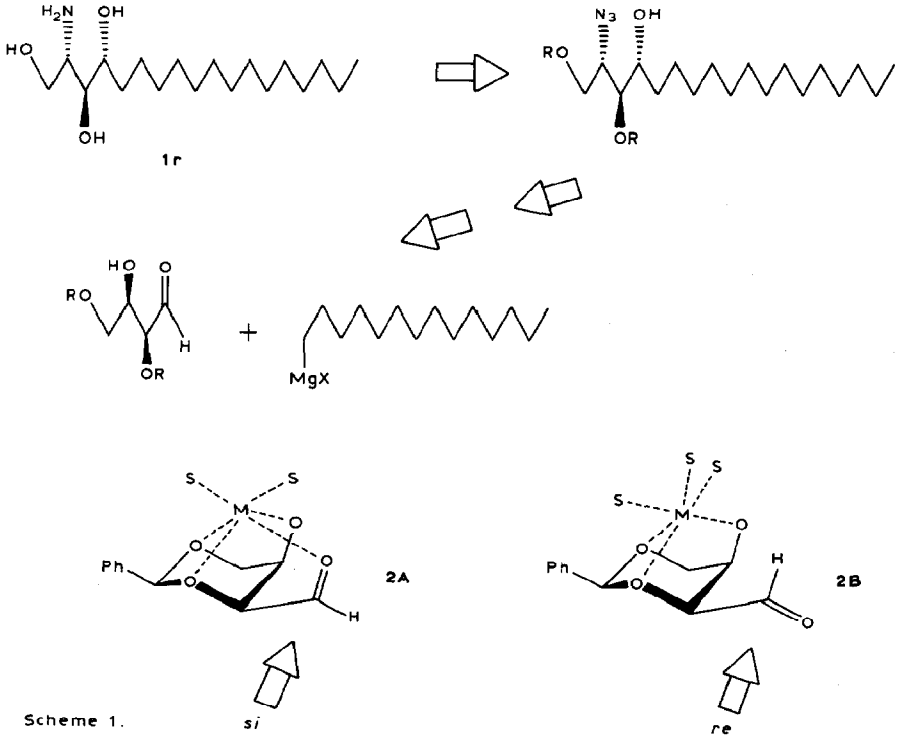
ine on which a new methodology for the synthesis of glycosphingolipids could be based[12–14]. 2,4-Disubstituted derivatives of D-threose and the azido derivative of D-*erythro*-sphingosine play important roles in these methodologies[11–14]. Inspection of the structure of D-*ribo*-phytosphingosine and similar disconnection between C-4 and C-5 indicates that the same 2,4-disubstituted D-threose derivative and a simple Grignard reagent offer a short route to the required D-*ribo*-aminotriol structure of **1r**. The intermediate azido derivative should be a convenient precursor for versatile syntheses of phytosphingosine-containing glycosphingolipids[15,16] as will be demonstrated below.

RESULTS AND DISCUSSION

A conveniently accessible 2,4-disubstituted D-threose is the 2,4-*O*-benzylidene derivative **2**[11,17], which is in equilibrium with a dimeric form[18]. Similarly, the corresponding 2,4-*O*-isopropylidene derivative could be used, which can be readily obtained from D-xylose[19]. Reaction of excess of the Grignard reagent obtained from tetradecyl bromide and magnesium with **2** in dry tetrahydrofuran at 60° afforded in good yield a 1:1 mixture of the D-*arabino*- (**3a**) and L-*xylo*-octadecanetetrol (**3x**) derivatives. The reaction could be performed on a large scale and the products could be separated easily, therefore making the required diastereoisomer



Scheme 1.

TABLE I

THE FORMATION OF **3a** and **3x** FROM **2**[a]

Reaction conditions *Solvent*	*Catalyst*	*Temperature (degrees)*	*Yield (%)*	*Ratio* **3a:3x**
THF[b]		60	71	1:1
THF		0	75	1:2
Et_2O		25	75	1:1
Et_2O	HMPT[c]	25	60	1:5
Et_2O	TMEDA[d]	0	60	1:10
THF	$ZnCl_2$	25	53	only **3x**
THF–Et_2O (1:1)	$CuBr \cdot SMe_2$	−40	74	1:20
THF–Et_2O (1:1)	$TiCl_4$	−40	76	only **3x**

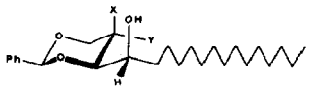
[a]For details, see Experimental. [b]Tetrahydrofuran [c]Hexamethylphosphoric triamide. [d]*N,N,N',N'*-Tetramethylethylenediamine.

3a readily accessible. Reactions at lower temperatures or in ether did not lead to a dramatic change in the ratio of **3a** and **3x** (see Table I). However, the addition of complexing agents, or the copper bromide–dimethyl sulfide complex, or titanium tetrachloride as catalyst led to preferential or exclusive formation of the L-*xylo* isomer **3x**. The reason for this seems to be *si*-attack due to the formation of complex **2A** rather than the preferred *re*-attack in complex **2B**.

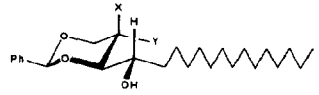
The required 2-*O*-activation of **3a** and **3x** for the azide displacement took an especially advantageous course. Independent of the configuration at C-4, increased reactivity for HO-2 was observed, thus providing with methanesulfonyl chloride in pyridine the desired 2-*O*-mesyl derivatives **4a** and **4x**, respectively. Likewise, pivaloylation of **3x** yielded **5x**. This favourable chemoselectivity is attributed to the oxygen atoms of the 1,3-dioxane ring causing increased nucleophilicity of HO-2 through the accumulation of lone-pair orbitals and/or through higher acidity because of hydrogen bonding. Treatment of **4a** and **4x** with sodium azide in *N,N*-dimethylformamide at 80° afforded the D-*ribo*- and the D-*lyxo*-azido derivatives (**6r** and **6l**), respectively, which were deprotected by acid treatment to give **7r** and **7l**, respectively. Subsequent azide reduction in **7r** with lithium aluminium hydride furnished the natural D-*ribo*-phytosphingosine (**1r**). Likewise L-*lyxo*-phytosphingosine (**1l**) was obtained from **7l**. The physical constants reported for **1r** accord with those found here (see Experimental).

According to the earlier methodology[12–14] for the synthesis of glycosphingolipids, the azido-phytosphingosine **7r** was first reacted with 2,2-dimethoxypropane–toluene-*p*-sulfonic acid to give the 3,4-*O*-isopropylidene derivative **8r**, which was useful for 1-*O*-glycosylation reactions. Thus, with the lactosyl donor **9**[20], the 1-*O*-(β-lactosyl)phytosphingosine derivative **10r** was obtained in good yield under boron trifluoride etherate catalysis. Azido group reduction with the nickel chloride–sodium borohydride system[22] then afforded the amino derivative **11r**, which is structurally related to the psychosines. *N*-Palmitoylation of **11r** with palmitoyl

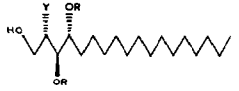
chloride in tetrahydrofuran provided the glycosphingolipid derivative **12r**, which was deacetylated with methanolic sodium methoxide to give **13r** and subsequently deisopropylidenated with trifluoroacetic acid to furnish the desired glycosphingolipid **14r** in a convenient five-step route from **8r**. Likewise the L-*lyxo*-glycosphingolipid **14l** was obtained from the azido-phytosphingosine **7l** *via* **8l**, **10l**, **11l**, **12l**, and **13l**.



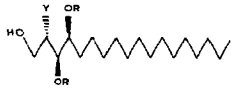
3e X = OH, Y = H
4e X = OMs, Y = H
X = OPiv, Y = H
6r X = H, Y = N_3



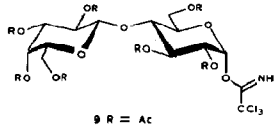
3x
4x
5x
6l



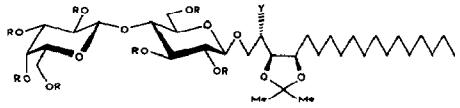
7r Y = N_3, R = H
1r Y = NH_2, R = H
8r Y = N_3, R = Me_2C



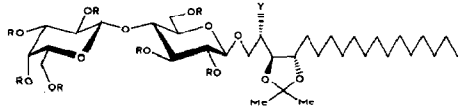
7l
1l
8l



9 R = Ac

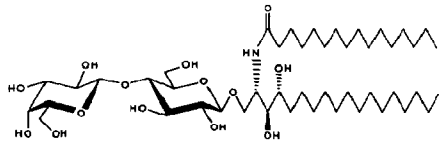


10r Y = N_3, R = Ac
11r Y = NH_2, R = Ac
12r Y = NH–CO–$(CH_2)_{14}$–CH_3, R = Ac
13r Y = NH–CO–$(CH_2)_{14}$–CH_3, R = H

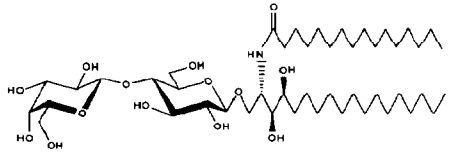


8 = D-*arabino*
x = L-*xylo*
r = D-*ribo*
l = L-*lyxo*

10l
11l
12l
13l



14r



14l

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 MC polarimeter. ^{1}H-N.m.r. spectra (internal Me_4Si) were recorded for solutions in the solvents noted with a Bruker WM 250 Cryospec instrument. R_F values refer to t.l.c. performed on silica gel (Merck). Column chromatography was performed under normal pressure with silica gel (Merck, 70–230 mesh ASTM and 230–400 mesh ASTM for flash chromatography) and under elevated pressure with LiChroprep Si 60 (Merck, 15–25 μm). The b.p. of the light petroleum was 40–70°.

*1,3-*O*-Benzylidene-*D-arabino- (**3a**) *and* -D-xylo-*1,2,3,4-octadecanetetrol* (**3x**). — Magnesium (1.8 g, 74 mmol) in dry tetrahydrofuran (20 mL) was treated under nitrogen with *n*-tetradecyl bromide (20.6 g, 74 mmol) to provide the required Grignard reagent. The mixture was heated to 60°, a solution of 2,4-*O*-benzylidene-D-threose[11,17] (**2**; 5.0 g, 24 mmol) in dry tetrahydrofuran (20 mL) was added, and the mixture was stirred until t.l.c. showed no remaining **2**. Treatment with ice and ammonium chloride gave, with additional tetrahydrofuran, two layers. The aqueous phase was washed with tetrahydrofuran (3 × 20 mL), and the organic phases were combined, dried (Na_2SO_4), and concentrated. Column chromatography of the residue (1:1 light petroleum–ethyl acetate) yielded **3a** (3.4 g, 35%) and **3x** (3.6 g, 36%).

Compound **3a** had m.p. 117°, R_F 0.32. ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 7.53–7.36 (m, 5 H, Ph), 5.59 (s, 1 H, C*H*Ph), 4.27 (dd, 1 H, $J_{1,1'}$ 12.2, $J_{1,2}$ 1.8 Hz, H-1), 4.03 (dd, 1 H, $J_{1,1'}$ 12.2, $J_{1',2}$ 1.8 Hz, H-1′), 3.91–3.87 (m, 2 H, H-2,3), 3.71–3.68 (m, 1 H, H-4), 3.26 (d, 1 H, $J_{4,HO-4}$ 9 Hz, HO-4), 2.33 (d, 1 H, $J_{2,HO-2}$ 4.5 Hz, HO-2), 1.70–1.60 (m, 2 H, H-5,5), 1.45–1.10 (m, 24 H, 12 CH_2), 0.88 (t, 3 H, 6.2 Hz, CH_3).

Anal. Calc. for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.86; H, 10.23.

Compound **3x** had m.p. 71°, R_F 0.79. ^{1}H-N.m.r. data: δ 7.53–7.38 (m, 5 H, Ph), 5.60 (s, 1 H, C*H*Ph), 4.23 (dd, 1 H, $J_{1,1'}$ 12.0, $J_{1,2}$ 1.5 Hz, H-1), 4.04 (dd, 1 H, $J_{1,1'}$ 12.0, $J_{1',2}$ 1.5 Hz, H-1′), 3.98–3.89 (m, 1 H, C*H*OH), 3.75–3.68 (m, 2 H, 2 C*H*OH), 3.05 (d, 1 H, $J_{4,HO-4}$ 9.5 Hz, HO-4), 2.54 (d, 1 H, $J_{2,HO-2}$ 3.3 Hz, HO-2), 1.52–1.45 (m, 2 H, H-5,5), 1.42–1.12 (m, 24 H, 12 CH_2), 0.88 (t, 3 H, 6.2 Hz, CH_3).

Anal. Found: C, 73.93; H, 10.34.

The experiments in Table I were carried out as described above. HMPT, TMEDA, and $ZnCl_2$, respectively, were added to the Grignard reagent in equimolar amounts followed by **2**. $CuBr \cdot SMe_2$ or $TiCl_4$ was dissolved in dry tetrahydrofuran (20 mL) at −78° and an equimolar amount of Grignard reagent in ether (20 mL) was introduced. After 30 min, the mixture was warmed to −40° and **2** was added.

*1,3-*O*-Benzylidene-2-*O*-methanesulfonyl-*D-arabino-*1,2,3,4-octadecanetetrol* (**4a**). — To a solution of **3a** (1.45 g, 3.56 mmol) in dry pyridine (50 mL) at −30° was added methanesulfonyl chloride (0.3 mL, 3.5 mmol). The mixture was stirred

for 12 h at −30° and then warmed to room temperature. The pyridine was evaporated with toluene and the residue was purified by column chromatography (39:1 dichloromethane–methanol) to give **4a** (1.30 g, 75%), m.p. 90°, R_F 0.54. ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 7.51–7.38 (m, 5 H, Ph), 5.60 (s, 1 H, C*H*Ph), 4.99–4.98 (m, 1 H, H-2), 4.52 (dd, 1 H, $J_{1,1'}$ 11.6, $J_{1,2}$ 1.5 Hz, H-1), 4.17 (dd, 1 H, $J_{1,1'}$ 11.6, $J_{1',2}$ 1.5 Hz, H-1′), 3.80–3.76 (m, 2 H, H-3,4), 3.20 (s, 3 H, Ms), 2.80 (d, 1 H, $J_{4,HO\text{-}4}$ 4.6 Hz, HO-4), 1.40–1.24 (m, 26 H, 13 CH_2), 0.87 (t, 3 H, *J* 6.2 Hz, CH_3).

Anal. Calc. for $C_{26}H_{44}O_6S$: C, 64.43; H, 9.15. Found: C, 64.19; H, 9.28.

1,3-O-Benzylidene-2-O-methanesulfonyl-L-xylo-*1,2,3,4-octadecanetetrol* (**4x**). — This compound, synthesised (78%) from **3x** as described for **4a**, had m.p. 96°, R_F 0.34 (100:1 dichloromethane–methanol). ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 7.53–7.38 (m, 5 H, Ph), 5.60 (s, 1 H, C*H*Ph), 4.75–4.74 (m, 1 H, H-2), 4.57 (dd, 1 H, $J_{1,1'}$ 12.0, $J_{1,2}$ 1.4 Hz, H-1), 4.11 (dd, 1 H, $J_{1,1'}$ 12.0, $J_{1',2}$ 1.4 Hz, H-1′), 3.90–3.79 (m, 2 H, H-3,4), 3.14 (s, 1 H, HO-4), 1.66–1.25 (m, 26 H, 13 CH_2), 0.87 (t, 3 H, *J* 6.2 Hz, CH_3).

Anal. Calc. for $C_{26}H_{44}O_6S$: C, 64.43; H, 9.15. Found: C, 64.31; H, 9.01.

1,3-O-Benzylidene-2-O-pivaloyl-L-xylo-*1,2,3,4-octadecanetetrol* (**5x**). — To a solution of **3x** (0.50 g, 1.23 mmol) in dry pyridine (20 mL) at −20° was added pivaloyl chloride (0.15 mL, 1.23 mmol). The mixture was stirred for 12 h at −20°, more pivaloyl chloride (0.01 mL, 0.82 mmol) was added, and, after 3 h, the mixture was warmed to room temperature. The pyridine was evaporated with toluene, and the oily residue was purified by column chromatography (4:1 light petroleum–ethyl acetate) to give **5x** (0.40 g, 68%) as a colourless oil, R_F 0.5. ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 7.53–7.38 (m, 5 H, Ph), 5.57 (s, 1 H, C*H*Ph), 4.77–4.76 (m, 1 H, H-2), 4.25 (dd, 1 H, $J_{1,2'}$ 11.0, $J_{1,2}$ 1.4 Hz, H-1), 4.02 (dd, 1 H, $J_{1,1'}$ 11.0, $J_{1',2}$ 1.4 Hz, H-1′), 3.86–3.77 (m, 2 H, H-3,4), 2.5 (bs, 1 H, HO-4), 1.60–1.17 (m, 35 H, 13 CH_2, ^{t}Bu), 0.87 (t, 3 H, *J* 6.2 Hz, CH_3).

Anal. Calc. for $C_{30}H_{50}O_5$: C, 73.43; H, 10.27. Found: C, 73.58; H, 10.18.

2-Azido-1,3-O-benzylidene-D-ribo- (**6r**) *and* -L-lyxo-*1,3,4-octadecanetriol* (**6l**). — To a solution of **4a** (1.20 g, 2.5 mmol) in dry *N,N*-dimethylformamide (50 mL) was added sodium azide (1.95 g, 30 mol). The mixture was heated to 90° for 2 days and then treated with dichloromethane (200 mL), filtered, and concentrated at 10^{-2} Torr. The residue was purified by column chromatography (10:1 light petroleum–ethyl acetate) to yield **6r** (0.70 g, 63%) as a colourless wax, R_F 0.52 (5:1 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 7.48–7.36 (m, 5 H, Ph), 5.48 (s, 1 H, C*H*Ph), 4.41 (dd, 1 H, $J_{1,1'}$ 11.2, $J_{1,2}$ 2.6 Hz, H-1), 3.89 (dd, 1 H, $J_{1,1}$ 11.2, $J_{1',2}$ 2.6 Hz, H-1′), 3.74–3.65 (m, 3 H, H-2,3,4), 2.06 (d, 1 H, $J_{4,HO\text{-}4}$ 5 Hz, HO-4), 1.68–1.64 (m, 2 H, H-5,5′), 1.45–1.25 (m, 24 H, 12 CH_2), 0.87 (t, 3 H, *J* 6.2 Hz, CH_3).

Compound **6l** (63%), synthesised from **4x** as described for **6r**, was a colourless wax, R_F 0.27 (10:1 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 7.47–7.36 (m, 5 H, Ph), 5.50 (s, 1 H, C*H*Ph), 4.44 (dd, 1 H, $J_{1,1'}$ 11.0, $J_{1,2}$ 5.0 Hz, H-1), 3.99 (dd, 1 H, $J_{1,1'}$ 11.0, $J_{1',2}$ 5 Hz, H-1′), 3.94–3.80 (m, 1 H, H-2),

3.77–3.63 (m, 1 H, H-4), 3.49–3.46 (m, 1 H, H-3), 1.72 (d, 1 H, $J_{4,HO-4}$ 5.5 Hz, HO-4), 1.65–1.25 (m, 26 H, 13 CH_2), 0.88 (t, 3 H, *J* 6.2 Hz, CH_3).

These compounds were unstable and were used immediately in the next steps.

2-Azido-D-ribo-*1,3,4-octadecanetriol* (**7r**). — To a solution of **6r** (1.0 g, 2.3 mmol) in methanol (20 mL) and water (2 mL) was added conc. hydrochloric acid (0.2 mL). After 15 h, t.l.c. showed no further reaction. The solvent was evaporated and the residue purified by column chromatography (9:1 dichloromethane–methanol) to yield **7r** (0.67 g, 65%), m.p. 91–92°, R_F 0.49. ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 4.10–3.65 (m, 5 H, H-1,1',2,3,4), 2.70 (t, 1 H, *J* 5.5 Hz, HO-1), 2.50 (d, 1 H, *J* 5 Hz, OH), 2.20 (d, 1 H, *J* 4.8 Hz, OH), 1.50–1.20 (m, 26 H, 13 CH_2), 0.89 (t, 3 H, *J* 6.2 Hz, CH_3).

Anal. Calc. for $C_{18}H_{37}N_3O_3$: C, 62.94; H, 10.85; N, 12.23. Found: C, 62.88; H, 10.72; N, 12.51.

2-Azido-L-lyxo-*1,3,4-octadecanetriol* (**7l**). — This compound, synthesised (65%) from **6l** as described for **7r**, had m.p. 69–70°, R_F 0.45. ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 4.05–3.50 (m, 5 H, H-1,1',2,3,4), 2.54 (d, 1 H, *J* 6 Hz, OH), 2.31 (t, 1 H, *J* 5.5 Hz, HO-1), 2.02 (d, 1 H, *J* 5.2 Hz, OH), 1.60–1.20 (m, 26 H, 13 CH_2), 0.87 (t, 3 H, *J* 6.2 Hz, CH_3).

Anal. Calc. for $C_{18}H_{37}N_3O_3$: C, 62.94; H, 10.85; N, 12.23. Found: C, 63.28; H, 10.76; N, 12.00.

2-Amino-D-ribo-*1,3,4-octadecanetriol* (**1r**). — To a suspension of lithium aluminium hydride (10 mg) in dry tetrahydrofuran (20 mL) was added **7r** (0.1 g, 0.3 mmol). The mixture was stirred for 30 min at room temperature and then for 1 h under reflux. The excess of reductant was destroyed with water (1 mL), the mixture was filtered and concentrated, and the residue was purified by column chromatography (40:10:1 chloroform–methanol–2M NH_3) to yield **1r** (88 mg, 95%), m.p. 95°, $[\alpha]_{578}^{23}$ +8.5° (*c* 1, pyridine), R_F 0.21; lit.[7] m.p. 95–97°, $[\alpha]_{578}^{23}$ +7.7° (pyridine); lit.[22] m.p. 104–108°, $[\alpha]_D^{20}$ +8.2° (pyridine); lit.[16] m.p. 103°, $[\alpha]_D^{20}$ +10.3° (pyridine); lit.[10] $[\alpha]_D^{20}$ +7.2° (pyridine).

2-Amino-L-lyxo-*1,3,4-octadecanetriol* (**1l**). — This compound, obtained (95%) from **7l** as described for **1r**, had m.p. 95°, $[\alpha]_{578}^{23}$ −6.2° (*c* 1, pyridine), R_F 0.23.

Anal. Calc. for $C_{18}H_{39}NO_3 \cdot 2\ H_2O$: C, 61.15; H, 12.25; N, 3.96. Found: C, 61.14; H, 11.98; N, 3.95.

2-Azido-3,4-O-*isopropylidene*-D-ribo-*1,3,4-octadecanetriol* (**8r**). — Compound **7r** (0.50 g, 1.45 mmol) and 2,2-dimethoxypropane (40 mL) were treated with toluene-*p*-sulfonic acid (20 mg) for 14 h at room temperature. The mixture was then neutralised with saturated aqueous sodium hydrogencarbonate (10 mL), and the organic layer was washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (5:1 light petroleum–ethyl acetate) to yield **8r** (335 mg, 80%) as a colourless oil, R_F 0.65 (10:1 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 4.25–3.35 (m, 5 H, H-1,1',2,3,4), 2.09 (t, 1 H, *J* 0.35 Hz, HO-1),

1.45 (s, 3 H, CMe), 1.27 (s, 3 H, CMe), 1.3–1.1 (m, 26 H, 13 CH_2), 0.89 (t, 3 H, *J* 6.2 Hz, CH_3).

Anal. Calc. for $C_{21}H_{41}N_3O_3$: C, 65.80; H, 10.70. Found: C, 66.10; H, 10.46.

*2-Azido-3,4-O-isopropylidene-*L-lyxo*-1,3,4-octadecanetriol* (**8l**). — This compound, synthesised (63%) from **7l** as described for **8r**, was a colourless oil, R_F 0.60.

Anal. Calc. for $C_{21}H_{41}N_3O_3$: C, 65.80; H, 10.70. Found: C, 66.03; H, 10.78.

*2-Azido-1-O-(2,3,6,2',3',4',6'-hepta-O-acetyl-β-lactosyl)-3,4-O-isopropylidene-*D-ribo*-1,3,4-octadecanetriol* (**10r**). — A solution of compound **8r** (400 mg, 10.5 mmol) and 2,3,6,2',3',4',6'-hepta-*O*-acetyl-α-lactosyl trichloroacetimidate[2] (**9**; 930 mg, 1.2 mmol) in dry dichloromethane (20 mL) was stirred in the presence of molecular sieves (4 Å, 0.5 g) for 30 min at room temperature. A 0.1M solution of boron trifluoride etherate in dichloromethane (2.5 mL, 0.25 mmol) was then added. After 10 h, t.l.c. showed the complete disappearance of **8r** and **9**. The mixture was diluted with dichloromethane (50 mL) and treated with saturated aqueous sodium hydrogen carbonate (2 × 50 mL), and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (4:1 toluene–acetone) to give amorphous **10r** (725 mg, 69%), m.p. 109°, $[\alpha]_{578}^{23}$ −7° (*c* 1, chloroform), R_F 0.53, ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 5.32 (d, 1 H, $J_{3',4'}$ 2.5 Hz, H-4'), 5.17 (dd, 1 H, $J_{3,4} = J_{2,3}$ 9.03 Hz, H-3), 5.09 (dd, 1 H, $J_{2,3'}$ 10.4 Hz, $J_{1',2'}$ 7.9 Hz, H-2'), 4.95–4.91 (m, 2 H, H-2,3'), 4.55 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 4.52–4.51 (m, 1 H, N_3CH), 4.74 (d, 1 H, $J_{1',2'}$ 8 Hz, H-1'), 4.15–3.78 (m, 9 H, H-4,5',6,6,6,6', OCH_2CHN_3, $OCHCH_2$), 3.63–3.58 (m, 1 H, $OCHCHOCH_2$), 3.51–3.44 (m, 1 H, H-5), 2.18–1.91 (m, 21 H, 7 Ac), 1.42–1.18 (m, 32 H, 13 CH_2, 2 CH_3), 0.87 (t, 3 H, *J* 6.2 Hz, CH_3).

Anal. Calc. for $C_{47}H_{75}N_3O_{20}$: C, 56.34; H, 7.54; N, 4.19. Found: C, 56.00; H, 7.45; N, 4.17.

*2-Azido-1-O-(2,3,6,2',3',4',6'-hepta-O-acetyl-β-lactosyl)-3,4-O-isopropylidene-*L-lyxo*-1,3,4-octadecanetriol* (**10l**). — Obtained from **8l** and **9** as described for **10r**, amorphous **10l** (663 mg, 63%) had m.p. 49°, $[\alpha]_{578}^{22}$ −13.5° (*c* 1, chloroform), R_F 0.63 (25:1 dichloromethane–methanol). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 5.34 (d, 1 H, $J_{3',4'}$ 2.4 Hz, H-4'), 5.19 (dd, 1 H, $J_{3,4} = J_{3,2}$ = 9.05 Hz, H-3), 5.11 (dd, 1 H, $J_{2',3'}$ 10.3, $J_{1',2'}$ 8 Hz, H-2), 4.97–4.91 (m, 2 H, H-3',2), 4.55 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1); 4.53–4.50 (m, 1 H, N_3CH), 4.47 (d, 1 H, $J_{1',2'}$ 8 Hz, H-1'), 4.15–3.52 (m, 11 H, H-4,5,6,6,5',6',6', OCH_2CHN_3, $OCHCH_2$, $OCHCHOCH_2$), 2.20–1.99 (m, 21 H, 7 Ac), 1.52–1.18 (m, 32 H, 13 CH_2, 2 CH_3), 0.87 (t, 3 H, *J* 6.2 Hz, CH_3).

Anal. Calc. for $C_{47}H_{75}N_3O_{20}$: C, 56.34; H, 7.54; N, 4.19. Found: C, 56.12; H, 7.41; N, 4.11.

*2-Amino-1-O-(2,3,6,2',3',4',6'-hepta-O-acetyl-β-lactosyl)-3,4-O-isopropylidene-*D-ribo*-1,3,4-octadecanetriol* (**11r**). — To a solution of **10r** (400 mg, 0.40 mmol) in ethanol (40 mL) containing nickel chloride (4%) and boric acid (2%) was added a suspension of lithium aluminium hydride in ethanol until it remained black. After stirring for 1 h, the mixture was filtered and concentrated under reduced pressure, and the residue was purified by column chromatography to yield **11r** (344 mg, 88%)

as a colourless wax which was immediately used for the next step; R_F 0.45 (15:1 dichloromethane–methanol). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 5.32 (d, 1 H, $J_{3',4'}$ 2.2 Hz, H-4'), 5.18 (dd, 1 H, $J_{3,4} = J_{2,3}$ 9 Hz, H-3), 5.09 (dd, 1 H, $J_{2',3'}$ 10, $J_{1',2'}$ 8 Hz, H-2'), 4.96–4.82 (m, 2 H, H-2,3'), 4.55–4.39 (m, 3 H, H-1,1', N_3CH), 4.19–3.5 (m, 10 H, H-4,5,6,6,5',6',6' OCH_2CHN_3, $OCHCH_2$), 3.05–2.95 (m, 1 H, $OCHCHOCH_2$), 2.18–1.89 (m, 21 H, 7 Ac), 1.55–1.18 (m, 34 H, 13 CH_2, 2 CH_3, NH_2), 0.87 (t, 3 H, *J* 6.2 Hz, CH_3).

*2-Amino-1-*O*-(2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-lactosyl)-3,4-*O*-isopropylidene-*L*-lyxo-1,3,4-octadecanetriol* (**11l**). — Obtained from **10l** as described for **11r**, **11l** (81%) was a colourless oil, R_F 0.38 (15:1 dichloromethane–methanol). ^{1}H-N.m.r. data (400 MHz $CDCl_3$): δ 5.31 (d, 1 H, $J_{3',4'}$ 2.4 Hz, H-4'), 5.1 (dd, 1 H, $J_{3,4} = J_{2,3}$ = 8 Hz, H-3), 5.07 (dd, 1 H, $J_{2',3'}$ 10.1, $J_{1',2'}$ 8 Hz, H-2'), 4.94–4.85 (m, 2 H, H-2,3'), 4.47–4.44 (m, 3 H, H-1,1', N_3CH), 4.11–3.47 (m, 10 H, H-4,5,6,6,5',6',6', OCH_2CHN_3, $OCHCH_2$), 2.99–2.98 (m, 1 H, $OCHCHCH_2$), 2.12–1.93 (m, 21 H, 7 Ac), 1.47–1.2 (m, 34 H, 13 CH_2, 2 CH_3).

*1-*O*-(2,3,6,2',3',4',6'-Hepta-*O*-acetyl-β-lactosyl)-2-hexadecanoylamino-3,4-*O*-isopropylidene-*D*-ribo-1,3,4-octadecanetriol* (**12r**). — To a solution of **11r** (300 mg, 0.31 mmol) in dry tetrahydrofuran (20 mL) was added hexadecanoyl chloride (85 mg, 0.31 mmol) with vigorous stirring. After 10 min, t.l.c. showed complete disappearance of **11r**. The mixture was then treated with saturated aqueous sodium hydrogencarbonate (3 × 20 mL), and the organic layer was separated and concentrated. The residue was purified by column chromatography (1:1 light petroleum–ethyl acetate) to yield amorphous **12r** (230 mg, 62%), m.p. 152°, R_F 0.46. ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 5.57 (d, 1 H, *J* 9.3 Hz, NH), 5.34 (d, 1 H, $J_{3',4'}$ 2.6 Hz, H-4'), 5.19 (dd, 1 H, $J_{3,4} = J_{2,3}$ = 9.3 Hz, H-3), 5.11 (dd, 1 H, $J_{2',3'}$ 10.2, $J_{1',2'}$ 7.8 Hz, H-2'), 4.94 (dd, 1 H, $J_{3',4'}$ 2.6 Hz, H-3'), 4.88 (dd, 1 H, $J_{2,3}$ 9.3, $J_{1,2}$ 7.9 Hz, H-2), 4.49–4.45 (m, 3 H, H-1,1', N_3CH), 4.14–3.84 (m, 8 H, H-6,6,5',6',6', OCH_2CHNH, $OCHCH_2$), 3.80–3.70 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 9.4 Hz, H-4), 3.64–3.57 (m, 2 H, H-5, $OCHCHOCH_2$), 2.35 (t, 1 H, *J* 7.57 Hz, O=CCH), 2.2–1.96 (m, 22 H, 7 Ac, O=CCH), 1.6–1.18 (m, 58 H, 26 CH_2, 2 CH_3), 0.87 (t, 6 H, *J* 6.5 Hz, 2 CH_3).

Anal. Calc. for $C_{63}H_{107}NO_{21}$: C, 62.61; H, 8.88. Found: C, 63.06; H, 9.06.

*1-*O*-(2,3,6,2',3',4',6'-Hepta-*O*-acetyl-β-lactosyl)-2-hexadecanoylamino-3,4-*O*-isopropylidene-*L*-lyxo-1,3,4-octadecanetriol* (**12l**). — Obtained from **11l** as described for **12r**, amorphous **12l** (65%) had m.p. 170–171°, R_F 0.40 (1:1 light petroleum–ethyl acetate). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 5.67 (d, 1 H, *J* 9.3 Hz, NH), 5.34 (d, 1 H, $J_{3',4'}$ 3 Hz, H-4'), 5.19 (dd, 1 H, $J_{3,4} = J_{2,3}$ = 9.3 Hz, H-3), 5.11 (dd, 1 H, $J_{2',3'}$ 10.1, $J_{1',2'}$ 7.7 Hz, H-2'), 4.95 (dd, 1 H, $J_{3',4'}$ 3 Hz, H-3'), 4.88 (dd, 1 H, $J_{2,3}$ 9.3, $J_{1,2}$ 7.9 Hz, H-2), 4.49–4.46 (m, 3 H, H-1,1', N_3CH), 4.2–3.59 (m, 11 H, H-4,5,6,6,5',6',6' OCH_2CHNH, $OCHCH_2$, $OCHCHOCH_2$), 2.34 (t, 1 H, *J* 7.7 Hz, O=CCH), 2.18–1.96 (m, 22 H, 7 Ac, O=CCH), 1.63–1.2 (m, 58 H, 26 CH_2, 2 CH_3), 0.87 (t, 6 H, *J* 6.6 Hz, 2 CH_3).

Anal. Calc. for $C_{63}H_{107}NO_{21}$: C, 62.61; H, 8.88; N, 1.15. Found: C, 63.11; H, 9.19; N, 1.05.

2-Hexadecanoylamino-3,4-O-isopropylidene-1-O-(β-lactosyl)-D-ribo-*1,3,4-octadecanetriol* (**13r**). — A solution of **12r** (220 mg, 0.18 mmol) in methanol–tetrahydrofuran (1:1, 10 mL) containing sodium methoxide (0.02 mmol) was kept for 14 h at room temperature, then neutralised with ion-exchange (H^+) resin, and concentrated. The residue was purified by flash chromatography (15:1 dichloromethane–methanol) to yield amorphous **13r** (165 mg, 99%), m.p. 141–142°, R_F 0.25. ^{1}H-N.m.r. data (400 MHz, Me_2SO): δ 7.78 (d, 1 H, *J* 9.03 Hz, NH), 5.09–4.52 (m, 7 H, OH), 4.18 (d, 1 H, $J_{1,2}$ 6.8 Hz, H-1), 4.13 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.04–3.27 (m, 16 H), 3.03–3.0 (m, 1 H, OC*H*CHOCH_2), 2.16 (t, 1 H, *J* 7.3 Hz, O=CH), 2.02 (t, 1 H, *J* 7.1 Hz, O=CCH), 1.45–1.18 (m, 58 H, 26 CH_2, 2 CH_3), 0.87 (t, 6 H, *J* 6.6 Hz, 2 CH_3).

Anal. Calc. for $C_{49}H_{93}NO_{14}$: C, 64.00; H, 10.11. Found: C, 64.44; H, 10.10.

2-Hexadecanoylamino-3,4-O-isopropylidene-1-O-(β-lactosyl)-L-lyxo-*1,3,4-octadecanetriol* (**13l**). — Obtained from **12l** as described for **13r**, amorphous **13l** (99%) had m.p. 178°, R_F 0.22 (15:1 dichloromethane–methanol). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 7.77 (d, 1 H, *J* 9.03 Hz, NH), 5.2–4.45 (m, 7 H, OH), 4.18–4.12 (m, 2 H, H-1,1'), 4.04–3.19 (m, 16 H), 3.05–3.0 (m, 1 H, OC*H*CHOCH_2), 2.19 (t, 1 H, *J* 7.4 Hz, O=CCH), 2.05 (t, 1 H, *J* 7.2 Hz, O=CCH), 1.65–1.18 (m, 58 H, 26 CH_2, 2 CH_3), 0.87 (t, 6 H, *J* 6.6 Hz, 2 CH_3).

Anal. Calc. for $C_{49}H_{93}NO_{14}$: C, 64.00; H, 10.11. Found: C, 64.45; H, 10.30.

2-Hexadecanoylamino-1-O-(β-lactosyl)-D-ribo-*1,3,4-octadecanetriol* (**14r**). — To a solution of **13r** (150 mg, 0.16 mmol) in dichloromethane–methanol (10.1, 30 mL) was added trifluoroacetic acid (0.1 mL). The mixture was stirred for 2.5 days, then neutralised with ion-exchange (HO^-) resin, filtered, and kept in the refrigerator for 14 h. The product was collected and recrystallised from dichloromethane–methanol (10:1, 5 mL) to yield **14r** (75 mg, 51%), m.p. 149°, $[\alpha]_{578}^{23}$ +12° (*c* 1, pyridine). ^{1}H-N.m.r. data (400 MHz, Me_2SO): δ 7.64 (d, 1 H, *J* 8.8 Hz, NH), 5.1–4.51 (m, 7 H, 1 OH), 4.22–3.0 (m, 21 H), 2.07–2.02 (m, 2 H, O=CCH_2), 1.46–1.15 (m, 52 H, 26 CH_2), 0.87 (t, 6 H, *J* 6.5 Hz, 2 CH_3).

2-Hexadecanoylamino-1-O-(β-lactosyl)-L-lyxo-*1,3,4-octadecanetriol* (**14l**). — Obtained from **13l** as described for **14r, 14l** (52%) had m.p. 189–191°, $[\alpha]_{578}^{23}$ −3.2° (*c* 1, pyridine). ^{1}H-N.m.r. data (250 MHz, Me_2SO): δ 7.73 (d, 1 H, *J* 10 Hz, NH), 5.17–4.38 (m, 7 H, OH), 4.21–3.0 (m, 21 H), 2.08–2.03 (m, 2 H, O=CCH_2), 1.49–1.13 (m, 52 H, 26 CH_2), 0.87 (t, 6 H, *J* 6.6 Hz, 2 CH_3).

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