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SYNTHESIS OF ANALOGUES OF 3-DEOXY-D-*manno*-OCTULOSONIC ACID (KDO) AS POTENTIAL INHIBITORS OF CMP-KDO SYNTHETASE

KRISTINA LUTHMAN, ALF CLAESSON*,
Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, University of Uppsala, P.O. Box 574, S-751 23 Uppsala (Sweden)

ANITA M. JANSSON, AND BRIAN G. PRING
Research and Development Laboratories, Antibacterial Chemotherapy, Astra Alab AB, S-151 85 Södertälje (Sweden)

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ABSTRACT

A series of derivatives of the 2-deoxy analogue of β-KDO (2,6-anhydro-3-deoxy-D-*glycero*-D-*talo*-octonic acid; ammonium salt, **2**) has been synthesised as potential inhibitors of CMP-KDO synthetase, starting from methyl 2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octonate and replacing the CO_2Me group attached to C-2 variously by $CONH_2$, CONHOH, CH_2OH, $CH_2PO(OH)(O^-NH_4^+)$, $COCH_2PO(OH)(O^-H_3\overset{+}{N}\langle\rangle)$, $CH_2CO_2^-NH_4^+$, $CONHCH_2CO_2^-NH_4^+$, CONHBn, CONHHexyl, CO_2Bn, and CO_2Hexyl. Of these derivatives, the hydroxamic acid (CONHOH) was the best inhibitor of CMP-KDO synthetase, but was less potent than **2**.

INTRODUCTION

In a search for novel antibacterial agents with specificity for Gram-negative bacteria, a synthesis programme has been started aimed at potential inhibitors of enzymes involved in the metabolism of 3-deoxy-D-*manno*-octulosonic acid[1,2] (KDO). KDO is a constituent of the lipopolysaccharide (LPS) of Gram-negative bacteria, which links the polysaccharide and lipid A, a di-(2-amino-2-deoxy-D-glucose) phosphate polymer[3,4]. The biosynthesis of KDO and its incorporation into LPS is shown in Fig. 1. The choice of KDO metabolism as a target for antibacterial action is based on the facts that (*a*) KDO is found in Gram-negative bacteria[5], possibly in the protozoan *Trypanosoma cruzi*[6], and some higher plants[7], (*b*) KDO is a component of the LPS of almost all Gram-negative bacteria examined[5] and is

*Present address: Research and Development Laboratories, Antibacterial Chemotherapy, Astra Alab AB, S-151 85 Södertälje, Sweden.

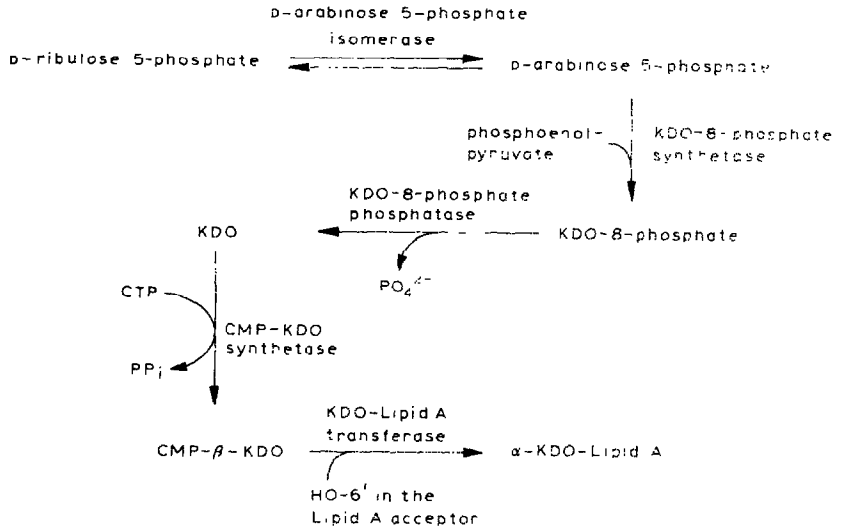
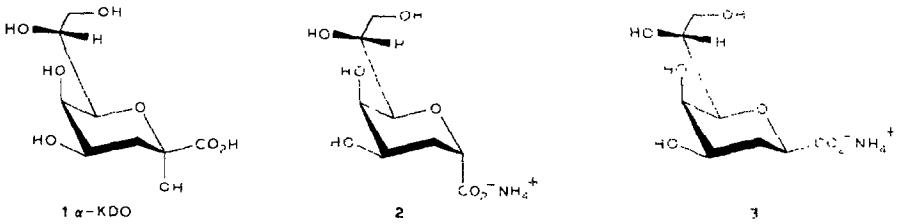


Fig. 1. Biosynthesis of KDO and its incorporation into LPS.

present also in the capsular polysaccharides of some strains[8-15], and (*c*) mutants defective in KDO biosynthesis are not viable, and hence the inhibition of any relevant enzyme involved will result in inhibition of cell growth[16,17].

We have concentrated on the inhibition of CTP: 3-deoxy-D-*manno*-octulosonate cytidylyltransferase (CMP-KDO synthetase, EC 2.7.7.38)[18-20], which catalyses the formation of CMP-KDO from KDO and cytidine triphosphate (CTP). The activation of KDO before transfer to lipid A (Fig. 1) is believed to be the rate-limiting step in LPS biosynthesis[10].

Substrate analogues of KDO have been synthesised as potential inhibitors of CMP-KDO synthetase. 5-Azido-5-deoxy-KDO and 5,8-diazido-5,8-dideoxy-KDO inhibited the enzyme[2], whereas 8-azido-8-deoxy-KDO and 4-*O*-methanesulfonyl-D-*gluco*-KDO were alternative substrates for the CMP-KDO synthetase-mediated reaction[21]. Compound **2**, a deoxy analogue of β-KDO, is a competitive inhibitor of CMP-KDO synthetase, with a K_i of 3.9 μM (ref. 22), whereas its epimer **3** is inactive. This observation indicates that β-KDO is the substrate for CMP-KDO synthetase, which accords with the finding, based on ^{13}C-n.m.r. studies, that the enzyme utilizes the β-pyranose form[23].



The enzyme-catalysed transfer of KDO to lipid A (Fig. 1) is thought to proceed with inversion of the anomeric configuration by analogy with CMP–*N*-acetylneuraminic acid (CMP-NANA)[2]. Thus, KDO in native LPS ought to be α and this has been confirmed by n.m.r. experiments[24–26].

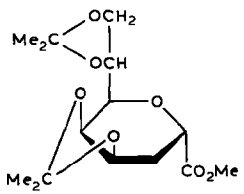
We now report on a series of derivatives of **2** with variations of the 2-α substituent, and their effects on CMP-KDO synthetase.

RESULTS AND DISCUSSION

The syntheses started with methyl 2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octonate[27] (**4**), obtained from a derivative of 2-chloro-2-deoxy-α-KDO (ref. 28).

The dicarboxylate **9** was synthesised as follows. Reaction of the lithium enolate of **4** with carbon dioxide[29] afforded a 1:1 mixture of epimeric lithium carboxylates **5**, which was converted into the diester **6** with iodomethane. The isopropylidene groups were hydrolysed from **6** with Amberlite IR-120 (H^+) resin to afford **7**. Saponification (0.2M NaOH, 25°) of **7** gave the half-ester **8**, and further treatment (2M NaOH, 60°) afforded **9**, without detectable decarboxylation, and which was isolated as the diammonium salt. The amide **10** was easily obtained from **4** by treatment with saturated methanolic ammonia and deprotection then gave **11**. The hydroxamic acid **12** was prepared by reaction of **4** with hydroxylamine hydrochloride in methanol in the presence of triethylamine.

Reduction of **4** with $LiAlH_4$ gave the alcohol **14** which, with triphenylphosphine and *N*-bromosuccinimide, gave the bromide **16**. An Arbuzov reaction in triethyl phosphite then afforded **17**. Treatment of **17** with bromotrimethylsilane in chloroform[30] effected transesterification to give the bis(trimethylsilyl)phosphonate



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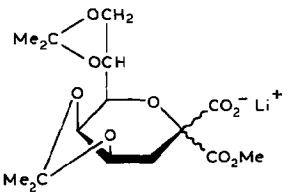

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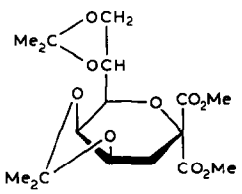

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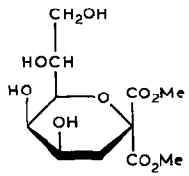

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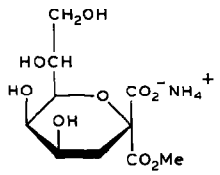

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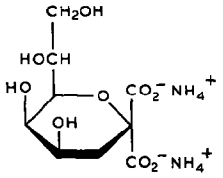

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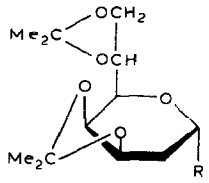
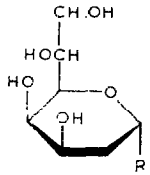




10 R = $CONH_2$
12 R = CONHOH
14 R = CH_2OH
16 R = CH_2Br
17 R = $CH_2PO(OEt)_2$
19 R = $COCH_2PO(OMe)_2$
21 R = CH_2OTs
22 R = CH_2CN
25 R = $CO_2^-\overset{+}{N}HEt_3$
26 R = $CONHCH_2CO_2Me$
28 R = CONHBn
30 R = CONHHexyl
32 R = CO_2Bn
34 R = CO_2Hexyl

11 R = $CONH_2$
13 R = CONHOH
15 R = CH_2OH
18 R = $CH_2PO(OH)(O^-NH_4^+)$
20 R = $COCH_2PO(OH)(O^-\overset{+}{N}H_3$ 
23 R = CH_2CO_2Me
24 R = $CH_2CO_2^-NH_4^+$
27 R = $CONHCH_2CO_2^-NH_4^+$
29 R = CONHBn
31 R = CONHHexyl
33 R = CO_2Bn
35 R = CO_2Hexyl

that was cleaved by water to yield the phosphonic acid, which catalysed acetal hydrolysis to give **18**, isolated as the ammonium salt.

The β-ketophosphonate **19** was obtained from **4** and lithium dimethyl methylphosphonate[31] and deprotected to give **20** isolated as the cyclohexylammonium salt.

The homocarboxylic acid analogue **24** was synthesised as follows. The tosylate **21** of **14** was treated with KCN to give the nitrile **22**. Acid-catalysed methanolysis of **22** with chlorotrimethylsilane as a water scavenger afforded the methyl ester **23**, which was saponified to yield **24**, isolated as the ammonium salt. The glycine derivative **27** was obtained *via* **26**, which was prepared from a mixed anhydride of the carboxylate **25** and glycine methyl ester hydrochloride in the presence of triethylamine. Likewise, the benzyl- (**29**) and hexyl-amide (**31**) were obtained *via* **28** and **30**, respectively, which were synthesised from **25**. The esters **33** and **35** were prepared by deprotection of **32** and **34**, respectively, which were synthesised by transesterification of **4** with catalytic amounts of magnesium methoxide in benzyl alcohol or 1-hexanol, respectively. Magnesium methoxide was used instead of sodium methoxide in order to avoid epimerisation during the transesterification step.

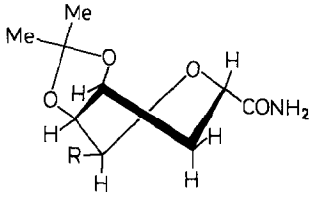
N.m.r. data. — The structures of the foregoing compounds were assigned on the basis of ^1H-, ^{13}C-, and ^{31}P-n.m.r. data. The ^{13}C-n.m.r. spectra were proton noise-decoupled and the signals of **10** were assigned by using a graphical method involving proton off-resonance spin-decoupled spectra[32,33]. The ^{13}C-n.m.r. spectra

of **12, 26, 28,** and **30** were interpreted by comparison with data for **10**, since variations in the 2-substituent had little effect on the ^{13}C resonances.

The configuration at C-2 in **8** was determined by analogy with a method used for determination of the anomeric configurations in CMP-NANA (ref. 34) and KDO-glycosides[25,35]. The *J* values for the carbonyl carbons and H-3,3 provided evidence for the configuration at C-2. The resonances of the carbonyl carbons were assigned on the basis of the respective multiplets in the proton-coupled ^{13}C-n.m.r. spectra. The carboxylate signal appeared as a doublet ($^3J_{C,H\text{-}3a}$ 3 Hz) and the ester carbonyl signal as an unresolved multiplet. Selective ^{13}C–[^1H] decoupling centered at the chemical shift of the methyl ester protons at 3.74 p.p.m. collapsed the multiplet at 174.82 p.p.m. to a doublet of doublets with $^3J_{C,H\text{-}3a}$ 9 Hz, and $^3J_{C,H\text{-}3e}$ 3 Hz, thereby supporting the structure assigned to **8**.

The 400-MHz ^1H-n.m.r. spectra indicated the amide **10** to exist in solution preponderantly in the distorted boat conformation **36**. The $^5C_2$ chair conformation is ruled out because the coupling constants $J_{2,3a}$ 11.6 and $J_{2,3e}$ 5.8 Hz are too large to account for an axial–equatorial and equatorial–equatorial relationship, respectively. In addition, the value $J_{3a,4}$ 2.7 Hz does not correspond to a diaxial coupling. However, the large value (11.6 Hz) of $J_{2,3a}$ indicated a *trans*-diaxial relationship of H-2,3*a*. Thus, H-2 must occupy an axial or pseudo-axial position. The alternative $^2C_5$ chair conformation is unlikely due to a considerable 4,6-diaxial interaction.

The *J* values for **10** are compared in Table I with data determined for derivatives of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose[36,37]. Variations in the structure of the side chain do not affect the *J* values for the ring protons. When comparing experimental and calculated *J* values, Cone and Hough[36] established that the galactose derivatives must adopt a conformation intermediate between skew and boat forms. The *J* values for **10** and the other *O*-isopropylidene derivatives accord with these results (Table I). Recently, Krajewski *et al.*[38] reported that the pyranose ring in 6-*C*-(2-furyl)-1,2:3,4-di-*O*-isopropylidene-α-D-*glycero*-D-*galacto*-hexopyranose adopted a hybrid twist-boat conformation ($^oT_2$ + $B_{2,5}$), thus further supporting the conformation proposed for **10**. However, the pyranose ring in crystalline 3,4,5-tri-*O*-acetyl-1,2-*O*-(*R*)-(1-cyanoethylidene)-α-D-galactopyranose adopts a flattened $^4C_1$ conformation[39]. The values $J_{2,3}$ 7.4 and $J_{3,4}$ 3.0 Hz for compound **C** (Table I) do not accord with those for the other derivatives in Table I. Thus, the conformational restraints imposed on the pyranose ring by the 3,4-*O*-iso-



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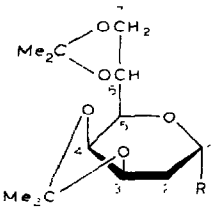

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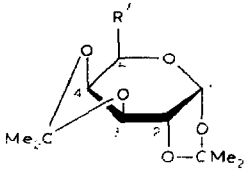

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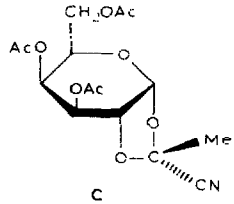

C

TABLE I

COUPLING CONSTANTS[a]

Compound	$J_{1,2a}$	$J_{1,2c}$	$J_{2a,3}$	$J_{2c,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
Series **A**							
4 R = CO_2Me[30]	11.8	5.9	2.7	3.2	8.0	1.5	7.8
10 R = $CONH_2$	11.6	5.8	2.7	2.8	8.0	1.5	4.3
12 R = CONHOH	11.8	6.0	2.5	2.8		1.5	4.0
14 R = CH_2OH	3.1	2.9	2.9	8.3	1.5		7.2
19 R = $COCH_2PO(OMe)_2$	11.4	5.1	2.7	2.7	8.1	1.7	6.8
21 R = CH_2OTs			3.0	3.0	8.0	1.5	8.0
22 R = CH_2CN			3.0	3.0	8.0	1.5	8.0
25 R = $CO_2^-TEA^+$	11.0	6.0	3.0	3.2	8.0	1.5	8.0
26 R = $CONHCH_2CO_2Me$	11.8	5.5	2.5	2.8		1.5	4.8
28 R = CONHBn	11.6	6.0	2.6	3.0		1.5	3.5
30 R = $CONHC_6H_{13}$	11.7	6.0	2.5	3.0	8.0	1.5	4.0
32 R = CO_2Bn	11.7	5.9	2.4	3.4	7.8	1.5	8.3
34 R = $CO_2C_6H_{13}$	11.7	5.9	2.4	3.2	7.8	1.5	8.0
Series **B**							
R′ = H		5.0		2.4	7.8	1.4; 2.0	
R′ = COSBn		5.1		2.4	8.0	1.4	
R′ = CH_2I		5.0		2.4	7.8	1.6	5.9; 7.7
R′ = CH_2OH		5.0		2.4	8.0	1.4	
R′ = CH_2OTs		5.0		2.4	7.8		
Compound **C**		4.6		7.4	3.0	2.4	

[a]For the 4,5:7,8-di-*O*-isopropylidene derivatives (**A**), 1,2:3,4-di-*O*-isopropylidenegalactose derivatives[36,37] (**B**), and 3,4,6-tri-*O*-acetyl-1,2-*O*-(*R*)-(1-cyanoethylidene)-α-D-galactopyranose[19] (**C**) (for convenience, all derivatives are numbered in the same way).

propylidene ring dominate those of the same ring in the 1,2-positions.

If, in solution, a rapid interconversion between the skew and boat forms of **10** occurs, the observed chemical shifts and coupling constants will be weighted averages. However, determination of the ^{1}H-n.m.r. spectra at −40° and −60° did not change the chemical shifts and coupling constants, suggesting that **10** exists in only one conformation. It is possible that **10** exists in two conformations with a low barrier of interconversion. In the deduced conformation of **10**, the bulky side-chain at C-6 occupies the more stable equatorial position. Studies of molecular models reveal that a diaxial relationship of H-6,7 corresponds to the most stable conforma-

TABLE II

RELATIVE INHIBITORY ACTIVITY IN THE CMP-KDO SYNTHETASE ASSAY

Compound[a]	*Relative activity*[b–d]
2	+++++
8	I
9	I
11	++
13	+++
15	I
18	I
20	+
24	I
25	I
27	+

[a]Compounds **29, 31, 32,** and **35** were inactive. [b]Equimolar concentrations of KDO and inhibitor. [c]Key: I, inactive; +, <50% inhibition; ++, 50–80%; +++, 80–90%; ++++, 90–99%; +++++, 100%. [d]All compounds tested were analysed by h.p.l.c.[41] to ensure the absence of contamination by **2**.

tion, due to minimal steric interactions with the ring. However, the small $J_{6,7}$ value of 4 Hz for **10** suggests a *gauche* relationship. Approximately the same $J_{6,7}$ value was found for **12, 26, 28,** and **30** (Table I). This side-chain conformation might be due to the formation of a hydrogen bond between NH and O-7, which is not possible in **21, 22, 25, 32,** and **34** where $J_{6,7}$ is ~8 Hz, a value consistent with a diaxial coupling. The presumed hydrogen bond between NH and O-7 could not be disrupted even in a methanolic solution of **10** at 55°.

Biological activity. — The compounds described above were tested as inhibitors of CMP-KDO synthetase from *Escherichia coli* D21 or a mutant of *Salmonella typhimurium* (SL 1102). The CMP-KDO synthetase screening-assay was based essentially on that described by Ghalambor and Heath[18]. The KDO liberated from the nucleotide was determined by a modified thiobarbituric acid assay[40]. All of the compounds were less potent than **2** (Table II). The most potent was **13**, followed by **11**. The β-ketophosphonate **20** and the glycine analogue **27** were weak inhibitors, and the dicarboxylate **9**, the phosphonate **18**, and the homocarboxylate **24** were inactive. The inhibitory activity of the hydroxamic acid **13**, which is a weak acid, is probably due to the location of a negative charge at the same relative spatial position as that in **2**. However, a negative charge is not absolutely essential since the amide **11** was also a rather good inhibitor. Thus, the polarity of a correctly positioned amide group appears to be sufficient for activity. The importance of an appropriate spatial location of the polar group is shown by moving the anionic centre further from the ring, as in compounds **18, 20, 24,** and **27** which were much less potent as inhibitors. Compound **9** was inactive even though the negative charge is at the same position as in **2**. This effect might be due to the equatorial carboxylate group preventing simultaneous binding of **9** and CTP to the active site of the enzyme[22].

The alcohol **15** and the carboxylates **8** and **25**, which are intermediates in the synthetic pathways, were also inactive.

In order to investigate whether penetration of the bacterial cell wall might be improved, some hydrophobic derivatives of **2** were synthesised, namely, the amides **29** and **31** and the esters **33** and **35**, with the idea that intracellular hydrolysis might liberate the potent inhibitor **2**. However, these compounds, in addition to **11, 13, 25,** and **27**, did not inhibit the growth[42] of *Salmonella typhimurium* SL 1102, *Salmonella typhimurium* LT2 MI, and *Escherichia coli* ATCC 11303 at 37° and *Salmonella typhimurium* AG701i50 at 25°.

EXPERIMENTAL

General methods. — Melting points were determined in open capillary tubes and are uncorrected. Optical rotations were measured at 20° with a Perkin–Elmer 241 or Optical Activity AA100 polarimeter. I.r. spectra were recorded with a Perkin–Elmer 298 spectrometer. N.m.r. spectra were recorded with a JEOL FX90Q, JEOL FX200, or JEOL GX-400 instrument on solutions in $CDCl_3$ and CD_3OD (internal Me_4Si), D_2O (internal ^{t}BuOH, δ_H 1.23, δ_C 32.2), or as indicated otherwise. H_3PO_4 (δ 0) was used as external standard for ^{31}P-n.m.r. spectra. High-resolution f.a.b.-mass spectra were recorded with a JEOL DX 303 instrument. T.l.c. was performed on Merck Silica Gel 60 F_{254} with detection by u.v. light and by charring with sulphuric acid. Column chromatography was performed on Merck Silica Gel 60 (0.040–0.063 mm), using the flash technique[43]. All solvents used were anhydrous and kept over 3Å and 4Å molecular sieves. *N,N*-Dimethylformamide was distilled from P_2O_5 and then kept over 4Å molecular sieves. Butyl-lithium in hexane was titrated prior to use[44]. Solutions were concentrated *in vacuo* at <30°.

Hydrolysis of di-O-isopropylidene derivatives. — A solution of the di-*O*-isopropylidene derivative in methanolic 20% trifluoroacetic acid was stirred at room temperature until hydrolysis was complete (t.l.c.) and then co-concentrated several times with toluene, and the residue was recrystallised or purified as indicated.

*Methyl 2,6-anhydro-3-deoxy-4,5:7,8-di-O-isopropylidene-2-methoxycarbonyl-*D-glycero-D-talo-*octonate* (**6**). — 1.6M Butyl-lithium in hexane (3.4 mL, 5.4 mmol) was added to a solution of di-isopropylamine (560 mg, 5.5 mmol) in dry tetrahydrofuran (20 mL) at −20° under nitrogen. After 20 min, the mixture was cooled to −75° and a solution of **4** (1.70 g, 5.4 mmol) in dry tetrahydrofuran (5 mL) was added dropwise. Carbon dioxide was bubbled through the solution for 15 min, the temperature was slowly raised to 0°, and, after the addition of water (17 mL), the solution was neutralised with Dowex (H^+) resin, washed three times with chloroform, and concentrated to give **5** (1.80 g, 95%) as a white powder, R_F 0.70 (chloroform–methanol–water, 10:10:1); ν_{max} ($CHCl_3$), 1730 (ester), 1640 and 1400 cm^{-1} (carboxylate). ^{1}H-N.m.r. data ($CDCl_3$): δ 3.70 and 3.72 (OMe). The n.m.r. data indicated this product to be a 1:1 mixture (**5**) of lithium 2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-2-methoxycarbonyl-D-*glycero*-D-*talo*- and -D-*galacto*-octonate, which was used as such in the next step.

Cesium carbonate (1.90 g, 5.8 mmol) and iodomethane (0.82 mL, 13 mmol) were added to a solution of **5** (1.80 g, 4.9 mmol) in dry tetrahydrofuran (25 mL). After 2 h at room temperature, ethyl acetate (25 mL) was added, and the mixture was filtered and concentrated. Column chromatography (ethyl acetate–toluene, 1:2) of the residue gave **6** (1.43 g, 78%), m.p. 103–104° (from ethyl acetate–hexane), $[\alpha]_D$ −6° (*c* 0.3, dichloromethane), R_F 0.38 (ethyl acetate–toluene, 1:2); ν_{max} ($CHCl_3$) 1735 cm^{-1} (ester). N.m.r. data ($CDCl_3$): ^1H, δ 1.34, 1.36, 1.42 (3 s, 12 H, 2 Me_2C), 2.25 (dd, 1 H, $J_{3a,3e}$ −15.6, $J_{3a,4}$ 2.2 Hz, H-3*a*), 2.95 (dd, 1 H, $J_{3e,4}$ 3.9 Hz, H-3*e*), 3.49 (dd, 1 H, $J_{6,7}$ 8.3, $J_{6,5}$ 1.5 Hz, H-6), 3.78 (s, 6 H, 2 OMe), 4.05–4.65 (m, 5 H, H-4,5,7,8,8′); ^{13}C, δ 24.86, 25.08, 25.34, 27.07 (2 C*Me*$_2$), 28.92 (C-3), 52.92, 53.17 (2 OMe), 67.23 (C-8), 69.47, 72.02, 73.48, 74.07 (C-4,5,6,7), 78.57 (C-2), 109.41, 109.70 (2 *C*Me$_2$), 169.20, 169.52.

Anal. Calc. for $C_{17}H_{26}O_9$: C, 54.5; H, 7.0. Found: C, 54.55, H, 7.1.

Methyl 2,6-anhydro-3-deoxy-2-methoxycarbonyl-D-glycero-D-talo-*octonate* (**7**). — A mixture of **6** (340 mg, 0.91 mmol), Amberlite IR-120 (H^+) resin (2 mL, prewashed with anhydrous methanol), and anhydrous methanol (12 mL) was heated under reflux for 2 h, then filtered, and concentrated. Column chromatography (ethyl acetate–methanol–toluene, 14:2:1) of the residue gave **7** (210 mg, 77%), m.p. 145–148° (from methanol–ether), $[\alpha]_D$ +77° (*c* 0.2, methanol), R_F 0.30 (ethyl acetate–methanol–toluene, 7:2:1); ν_{max} ($CHCl_3$) 1740 cm^{-1} (ester). N.m.r. data (CD_3OD): ^1H, δ 2.08 (dd, 1 H, $J_{3a,3e}$ −12.7, $J_{3a,4}$ 12.7 Hz, H-3*a*), 2.38 (dd, 1 H, $J_{3e,4}$ 4.6 Hz, H-3*e*), 3.35 (d, 1 H, $J_{6,7}$ 8.1 Hz, H-6), 3.59–3.93 (m, 11 H, H-4,5,7,8,8′ and OMe at δ 3.76 and 3.78); ^{13}C, δ 32.84 (C-3), 53.64, 53.73 (2 OMe), 65.17 (C-8), 67.28, 67.96 (C-4,5), 70.81, 77.42 (C-6,7), 83.17 (C-2), 169.62, 170.20 (2 C=O).

Anal. Calc. for $C_{11}H_{18}O_9$: C, 44.9; H, 6.2. Found: C, 44.5; H, 6.3.

Ammonium 2,6-anhydro-3-deoxy-2-methoxycarbonyl-D-glycero-D-galacto-*octonate* (**8**). — A solution of **7** (240 mg, 0.81 mmol) in 0.2M NaOH (10 mL) was stored at room temperature for 45 min, then passed through Dowex 50W-X8 (NH_4^+) resin, and concentrated to give **8** (240 mg, 100%), as a semi-crystalline product after prolonged storage in the refrigerator, m.p. 150° (dec.), $[\alpha]_D$ +107° (*c* 1.5, water), R_F 0.35 (chloroform–methanol–water, 10:10:1); ν_{max}^{KBr} 1730 (ester), 1600 cm^{-1} (carboxylate). N.m.r. data (D_2O): ^1H, δ 1.84 (dd, 1 H, $J_{3a,3e}$ −13.1, $J_{3a,4}$ 13.1 Hz, H-3*a*), 2.49 (dd, 1 H, $J_{3e,4}$ 4.8 Hz, H-3*e*), 3.21 (d, 1 H, $J_{6,7}$ 8.3 Hz, H-6), 3.6–3.94 (m, 8 H, H-4,5,7,8,8′, OMe at δ 3.74); ^{13}C, δ 34.10 (C-3), 55.70 (OMe), 65.94 (C-8), 68.54, 69.42, 71.87, 77.83 (C-4,5,6,7), 86.37 (C-2), 174.82 (ester C=O), 176.33 (carboxylate C=O).

Anal. Calc. for $C_{10}H_{19}NO_9 \cdot H_2O$: C, 38.1; H, 6.7; N, 4.4. Found: C, 37.8; H, 6.9; N, 4.45.

Diammonium 2,6-anhydro-3-deoxy-2-carboxy-D-glycero-D-talo-*octonate* (**9**). — Hydrolysis of **8** (150 mg, 0.5 mmol) in 2M NaOH (2 mL) at 60° for 20 min gave, after passage through Dowex 50W-X8 (NH_4^+) resin and concentration, **9** (150 mg, 100%), which crystallised on storage, m.p. 140° (dec.), $[\alpha]_D$ +100° (*c* 2, water);

ν_{max}^{KBr} 1590–1600 cm^{-1} (carboxylates). N.m.r. data (D_2O): ^1H, δ 1.70 (dd, 1 H, $J_{3a,3e}$ −12.7, $J_{3a,4}$ 12.7 Hz, H-3*a*), 2.50 (dd, 1 H, $J_{3e,4}$ 4.4 Hz, H-3*e*), 3.24 (d, 1 H, $J_{6,7}$ 7.8 Hz, H-6), 3.72–3.95 (m, 5 H, H-4,5,7,8,8'); ^{13}C, δ 35.36 (C-3), 66.55 (C-8), 68.78, 70.22, 71.70, 76.93 (C-4,5,6,7), 87.90 (C-2), 178.64, 179.22 (C=O).

Anal. Calc. for $C_9H_{20}N_2O_9 \cdot H_2O$: C, 34.0; H, 7.0; N, 8.8. Found: C, 34.2; H, 6.7; N, 8.7.

2,6-Anhydro-3-deoxy-4,5:7,8-di-O-isopropylidene-D-glycero-D-talo-*octonamide* (**10**). — A solution of **4** (490 mg, 1.48 mmol) in saturated methanolic ammonia (10 mL) was stirred at room temperature for 2 days, and then concentrated. Recrystallisation of the residue from chloroform–pentane gave **10** (317 mg, 71%), m.p. 129–131°, $[\alpha]_D$ −38° (*c* 1.8, chloroform), R_f 0.76 (ether–acetone, 2:1). N.m.r. data ($CDCl_3$): ^1H (400 MHz), δ 1.35, 1.39, 1.43, 1.47 (4 s, 12 H, 2 Me_2C), 1.80 (ddd, 1 H, $J_{3a,3e}$ −15.5, $J_{3a,2}$ 11.6, $J_{3a,4}$ 2.7 Hz, H-3*a*), 2.50 (ddd, 1 H, $J_{3e,2}$ 5.8, $J_{3e,4}$ 2.8 Hz, H-3*e*), 3.72 (dd, 1 H, $J_{6,7}$ 4.3, $J_{6,5}$ 1.5 Hz, H-6), 4.06–4.10 (m, 2 H, H-8,8'), 4.23–4.27 (m, 2 H, H-5,7), 4.48 (dd, 1 H, H-2), 4.61 (ddd, 1 H, $J_{4,3}$ 8.0 Hz, H-4), 5.8, 6.9 (NH_2); ^{13}C, δ 24.53, 25.47, 25.97, 26.47 (2 CMe_2), 26.97 (C-3), 65.36 (C-8), 69.24 (C-2), 70.24 (C-4), 71.39 (C-6), 72.28 (C-7), 75.38 (C-5), 108.38, 109.22 (2 CMe_2), 176.42 (C-1).

Anal. Calc. for $C_{14}H_{23}NO_6$: C, 55.8; H, 7.7; N, 4.65. Found: C, 56.0; H, 7.9; N, 4.4.

2,6-Anhydro-3-deoxy-D-glycero-D-talo-*octonamide* (**11**). — Compound **10** (200 mg, 0.66 mmol) was deprotected according to the standard procedure, to give **11** (145 mg, 98%). Recrystallisation from methanol–2-propanol gave material with m.p. 191–193°, $[\alpha]_D$ +71° (*c* 0.7, methanol–water 2:1). R_f 0.56 (chloroform–methanol–water, 10:10:1). N.m.r. data (D_2O): ^1H, δ 2.00 (ddd, 1 H, $J_{3a,3e}$ −12, $J_{3a,4}$ 12, $J_{3a,2}$ 6.5 Hz, H-3*a*), 2.25 (ddd, 1 H, $J_{3e,4}$ 5.5, $J_{3e,2}$ 1.5 Hz, H-3*e*), 3.52 (dd, 1 H, $J_{6,7}$ 8, $J_{6,5}$ 1 Hz, H-6), 3.66–4.0 (m, 5 H, H-4,5,7,8,8'), 4.58 (dd, 1 H, H-2); ^{13}C, δ 27.38 (C-3), 64.22 (C-8), 67.31, 67.39 (C-4,5), 70.15 (C-7), 74.44 (C-6), 75.44 (C-2), 177.18 (C-1).

Anal. Calc. for $C_8H_{15}NO_6$: C, 43.4; H, 6.8; N, 6.3. Found: C, 43.1; H, 6.8; N, 6.3.

2,6-Anhydro-3-deoxy-N-*hydroxy-4,5:7,8-di-O-isopropylidene*-D-glycero-D-talo-*octonamide* (**12**). — Hydroxylamine hydrochloride (440 mg, 6.33 mmol) was added to a solution of **4** (400 mg, 1.26 mmol) and triethylamine (1.3 mL) in methanol (10 mL). The mixture was heated under reflux under nitrogen for 2 h, then stirred at room temperature overnight, and concentrated. Column chromatography (ether–acetone, 2:1) of the residue gave **12** (240 mg, 60%), isolated as a colourless syrup, $[\alpha]_D$ −31° (*c* 1, chloroform), R_f 0.75 (ether–acetone, 2:1). N.m.r. data ($CDCl_3$): ^1H, δ 1.26, 1.34, 1.39, 1.45 (4 s, 12 H, 2 Me_2C), 1.78 (ddd, 1 H, $J_{3a,3e}$ −15, $J_{3a,2}$ 11.8, $J_{3a,4}$ 2.5 Hz, H-3*a*), 2.48 (ddd, 1 H, $J_{3e,2}$ 6, $J_{3e,4}$ 2.8 Hz, H-3*e*), 2.63 (s, 1 H, OH), 3.71 (dd, 1 H, $J_{6,7}$ 4, $J_{6,5}$ 1.5 Hz, H-6), 3.95–4.35 (m, 4 H, H-5,7,8,8'), 4.50–4.75 (m, 2 H, H-2,4), 9.40 (s, 1 H, NH); ^{13}C, δ 24.52, 25.45, 25.94, 26.37 (2 CMe_2), 26.93 (C-3), 65.10 (C-8), 68.93 (C-2), 70.17 (C-4), 71.40 (C-6), 72.27 (C-7), 75.29 (C-5), 108.46, 109.39 (2 CMe_2), 169.92 (C-1).

Anal. Calc. for $C_{14}H_{23}NO_7 \cdot 0.5\ H_2O$: C, 51.5; H, 7.4; N, 4.3. Found: C, 51.9; H, 7.2; N, 3.8.

2,6-Anhydro-3-deoxy-N-*hydroxy*-D-glycero-D-talo-*octonamide* (**13**). — Deprotection of **12** (123 mg; 0.4 mmol) by the standard procedure and crystallisation of the product from methanol–ether gave **13** (75 mg, 83%), m.p. 148–151°, $[\alpha]_D$ +76° (*c* 1, methanol), R_F 0.57 (chloroform–methanol–water, 10:10:1). N.m.r. data (D_2O): ^1H, δ 2.00 (ddd, 1 H, $J_{3a,3e}$ −12, $J_{3a,4}$ 12, $J_{3a,2}$ 6 Hz, H-3*a*), 2.25 (ddd, 1 H, $J_{3e,4}$ 6, $J_{3e,2}$ 2 Hz, H-3*e*), 3.46 (d, 1 H, $J_{6,7}$ 8 Hz, H-6), 3.57–4.05 (m, 5 H, H-4,5,7,8,8′), 4.62 (dd, 1 H, H-2); ^{13}C, δ 28.80 (C-3), 65.67 (C-8), 68.52 (overlapping signals C-4,5), 71.29 (C-7), 74.94 (C-6), 76.86 (C-2), 172.10 (C-1).

Anal. Calc. for $C_8H_{15}NO_7$: C, 40.5; H, 6.4; N, 5.9. Found: C, 40.6; H, 6.4; N, 5.5.

2,6-Anhydro-3-deoxy-4,5:7,8-di-O-*isopropylidene*-D-glycero-D-talo-*octitol* (**14**). — A solution of **4** (2.2 g, 6.9 mmol) in dry ether was added dropwise during 5 min to a suspension of $LiAlH_4$ (270 mg, 7.1 mmol) in dry ether (100 mL) under nitrogen. The mixture was heated under reflux for 35 min, water (1.6 mL) and 2M NaOH (0.7 mL) were then added, and the ether layer was dried (K_2CO_3), filtered, and concentrated to give **14** (2.0 g, 100%). Recrystallisation from ether–light petroleum gave material with m.p. 59–63°, $[\alpha]_D$ +0.7° (*c* 0.7, dichloromethane), R_F 0.40 (ethyl acetate). N.m.r. data ($CDCl_3$): ^1H, δ 1.38, 1.42, 1.50 (3 s, 12 H, 2 CMe_2), 1.7–1.9 (m, 2 H, H-3*a*,3*e*), 3.4–3.7 (m, 3 H, H-6, CH_2), 4.0–4.3 (m, 4 H, H-5,7,8,8′), 4.32 (dd, 1 H, $J_{5,4}$ 8.3, $J_{5,6}$ 1.5 Hz, H-5), 4.59 (ddd, 1 H, $J_{4,3a}$ 2.9, $J_{4,3e}$ 2.9 Hz, H-4): ^{13}C, δ 24.45, 25.27, 26.13, 26.88 (2 CMe_2), 26.88 (C-3), 65.56, 66.87 (C-1,8), 69.16 (C-2), 70.20, 71.52, 72.37, 74.58 (C-4,5,6,7), 108.81, 109.10 (2 CMe_2).

Anal. Calc. for $C_{14}H_{24}O_6$: C, 58.3; H, 8.4. Found: C, 58.2; H, 8.2.

2,6-Anhydro-3-deoxy-D-glycero-D-talo-*octitol* (**15**). — Compound **14** (300 mg, 1 mmol) was heated under reflux with Amberlite IR-120 (H^+) resin (3 mL, prewashed with methanol and dried) in anhydrous methanol (10 mL) for 6 h. The mixture was then filtered and concentrated. Column chromatography (ethyl acetate–methanol–toluene, 65:25:10) of the residue gave **15** (100 mg, 50%), m.p. 93–94°, $[\alpha]_D$ +51° (*c* 1, methanol), R_F 0.29 (ethyl acetate–methanol–toluene, 13:5:2). N.m.r. data (CD_3OD): ^1H, δ 1.60 (dd, 1 H, $J_{3e,3a}$ −13, $J_{3e,2}$ 5 Hz, H-3*e*), 2.0 (ddd, 1 H, $J_{3a,2}$ 7, $J_{3a,4}$ 12 Hz, H-3*a*), 3.34–4.1 (m, 9 H, H-2,4,5,6,7,8,8′, CH_2); ^{13}C, δ 29.41 (C-3), 61.88 (C-1), 65.17 (C-8), 67.57, 68.77, 71.25, 72.78 (C-4,5,6,7), 74.43 (C-2).

Anal. Calc. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.75; H, 7.5.

Monoammonium 2,6-anhydro-1,3-dideoxy-D-glycero-D-talo-*octitol-1-ylphosphonate* (**18**). — A mixture of *N*-bromosuccinimide (258 mg, 1.45 mmol), triphenylphosphine (380 mg, 1.45 mmol), **14** (380 mg, 1.32 mmol), and chloroform (10 mL) was heated under reflux for 1 h. More triphenylphosphine (380 mg) and *N*-bromosuccinimide (258 mg) were then added, and the solution was heated overnight, cooled, diluted with light petroleum, filtered, and concentrated. Column

chromatography (ether–light petroleum, 2:3) of the residue gave 2,6-anhydro-1-bromo-1,3-dideoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octitol (**16**; 230 mg, 50%), R_F 0.67 (ethyl acetate). ^{13}C-N.m.r. data ($CDCl_3$): δ 24.47, 25.27, 26.15, 26.98 (2 CMe_2), 29.06 (C-1), 37.29 (C-3), 67.21, 67.36, 70.15, 72.15, 72.61, 74.14 (C-2,4,5,6,7,8), 109.27, 109.98 (2 CMe_2).

Compound **16** (230 mg, 0.65 mmol) was heated under reflux with freshly distilled triethyl phosphite (10 mL) under nitrogen for 40 h and the solution was then concentrated at 80°/0.5 mmHg. Column chromatography [ethyl acetate–hexane, 1:4 (1 L); ethyl acetate–hexane, 1:1 (750 mL); and ethyl acetate (750 mL)] gave diethyl 2,6-anhydro-1,3-dideoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octitol-1-ylphosphonate (**17**; 160 mg, 60%), R_F 0.14 (ethyl acetate). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.2–1.6 (m, 18 H, including 2 CMe_2 at 1.32, 1.35, 1.41 and 1.49, and 2 ethyl Me), 1.8–2.2 (m, 4 H, H-1a,1b,3*a*,3*e*), 3.42 (d, 1 H, $J_{6,7}$ 8 Hz, H-6), 4.0–4.6 (m, 10 H, H-2,4,5,7,8,8′, OCH_2CH_3); ^{13}C, δ 16.45 (CH_3, $^3J_{C,P}$ 6 Hz), 24.64, 25.27, 26.27, 27.07 (2 CMe_2), 31.64 (C-3, $^3J_{C,P}$ 7 Hz), 33.24 (C-1, $^1J_{C,P}$ 129 Hz), 61.55, 61.69 (2 CH_2, $^2J_{C,P}$ 6 Hz), 64.84, 67.13, 70.29, 71.32, 72.29, 74.28 (C-2,4,5,6,7,8), 108.90, 109.24 (2 CMe_2); ^{31}P, δ 27.63.

To a solution of **17** (160 mg, 0.39 mmol) in deuteriochloroform (2.5 mL with 1% of Me_4Si) was added bromotrimethylsilane (150 μL, 1.1 mmol), and the transesterification was followed by ^{1}H-n.m.r. spectroscopy. After 1 h, the solution was concentrated, the residue was dissolved in acetonitrile (2 mL) containing 5% of water, which, after 15 min, was concentrated. The residue was dissolved in water, the pH was adjusted to 8 with 0.2M ammonium hydroxide, and the solution was concentrated with methanol to dryness, to give **18** (50 mg, 44%). N.m.r. data (D_2O): ^{1}H, δ 1.6–2.3 (m, 4 H, H-1,1′,3*a*,3*e*), 3.5–4.1 (m, 6 H, H-2,5,6,7,8,8′), 4.3–4.5 (m, 1 H, H-4); ^{13}C, δ 32.43 (C-1, $^1J_{C,P}$ 131 Hz), 33.32 (C-3, $^3J_{C,P}$ 10 Hz), 65.14 (C-8), 67.81, 69.27, 71.92, 72.31, 72.92 (C-2,4,5,6,7); ^{31}P, δ 21.18 (an additional peak at 21.30). A correct elemental analysis was not obtained. Mass spectrum (f.a.b.): Calc. for $C_8H_{16}O_8P$ ($M - NH_4$)$^-$: *m/z* 271.0583. Found: *m/z* 271.0587.

*Dimethyl (2,6-anhydro-3-deoxy-4,5:7,8-di-O-isopropylidene-*D-glycero-D-talo-*octonyl)methylphosphonate* (**19**). — Dimethyl methylphosphonate (580 mg, 4.7 mmol) was added to 1.32M butyl-lithium (4.5 mmol) in tetrahydrofuran (30 mL) at −70°. After 8 min, a solution of **4** (640 mg, 2.0 mmol) in tetrahydrofuran (3 mL) was added, and the mixture was allowed to reach room temperature slowly. After neutralisation with ammonium sulphate (2 g) and the addition of water (0.5 mL), followed by stirring for 1 min, the solution was dried ($NaHCO_3$ and Na_2SO_4), filtered, and concentrated. Column chromatography (acetone–ethyl acetate, 1:1) of the residue gave **19** (536 mg, 64%), $[\alpha]_D$ −10° (*c* 1.4, dichloromethane), R_F 0.47 (acetone–ethyl acetate, 1:1). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.37, 1.42, 1.48 (3 s, 12 H, 2 CMe_2), 1.96 (ddd, 1 H, $J_{3a,3e}$ −15.0, $J_{3a,2}$ 11.4, $J_{3a,4}$ 2.7 Hz, H-3*a*), 2.18 (ddd, 1 H, $J_{3e,2}$ 5.1, $J_{3e,4}$ 2.7 Hz, H-3*e*), 3.11–3.61 (ABX, 2 H, CH_2P), 3.69 (dd, 1 H, $J_{6,7}$ 6.8, $J_{6,5}$ 1.7 Hz, H-6), 3.77 (d, 3 H, $^2J_{Me,P}$ 3.2 Hz, OMe), 3.83 (d, 3 H, $^2J_{Me,P}$ 3.2

Hz, OMe), 4.11–4.30 (m, 3 H, H-7,8,8′), 4.33 (dd, 1 H, $J_{5,4}$ 8.1 Hz, H-5), 4.47 (dd, 1 H, H-2), 4.59 (ddd, 1 H, H-4); ^{13}C, δ 24.46, 25.29, 26.13, 26.56, 26.78 (2 C*Me*$_2$ and C-3), 36.22 (CH_2, $^1J_{C,P}$ 130 Hz), 52.87, 53.15 (2 OMe, $^2J_{C,P}$ 6 Hz), 66.43 (C-8), 69.70, 71.99, 72.21, 74.29, 74.49 (C-2,4,5,6,7), 108.90 (overlapping signals, 2 *C*Me$_2$), 204.60 (C-1, $^2J_{C,P}$ 7 Hz); ^{31}P, δ 22.58. A correct elemental analysis was not obtained. Mass spectrum (f.a.b.): Calc. for $C_{17}H_{28}O_9P$ $(M - H)^-$: *m/z* 407.1471. Found: *m/z* 407.1471.

Monocyclohexylammonium (2,6-anhydro-3-deoxy-D-glycero-D-talo-*octonyl)-methylphosphonate* (**20**). — Bromotrimethylsilane (0.26 mL, 2.0 mmol) was stirred with a solution of **19** (400 mg, 0.98 mmol) in dichloromethane (3 mL) at room temperature for 20 min. Water (1 mL) was added and, after 1 h, the clear solution was concentrated. The phosphonic acid was converted into the monocyclohexylammonium salt by dissolution in water and addition of cyclohexylamine (110 mg, 1.1 mmol), to give **20** (160 mg, 41%), m.p. 133–134° (from water–ethanol). N.m.r. data (H_2O): ^{13}C, δ 26.16, 26.68, 32.87, 52.96 (cyclohexyl), 31.79 (C-3), 44.64 (CH_2, $^1J_{C,P}$ 108 Hz), 65.49 (C-8), 68.76, 71.59, 79.71, 82.19 (C-2,4,5,6,7), 209.85 (C-1, $^2J_{C,P}$ 6 Hz); ^{31}P, δ 5.40 (small additional peaks at 5.61, 5.64, and 5.67). A correct elemental analysis was not obtained. Mass spectrum (f.a.b.): Calc. for $C_9H_{16}O_9P$ $(M - C_{16}H_{14}N)^-$: *m/z* 299.0532. Found: *m/z* 299.0530.

2,6-Anhydro-3-deoxy-4,5:7,8-di-O-*isopropylidene-1*-O-*toluene*-p-*sulphonyl*-D-glycero-D-talo-*octitol* (**21**). — Toluene-*p*-sulphonyl chloride (470 mg, 2.5 mmol) was added to a solution of **14** (264 mg, 0.92 mmol) in dry dichloromethane (20 mL) and pyridine (4.5 mL), which was then heated under reflux overnight. Conventional work-up and column chromatography (ethyl acetate–hexane, 1:1) of the product gave **21** (370 mg, 76%). Recrystallisation from ether–light petroleum gave material with m.p. 82–83°, $[\alpha]_D$ +4° (*c* 0.5, dichloromethane), R_F 0.50 (ethyl acetate–hexane, 1:1). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.34, 1.35, 1.38, 1.45 (4 s, 12 H, 2 CMe$_2$), 1.80–1.86 (m, 2 H, H-3*a*,3*e*), 2.45 (s, 3 H, Ts Me), 3.40 (dd, 1 H, $J_{6,7}$ 8.2, $J_{6,5}$ 1.5 Hz, H-6), 3.79–4.20 (m, 6 H, H-1a,1b,2,7,8,8′), 4.33 (dd, 1 H, $J_{5,4}$ 8.2 Hz, H-5), 4.56 (ddd, 1 H, $J_{4,3a}$ 3.0, $J_{4,3e}$ 3.0 Hz, H-4), 7.36 (d, 2 H, aromatic), 7.80 (d, 2 H, aromatic); ^{13}C, δ 21.60 (CH_3), 24.42, 25.30, 26.08, 26.93 (2 C*Me*$_2$), 26.61 (C-3), 67.09 (C-8), 72.07 (C-1), 66.21, 69.76, 72.07, 72.24, 73.97 (C-2,4,5,6,7), 108.85, 109.22 (2 *C*Me$_2$), 127.92, 129.92, 132.96, 144.93 (aromatic).

Anal. Calc. for $C_{21}H_{30}O_8S$: C, 57.0; H, 6.8; S, 7.2. Found: C, 56.9; H, 6.9; S, 7.1.

3,7-Anhydro-2,4-dideoxy-5,6:8,9-di-O-*isopropylidene*-D-glycero-D-talo-*non*-*nonitrile* (**22**). — A mixture of **21** (270 mg, 0.61 mmol), potassium cyanide (200 mg, 3.1 mmol), and *N,N*-dimethylformamide (20 mL) was heated at 100° for 1.5 h and then concentrated. Column chromatography (ethyl acetate–hexane, 1:2) of the residue gave **22** (160 mg, 88%), m.p. 89–90°, $[\alpha]_D$ +3° (*c* 1.7, dichloromethane), R_F 0.67 (ethyl acetate). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.37, 1.38, 1.41, 1.50 (4 s, 12 H, 2 CMe$_2$), 1.8–2.1 (m, 2 H, H-4*a*,4*e*), 2.4–2.7 (ABX, 2 H, CH_2), 3.56 (dd, 1 H, $J_{7,8}$ 8.1, $J_{7,6}$ 1.5 Hz, H-7), 4.0–4.3 (m, 4 H, H-6,8,9,9′), 4.40 (dd, 1 H, $J_{6,5}$ 8.2 Hz,

H-6), 4.60 (ddd, 1 H, $J_{5,4a}$ 2.7, $J_{5,4e}$ 2.7 Hz, H-5); ^{13}C, δ 24.28, 25.30, 26.08, 26.88 (2 C*Me*$_2$), 24.81 (C-2), 30.09 (C-4), 64.29 (C-3), 67.09 (C-9), 69.67, 71.81, 72.10, 73.97 (C-5,6,7,8), 108.90, 109.29 (2 *C*Me$_2$), 117.35 (C-1).

Anal. Calc. for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.8; N, 4.7. Found: C, 60.35; H, 7.8; N, 4.5.

Methyl 3,7-anhydro-2,4-dideoxy-D-glycero-D-talo-*nononate* (**23**). — To a solution of **22** (520 mg, 1.75 mmol) in anhydrous methanol (15 mL) was added chlorotrimethylsilane (0.91 mL, 7.2 mmol) at −10°, and dry HCl was bubbled through the solution for 10 min. The mixture was then stirred for 2.5 h at −20°, the temperature was raised slowly to 0°, and water (1 mL) was added dropwise. The pH was adjusted to 5.5 with M sodium hydroxide and the solution was then concentrated with methanol to dryness. A solution of the residue in methanol was neutralised with Amberlite IR-45 (CO_3^{2-}) resin and then passed over Dowex 50W-X8 (H^+) resin with methanol as eluent. Concentration of the eluate gave **23** (270 mg, 63%), which, after recrystallisation from methanol–ether, had m.p. 113–117°, $[\alpha]_D$ +124° (*c* 0.7, methanol), R_F 0.25 (ethyl acetate–methanol–toluene, 7:2:1); ν_{max}^{KBr} 1730 cm^{-1} (ester). N.m.r. data (CD_3OD): ^1H, δ 1.57 (dd, 1 H, $J_{4e,4a}$ −13, $J_{4e,5}$ 4.5 Hz, H-4*e*), 2.09 (ddd, 1 H, $J_{4a,5}$ 13, $J_{4a,3}$ 6 Hz, H-4*a*), 2.45–2.93 (ABX, 2 H, H-2a,2b), 3.42–3.95 (m, 9 H, H-5,6,7,8,9,9′, OMe), 4.45 (ddd, 1 H, $J_{3,2b}$ 10, $J_{3,2a}$ 5 Hz, H-3); ^{13}C, δ 32.13 (C-4), 37.61 (C-2), 52.25 (OMe), 65.21 (C-9), 67.09, 68.64, 71.27, 73.24 (C-3,5,6,7,8), 173.56 (C-1).

Anal. Calc. for $C_{10}H_{18}O_7 \cdot 0.25\ H_2O$: C, 47.15; H, 7.3. Found: C, 47.0; H, 7.0.

Ammonium 3,7-anhydro-2,4-dideoxy-D-glycero-D-talo-*nononate* (**24**). — A solution of **23** (173 mg, 0.69 mmol) in M sodium hydroxide (3 mL) was stored for 30 min, and then eluted from Dowex 50W-X8 (NH_4^+) resin with water. Concentration of the eluate gave **24** (125 mg, 70%), $[\alpha]_D$ +67° (*c* 1, water), R_F 0.22 (chloroform–methanol–water, 10:10:1). N.m.r. data (D_2O): ^1H, δ 1.64 (dd, 1 H, $J_{4e,4a}$ −13.5, $J_{4e,5}$ 2.5 Hz, H-4*e*), 2.02 (ddd, 1 H, $J_{4a,5}$ 13, $J_{4a,3}$ 6 Hz, H-4*a*), 2.33–2.91 (ABX, 2 H, H-2a,2b), 3.45–4.11 (m, 6 H, H-5,6,7,8,9,9′), 4.47 (ddd, 1 H, $J_{3,2b}$ 10, $J_{3,2a}$ 5 Hz, H-3); ^{13}C, δ 32.42 (C-4), 40.13 (C-2), 62.10 (C-9), 64.14, 65.14, 67.56, 68.86, 69.08 (C-3,5,6,7,8), 164.77 (C-1). Mass spectrum (f.a.b.): Calc. for $C_9H_{15}O_7$ $(M - NH_4)^-$: *m/z* 235.0818. Found: *m/z* 235.0811.

Methyl N-*acetyl-2,6-anhydro-3-deoxy-4,5:7,8-di*-O-*isopropylidene*-D-glycero-D-talo-*octonamide* (**26**). — Compound **4** (500 mg, 1.58 mmol) was stirred with 2M NaOH (5 mL) for 2 h at room temperature, and the solution was passed through Dowex 50W-X8 ($Et_3\overset{+}{N}H$) resin and concentrated to afford **25** (497 mg, 78%), m.p. 100–103°, $[\alpha]_D$ −42° (*c* 1, chloroform), R_F 0.38 (ether). N.m.r. data ($CDCl_3$): ^1H, δ 1.26 (t, Me), 1.36, 1.37, 1.40, 1.49 (4 s, 12 H, 2 CMe$_2$), 1.89 (ddd, 1 H, $J_{3a,3e}$ −15, $J_{3a,2}$ 11, $J_{3a,4}$ 3 Hz, H-3*a*), 2.33 (ddd, 1 H, $J_{3e,2}$ 6, $J_{3e,4}$ 3.2 Hz, H-3*e*), 3.09 (q, CH_2), 3.56 (dd, 1 H, $J_{6,7}$ 8, $J_{6,5}$ 1.5 Hz, H-6), 4.06–4.36 (m, 4 H, H-5,7,8,8′), 4.44 (dd, 1 H, H-2), 4.58 (ddd, 1 H, $J_{4,5}$ 8 Hz, H-4), 9.17 (bs, NH); ^{13}C, δ 8.46 (CH_3), 25.14, 26.37, 27.08 (2 C*Me*$_2$), 27.52 (C-3), 44.91 (CH_2), 67.30 (C-8), 69.58 (C-2), 70.42 (C-4), 72.39, 72.45 (C-5,6), 74.06 (C-7), 108.99, 109.14 (2 *C*Me$_2$), 177.71 (C-1). This compound was used in the next step without further characterisation.

Triethylamine (0.15 mL, 1.1 mmol) and ethyl chloroformate (50 μL, 0.54 mmol) were added to a suspension of **25** (180 mg, 0.45 mmol) in *N,N*-dimethylformamide (5 mL) at −10°. After 5 min, a solution of glycine methyl ester hydrochloride (85 mg, 0.68 mmol) and triethylamine (0.15 mL) in *N,N*-dimethylformamide (2 mL) was added dropwise, and stirring was continued for 1 h. The mixture was then filtered and concentrated. Column chromatography (ethyl acetate–chloroform, 1:1) of the residue afforded a pale-yellow syrup which was filtered through silica gel with ether to give **26**, isolated as a colourless glass (140 mg, 82%), $[\alpha]_D$ −26° (*c* 1.6, chloroform), R_F 0.58 (ethyl acetate–chloroform, 1:1). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.28, 1.32, 1.37, 1.40 (4 s, 12 H, 2 CMe_2), 1.71 (ddd, 1 H, $J_{3a,3e}$ −15.5, $J_{3a,2}$ 11.8, $J_{3a,4}$ 2.5 Hz, H-3*a*), 2.42 (ddd, 1 H, $J_{3e,2}$ 5.5, $J_{3e,4}$ 2.8 Hz, H-3*e*), 3.63 (dd, 1 H, $J_{6,7}$ 4.8, $J_{6,5}$ 1.5 Hz, H-6), 3.69 (s, 3 H, OMe), 3.95–4.26 (m, 6 H, H-5,7,8,8′, CH_2), 4.3–4.65 (dd, 1 H, H-2; ddd, 1 H, H-4), 7.30 (t, 1 H, NH); ^{13}C, δ 24.53, 25.42, 25.97, 26.52 (2 CMe_2), 27.22 (C-3), 40.73 (CH_2), 52.29 (OMe), 65.70 (C-8), 69.34 (C-2), 70.14 (C-4), 71.64 (C-6), 72.23 (C-7), 75.18 (C-5), 108.57, 109.17 (2 CMe_2), 169.94, 173.23 (C-1, methyl ester C=O).

Anal. Calc. for $C_{17}H_{27}NO_8 \cdot 0.75\ H_2O$: C, 52.8; H, 7.4; N, 3.6. Found: C, 52.8; H, 7.0; N, 3.4.

Ammonium N-*acetyl-2,6-anhydro-3-deoxy*-D-glycero-D-talo-*octonamide* (**27**). — Compound **26** (100 mg, 0.27 mmol) was deprotected according to the standard procedure. After concentration, the residue was triturated with ether and pentane, to afford the ester as a white semi-crystalline residue (60 mg, 77%), R_F 0.52 (ethyl acetate–methanol–water, 7:2:1). N.m.r. data (CD_3OD): ^{1}H, δ 2.04 (ddd, 1 H, $J_{3a,3e}$ −12, $J_{3a,4}$ 12, $J_{3a,2}$ 6 Hz, H-3*a*), 2.32 (ddd, 1 H, $J_{3e,4}$ 5, $J_{3e,2}$ 1.5 Hz, H-3*e*), 2.92 (d, 2 H, CH_2), 3.50–4.05 (m, 9 H, H-4,5,6,7,8,8′, including OMe at δ 3.72), 4.48 (dd, 1 H, H-2); ^{13}C, δ 28.23 (C-3), 41.69 (CH_2), 52.69 (OCH_3), 64.86 (C-8), 67.94 (overlapping signals, C-4, C-5), 70.42 (C-7), 74.86 (C-6), 75.85 (C-2), 171.65, 174.37 (amide, ester).

The ester (60 mg, 0.20 mmol) was treated with 0.5M NaOH (5 mL) for 1 h and the residue was passed over Dowex 50W-X8 (NH_4^+) resin, and then concentrated to give **27** (60 mg, 100%) as a semi-crystalline residue, $[\alpha]_D$ +51.5° (*c* 1.2, methanol), R_F 0.19 (chloroform–methanol–water, 10:10:1). N.m.r. data (D_2O): ^{1}H, δ 2.00 (ddd, 1 H, $J_{3a,3e}$ −12, $J_{3a,4}$ 12, $J_{3a,2}$ 6 Hz, H-3*a*), 2.30 (ddd, 1 H, $J_{3e,4}$ 5, $J_{3e,2}$ ~1 Hz, H-3*e*), 3.58–3.96 (m, 8 H, H-4,5,6,7,8,8′, CH_2), 4.61 (dd, 1 H, H-2); ^{13}C, δ 28.91 (C-3), 45.61 (CH_2), 65.45 (C-8), 68.69, 68.54 (C-4,5), 71.43 (C-7), 75.92, 76.57 (C-2,6), 175.22, 178.96 (C-1, carboxylate). Mass spectrum (f.a.b.): Calc. for $C_{10}H_{16}NO_8$ $(M - NH_4)^-$: *m/z* 278.0876. Found: *m/z* 278.0869.

2,6-Anhydro-N-*benzyl-3-deoxy-4,5:7,8-di*-O-*isopropylidene*-D-glycero-D-talo-*octonamide* (**28**). — The amidation of **25** (280 mg, 0.69 mmol) in acetonitrile (5 mL) with triethylamine (140 μL), ethyl chloroformate (67 μL, 0.7 mmol), and benzylamine (110 μL, 1 mmol) was performed as described for **26**. Column chromatography (ether) of the product gave **28** (250 mg, 92%), m.p. 93–94°, $[\alpha]_D$ −61° (*c* 1.1, chloroform), R_F 0.60 (ether). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.12, 1.28,

1.34, 1.45 (4 s, 12 H, 2 CMe_2), 1.78 (ddd, 1 H, $J_{3a,3e}$ −15.5, $J_{3a,2}$ 11.6, $J_{3a,4}$ 2.6 Hz, H-3*a*), 2.57 (ddd, 1 H, $J_{3e,2}$ 6, $J_{3e,4}$ 3 Hz, H-3*e*), 3.70 (dd, 1 H, $J_{6,7}$ 3.5, $J_{6,5}$ 1.5 Hz, H-6), 3.94–4.30 (m, 4 H, H-5,7,8,8'), 4.46–4.70 (m, 4 H, H-2,4, CH_2), 7.3 (s, 5 H, Ph); ^{13}C, δ 24.53, 25.32, 25.92 (2 CMe_2), 26.92 (C-3), 43.17 (CH_2), 64.96 (C-8), 69.44 (C-2), 70.39 (C-4), 71.24 (C-6), 72.33 (C-7), 75.47 (C-5), 108.03, 109.27 (2 CMe_2), 127.52, 127.97, 128.62, 137.79 (aromatic), 172.64 (C-1).

Anal. Calc. for $C_{21}H_{29}NO_6 \cdot 0.25\ H_2O$: C, 63.7; H, 7.5; N, 3.5. Found: C, 63.5; H, 7.4; N, 3.5.

2,6-Anhydro-N-*benzyl-3-deoxy*-D-glycero-D-talo-*octonamide* (**29**). — Deprotection of **28** (200 mg, 0.51 mmol) by the general procedure and crystallisation of the product from methanol–ether gave **29** (110 mg, 69%), m.p. 155–156°, $[\alpha]_D$ +49° (*c* 0.4, methanol), R_F 0.60 (ethyl acetate–methanol–toluene, 7:2:1). N.m.r. data (CD_3OD): ^1H, δ 2.04 (ddd, 1 H, $J_{3a,3e}$ −12, $J_{3a,4}$ 12, $J_{3a,2}$ 6 Hz, H-3*a*), 2.35 (ddd, $J_{3e,4}$ 6, $J_{3e,2}$ 2 Hz, H-3*e*), 3.44–3.90 (m, 6 H, H-4,5,6,7,8,8'), 4.33–4.57 (m, 3 H, H-2, CH_2), 7.28 (s, 5 H, Ph); ^{13}C, δ 28.22 (C-3), 44.02 (CH_2), 64.71 (C-8), 67.85, 68.10 (C-4,5), 70.29 (C-7), 75.08 (C-6), 75.92 (C-2), 128.22, 128.67, 129.51, 139.38 (aromatic), 178.28 (C-1).

Anal. Calc. for $C_{15}H_{21}NO_6$: C, 57.9; H, 6.8; N, 4.5. Found: C, 58.1; H, 6.7; N, 4.3.

2,6-Anhydro-3-deoxy-N-*hexyl-4,5:7,8-di*-O-*isopropylidene*-D-glycero-D-talo-*octonamide* (**30**). — Compound **30** was prepared from **25** (250 mg, 0.62 mmol) in tetrahydrofuran (5 mL) by reaction with triethylamine (0.2 mL), ethyl chloroformate (66 μL, 0.68 mmol), and hexylamine (0.12 mL, 0.62 mmol) as described for **26**. Column chromatography (ethyl acetate–chloroform, 1:1) of the product gave **30** (170 mg, 71%), which crystallised after prolonged storage and had m.p. 33–35°, $[\alpha]_D$ −38° (*c* 1.9, chloroform), R_F 0.65 (ethyl acetate–chloroform, 1:1). N.m.r. data ($CDCl_3$): ^1H, δ 0.82 (t, 3 H, H-6',6',6'), 1.19–1.39 (m, 20 H, 2 CMe_2 and H-2',2',3',3',4',4',5',5'), 1.65 (ddd, 1 H, $J_{3a,3e}$ −15.5, $J_{3a,2}$ 11.7, $J_{3a,4}$ 2.5 Hz, H-3*a*), 2.45 (ddd, 1 H, $J_{3e,2}$ 6, $J_{3e,4}$ 3 Hz, H-3*e*), 3.19 (q, 2 H, H-1,1), 3.61 (dd, 1 H, $J_{6,7}$ 4, $J_{6,5}$ 1.5 Hz, H-6), 3.94–4.20 (m, 4 H, H-5,7,8,8), 4.39 (dd, 1 H, H-2), 4.52 (ddd, 1 H, $J_{4,5}$ 8 Hz, H-4), 6.9 (t, 1 H, NH); ^{13}C, δ 14.01 (C-6'), 22.53 (C-5'), 24.53, 25.42, 25.92, 26.47 (2 CMe_2), 26.57, 27.02, 29.56 (C-3,3',4'), 31.46 (C-2'), 38.93 (C-1'), 65.16 (C-8), 69.34 (C-2), 70.34 (C-4), 71.24 (C-6), 72.38 (C-7), 75.52 (C-5), 108.13, 109.22 (2 CMe_2), 172.58 (C-1).

Anal. Calc. for $C_{20}H_{35}NO_6$: C, 62.3; H, 9.15; N, 3.6. Found: C, 62.3; H, 9.3; N, 3.4.

2,6-Anhydro-3-deoxy-N-*hexyl*-D-glycero-D-talo-*octonamide* (**31**). — Compound **30** (170 mg, 0.44 mmol) was deprotected according to the standard procedure. Crystallisation of the product from methanol–ether afforded **31** (120 mg, 92%), m.p. 128–129°, $[\alpha]_D$ +59° (*c* 1, methanol), R_F 0.68 (ethyl acetate–methanol–toluene, 7:2:1). N.m.r. data (CD_3OD): ^1H, δ 0.90 (t, 3 H, H-6',6',6'), 1.23–1.70 (m, 8 H, H-2',2',3',3',4',4',5',5'), 2.00 (ddd, 1 H, $J_{3a,3e}$ −12, $J_{3a,4}$ 12, $J_{3a,2}$ 6 Hz, H-3*a*), 2.30 (ddd, 1 H, $J_{3e,4}$ 5, $J_{3e,2}$ 2 Hz, H-3*e*), 3.10–4.00 (m, 8 H, H-

1',1',4,5,6,7,8,8), 4.39 (dd, 1 H, H-2); ^{13}C, δ 14.41 (C-6'), 23.68 (C-5'), 27.82, 28.12, 30.31 (C-3,3',4'), 32.65 (C-2'), 40.43 (C-1'), 64.66 (C-8), 67.10, 67.85 (C-4,5), 70.24 (C-7), 75.03 (C-6), 75.72 (C-2), 173.03 (C-1).

Anal. Calc. for $C_{14}H_{27}NO_6 \cdot 0.25\ H_2O$: C, 54.3; H, 8.9; N, 4.5. Found: C, 54.2; H, 8.8; N, 4.6.

*Benzyl 2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-*D-glycero-D-talo-*octonate* (**32**). — Compound **4** (600 mg, 1.9 mmol) was heated at 120° with benzyl alcohol (20 mL) and a catalytic amount of magnesium methoxide for 7 h under nitrogen. The solution was neutralised with Amberlite IR-120 (H^+) resin (prewashed with methanol and dried), filtered, and concentrated. Column chromatography (ethyl acetate–toluene, 1:9) of the product gave **32** (600 mg, 81%), isolated as a colourless syrup, $[\alpha]_D$ −26° (*c* 1.2, dichloromethane), R_F 0.57 (ethyl acetate–toluene, 1:2). N.m.r. data ($CDCl_3$): ^{1}H, δ 1.30, 1.37, 1.40, 1.48 (4 s, 12 H, 2 CMe_2), 1.85 (ddd, 1 H, $J_{3a,3e}$ −15, $J_{3a,2}$ 11.7, $J_{3a,4}$ 2.4 Hz, H-3*a*), 2.31 (ddd, 1 H, $J_{3e,2}$ 5.9, $J_{3e,4}$ 3.4 Hz, H-3*e*), 3.51 (dd, 1 H, $J_{6,7}$ 8.3, $J_{6,5}$ 1.5 Hz, H-6), 4.03–4.26 (m, 3 H, H-7,8,8'), 4.33 (dd, $J_{5,4}$ 7.8 Hz, H-5), 4.55–4.63 (m, 2 H, H-2,4), 5.18 (s, 2 H, CH_2), 7.35 (s, 5 H, Ph); ^{13}C, δ 24.96, 25.20, 26.22, 26.85 (2 C*Me*$_2$), 27.00 (C-3), 66.60 (CH_2), 67.23 (C-8), 68.52 (C-2), 69.76 (C-4), 72.32 (C-5), 72.90 (C-6), 73.78 (C-7), 109.29 (overlapping signals, 2 *C*Me$_2$), 128.24, 128.29, 128.61, 135.61 (aromatic), 172.58 (C-1).

Anal. Calc. for $C_{21}H_{28}O_7$: C, 64.3; H, 7.2. Found: C, 64.6; H, 6.8.

*Benzyl 2,6-anhydro-3-deoxy-*D-glycero-D-talo-*octonate* (**33**). — Compound **32** (580 mg, 1.48 mmol) was deprotected according to the standard procedure. Column chromatography (ethyl acetate–methanol–toluene, 7:2:1) of the product gave **33** (210 mg, 45%). Recrystallisation from methanol gave material with m.p. 131–132°, $[\alpha]_D$ +60° (*c* 1.15, methanol), R_F 0.35 (ethyl acetate–methanol–toluene, 7:2:1). N.m.r. data (CD_3OD): ^{1}H, δ 2.12–2.19 (m, 2 H, H-3*a*,3*e*), 3.46–3.60 (m, 3 H), 3.73–3.80 (m, 2 H), 3.92 (d, 1 H), 4.60 (dd, 1 H), 5.20 (AB, 2 H, CH_2), 7.38 (s, 5 H, Ph); ^{13}C, δ 29.70 (C-3), 65.68 (C-8), 68.01, 68.11, 71.25, 73.95, 76.53 (C-2,4,5,6,7), 129.51, 129.70, 137.24 (aromatic), 173.29 (C-1).

Anal. Calc. for $C_{15}H_{20}O_7 \cdot 0.5\ CH_3OH$: C, 56.7; H, 6.75. Found: C, 56.8; H, 6.4.

*Hexyl 2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-*D-glycero-D-talo-*octonate* (**34**). — Transesterification of **4** (430 mg, 1.36 mmol) in 1-hexanol (17 mL) with magnesium methoxide was carried out as for **32**. Column chromatography (ethyl acetate–toluene, 1:6) of the product gave pure **34** (470 mg, 90%) as a colourless syrup, $[\alpha]_D$ −33° (*c* 1.55, chloroform), R_F 0.58 (ethyl acetate–toluene, 1:2). N.m.r. data ($CDCl_3$): ^{1}H, δ 0.89 (t, 3 H, H-6',6',6'), 1.2–1.7 (m, 20 H, 2 CMe_2 and H-2',2',3',3',4',4',5',5'), 1.85 (ddd, 1 H, $J_{3a,3e}$ −15, $J_{3a,2}$ 11.7, $J_{3a,4}$ 2.4 Hz, H-3*a*), 2.31 (ddd, 1 H, $J_{3e,2}$ 5.9, $J_{3e,4}$ 3.2 Hz, H-3*e*), 3.51 (d, 1 H, $J_{6,7}$ 8.0 Hz, H-6), 4.10–4.25 (m, 5 H, H-1',1',7,8,8), 4.35 (dd, 1 H, $J_{5,6}$ 1.5, $J_{5,4}$ 7.8 Hz, H-5), 4.5–4.6 (m, 2 H, H-2,4): ^{13}C, δ 13.99 (C-6'), 22.55 (C-5'), 25.61, 26.30, 28.68 (C-3,3',4'), 25.03, 25.25, 26.98, 27.10 (2 C*Me*$_2$), 31.45 (C-2'), 65.14 (C-1'), 67.33 (C-8), 68.57 (C-2), 69.91 (C-4), 72.42 (C-5), 72.95 (C-6), 73.88 (C-7), 109.34, 109.41 (2 *C*Me$_2$), 172.98 (C-1).

Anal. Calc. for $C_{20}H_{34}O_7$: C, 62.15; H, 8.9. Found: C, 61.9; H, 9.0.

Hexyl 2,6-anhydro-3-deoxy-D-glycero-D-talo-*octonate* (**35**). — Compound **34** was deprotected according to the standard procedure. Column chromatography (ethyl acetate–toluene–methanol, 7:1:1) of the product gave **35** (270 mg, 73%). Recrystallisation from ethanol–ether gave material with m.p. 114–116°, $[\alpha]_D$ +59° (*c* 0.1, methanol), R_f 0.36 (ethyl acetate–methanol–toluene, 7:2:1). N.m.r. data (CD_3OD): ^1H, δ 0.92 (t, 3 H, H-6′,6′,6′), 1.25–1.8 (m, 8 H, H-2′,2′,3′,3′,4′,4′,5′,5′), 2.1–2.2 (m, 2 H, H-3*a*,3*e*), 3.50 (d, 1 H, H-6), 3.48–3.83 (m, 4 H, H-4,7,8,8), 3.96 (d, 1 H, H-5), 4.16 (m, 2 H, OCH_2), 4.55 (dd, 1 H, H-2): ^{13}C, δ 14.33 (C-6′), 23.55 (C-5′), 26.68, 29.65 (C-3,3′,4′), 32.52 (C-2′), 65.65 (C-1′), 66.48 (C-8), 68.04, 71.08, 73.83, 76.38 (C-2,4,5,6,7), 173.51 (C-1).

Anal. Calc. for $C_{14}H_{26}O_7$: C, 54.9; H, 8.6. Found: C, 54.8; H, 8.3.

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