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Synthesis of some C-8-modified 3-deoxy-β-D-*manno*-2-octulosonic acid analogs as inhibitors of CMP-Kdo synthetase

Jack Tadanier, Cheuk-Man Lee, David Whittern, and Norman Wideburg
Antiinfective Research Division, Abbott Laboratories, Abbott Park, North Chicago, Illinois 60064 (U.S.A.)

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ABSTRACT

Selective C-8 modifications of 2,6-anhydro-3-deoxy-D-*glycero*-D-*talo*-octonic acid ("2,3-dideoxy-β-D-*manno*-2-octulosonic acid", 1a) were effected *via* the protected 8-hydroxy derivatives **2d** and **2e**. Swern oxidation of **2d** and **2e** gave the aldehydes **3a** and **3b**, respectively. Compounds **3a** and **3b** were converted into the oxime **13b** and the *O*-methyloxime **13c** derivatives, respectively. Methodology was developed for selective cleavage of the protecting groups of **13b** and **13c** to give the deprotected oxime **12m** and the deprotected *O*-methyloxime **12n**, respectively. Side chain-extended products were prepared from the aldehyde **3a** utilizing Wittig methodology. The branched chain allylic amine **12p** was prepared from **3a** in a sequence the keys steps of which were preparation of the methyl ketone **19a** using $LiCuMe_2$ followed by Swern oxidation, methylenation of **19a** using CH_2I_2–Zn–$TiCl_4$ to give the alkene **19b**, followed by Wohl–Ziegler bromination of **19b** to give the allylic bromide **19c**, and conversion of the latter to the allylic azide **19d**. A number of the analogs showed significant activities *vs.* CMP-Kdo synthetase. The most active of these was the side-chain extended alkene **12d**, which proved second in activity only to the 9-amino analog (**1c**).

INTRODUCTION

After the discovery in these laboratories that 2,6-anhydro-3-deoxy-D-*glycero*-D-*talo*-octonic acid **1a** was a potent inhibitor of CMP-Kdo synthetase[1a], a number of analogs of **1a** were prepared[1b] with the object of preparing more-potent inhibitors which might lead to antibacterial agents active against Gram-negative bacteria. Of the analogs of **1a** initially prepared, the most active were those modified at C-8, in particular the 8-deoxy-8-amine **1b** and the 8-aminomethyl-8-deoxy derivative **1c**. The syntheses of all these new C-8-modified analogs of **1a** were based on selective reaction of the C-8 hydroxyl group of the methyl ester of **1a**, and proceeded *via* the 8-deoxy-8-bromo derivative **1d**.

The object of the present work was to develop a versatile method for the preparation of additional C-8 modified analogs of **1a**, with potential as CMP-Kdo synthetase inhibitors, which would have been inaccessible by the earlier methodology[1]. For this purpose, we planned the preparation of derivatives of **1a** in which all functional groups other than the C-8 hydroxyl would be protected with suitable protecting groups that would allow extensive modification at C-8.

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DISCUSSION

Selective benzoylation of the methyl ester of **1a** gave the 8-*O*-benzoyl derivative **1e**. The latter, on treatment with acetone in the presence of acidic resin, gave the isopropylidene derivative **2a**. For requirements of selective deprotection of products to be described, the C-7 hydroxyl group of **2a** was protected with both MEM[2] and SEM[3] groups to give **2b** and **2c**, respectively. Zemplén methanolysis of **2b** and **2c** gave the corresponding 8-hydroxy analogs **2d** and **2e**, which on Swern oxidation[4] gave the corresponding aldehydes **3a** and **3b**.

Sodium borohydride reduction of the aldehyde **3a** regenerated the alcohol **2d**, while reductive amination of **3a** with sodium cyanoborohydride and ammonium acetate gave the amine **2f**. Deprotection of **2f** gave the 2-deoxy analog **1b**, identical with that prepared *via* the 8-bromo compound **1d** by the earlier methodology[1]. The syntheses of **1a** and **1b** *via* the aldehyde **3a** provided methodology for syntheses from **3a** with sodium borotritiide, and sodium cyanoborotritide and ammonium acetate, respectively, of the 8-tritiated derivatives of **1a** and **1b**, which were employed in studies of CMP-Kdo synthetase inhibition[5].

Treatment of the alcohol **2d** with DAST in CH_2Cl_2 gave a mixture of two products. Complete deprotection of the mixture followed by column chromatography led to isolation of the 8-fluoro analog **12a** and the 8-*O*-(2-methoxyethyl) analog **12b**. Isolation of **12b** must be a consequence of competition in the reaction of **2d** with DAST between direct C-8 fluorination and participation of the internal oxygen of the MEM group leading to transfer of the 2-methoxyethoxy moiety of the MEM group to the C-8 carbon.

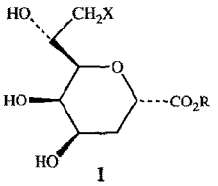
Treatment of the aldehyde **3a** with DAST in CH_2Cl_2 gave the *gem*-difluoride **4**.

Wittig reaction of the aldehyde **3a** with triphenylphosphonium methylide gave the alkene **5**, which was converted to the 8-deoxy-8-hydroxymethyl analog **6a** by hydroboration.

Osmylation of **5** gave a mixture of C-8-epimeric 8,9-diols **6b** (epimer 1) and **7a** (epimer 2) in a ratio of 6:1 as determined by ^{1}H-n.m.r. spectroscopy[6]. Selective *p*-toluenesulfonylation of the primary hydroxyl groups of the glycol mixture followed by treatment of the product mixture (**6c** + **7b**) with sodium azide in DMF gave a mixture of C-8 epimeric hydroxy azides **6d** (epimer 1) and **7c** (epimer 2), which were separated by chromatography.

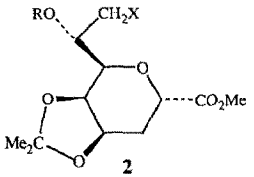
As the 9-amino-8-deoxy analog **1c** was the most active analog prepared[1], we were interested in preparing both of the two possible 9-amino-8-hydroxy analogs **12j** (epimer 1) and **12k** (epimer 2) for bioassay as CMP-Kdo synthetase inhibitors. In order to prepare a sufficient amount of a protected azide with the proper C-8 configuration for conversion to **12l**, the major hydroxy azide **6d** (epimer 1) was converted into the 8-*O*-methylsulfonyl derivative **6e**, and C-8 epimerization was effected by cesium acetate displacement to give the azido acetate **7d** (epimer 2).

To obtain an 8,9-diamino analog, the glycol mixture of **6c** and **7b** was converted into the corresponding 8,9-di-*O*-methylsulfonyl mixture of **6f** and **7e** which was treated



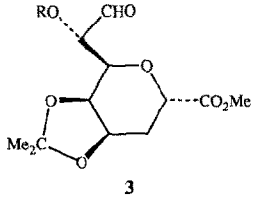
1

a. X = OH, R = H
b. X = NH_2, R = H
c. X = CH_2NH_2, R = H
d. X = Br, R = Me
e. X = OBz, R = Me



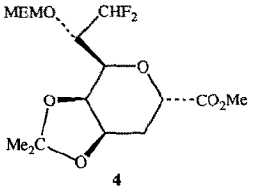
2

a. R = H, X = OCOPh
b. R = MEM, X = OCOPh
c. R = SEM, X = OCOPh
d. R = MEM, X = OH
e. R = SEM, X = OH
f. R = MEM, X = NH_2
g. R = MEM, X = F
h. R = H, X = OCH_2CH_2OMe



3

a. R = MEM
b. R = SEM



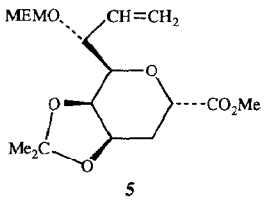
4

with sodium azide in DMF to give a mixture of diazides **6g** (epimer 1) and **7f** (epimer 2) in a ratio* of 1:6 as determined by ^{1}H-n.m.r. spectroscopy[6], in which the C-8 configuration of the major epimer **7f** is presumed opposite to that of the major glycol **6b** in the starting material.

An attempt to prepare the cyano azide **7g** by treatment of the azido methanesulfonate **6e** with tetrabutylammonium cyanide in acetonitrile gave instead the acetylene **8**. This unexpected conversion of the vicinal azido methanesulfonate to the acetylene is of particular interest in view of the recent report[7] of the conversion of both epimers of the geminal cyano methanesulfonate **9** into the acetylene **10** on treatment with sodium azide in DMF.

Deprotections of the new, neutral Kdo analogs were carried out by first removing the isopropylidene and MEM groups, as well as the *O*-acetyl group of **7d** by acid-catalyzed methanolysis using AG50W-X8(H^+), followed by hydrolysis of the resulting methyl esters **11** with triethylamine in water, and conversion of the resulting triethylamine salts into the free acids **12** with AG50-X8(H^+) resin in water. Catalytic hydro-

* This ratio was determined from the ratio of the areas of the quartets due to the absorptions of the internal methylene protons of the MEM groups of the C-8 epimers. Although the empirical rules of Kishi[6] for the stereochemistry of osmylation predict that the major diol would be formed with the *erythro* relationship of the configurations at C-7 and C-8, in the present case the configurations at C-8 of the diol epimers were not independently determined and are left unspecified. Structures **6** and **7** are used as a convention to distinguish the major (epimer 1) and minor (epimer 2) epimers, respectively, formed by osmylation of the alkene **5**.



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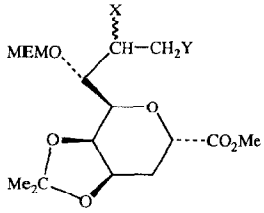
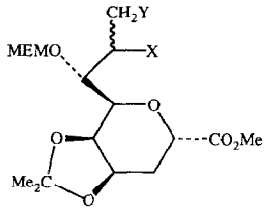


6

a. X = H, Y = OH
b. X = Y = OH
c. X = OH, Y = $OSO_2C_6H_4$-*p*-Me
d. X = OH, Y = N_3
e. X = OSO_2Me, Y = N_3
f. X = Y = OSO_2Me
g. X = Y = N_3



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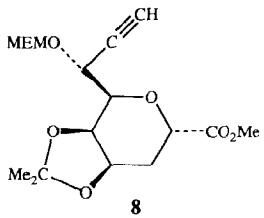


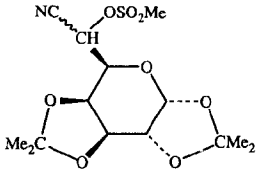
8

a. X = Y = OH
b. X = OH, Y = $OSO_2C_6H_4$-p-Me
c. X = OH, Y = N_3
d. X = $OCOCH_3$, Y = N_3
e. X = Y = OSO_2Me
f. X = Y = N_3
g. X = CN, Y = N_3

genation of the azido acids gave the amino acids which were purified by column chromatography. The C-8 epimeric composition of the glycol mixture **12f** (epimer 2/epimer 1) and the diamine mixture **12l** (epimer 1/epimer 2) was based on the compositions of the epimeric mixtures of the protected precursors (**6b** + **7a**) and (**6g** + **7f**), respectively, determined by ^{1}H-n.m.r. as already described. The activities of the Kdo analogs as inhibitors of CMP-Kdo synthetase inhibitors are recorded in Table I.

The most active of these new Kdo analogs **12a–l** was the alkene **12d**, which has proved to be exceeded in acivity only by the 9-amino-8-deoxy-analog[1] **1c**. This suggested the preparation of additional C-8 modified analogs having sp^2 hybridization at C-8, such as the oxime **12m** and the *O*-methyloxime **12n**.

Although the MEM aldehyde **3a** was readily converted into the oxime **13a**, attempted removal of the MEM and isopropylidene groups by acid-catalyzed methanolysis with AG50W-X8(H^+) as already described, gave a single epimer of the methyl glycoside **14a** rather than the desired oxime **15a**. The same product was obtained by similar acid-catalyzed methanolysis of the aldehyde **3a**. As formation of **14a** from **13a** was a consequence of cleavage of the oxime group during acid-catalyzed methanolysis, other deprotection conditions were required to allow retention of the oxime group.



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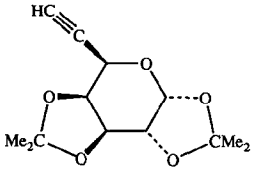

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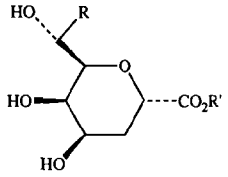
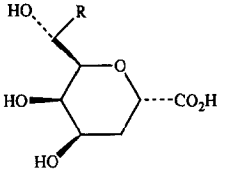


11

(a - m, o - s) R' = Me
(n) R' = Bn



12

R

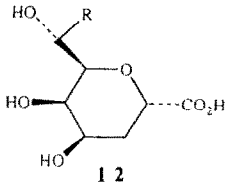
a. CH_2F
b. CH_2OCH_2OMe
c. CHF_2
d. $CH{=}CH_2$
e. CH_2CH_2OH
f. $CH(OH)CH_2OH$
g. $CH(OH)CH_2N_3$ (1)
h. $CH(OH)CH_2N_3$ (2)
i. $C{\equiv}CH$
j. $CH(OH)CH_2NH_2$ (1)
k. $CH(OH)CH_2NH_2$ (2)
l. $CH(NH_2)CH_2NH_2$
m. $CH{=}NOH$
n. $CH{=}NOMe$
o. *trans*-$CH{=}CHCH_2NH_2$
p. $C(=CH_2)CH_2NH_2$
q. *trans*-$CH{=}CHCH_2OH$
r. $C(=CH_2)CH_2N_3$
s. *cis*-$CH{=}CHCH_2NH_2$

TABLE I

CMP-Kdo Synthetase Inhibition

Compound	*R*	*IC50*(μM)
1c[a,d]	$CH_2CH_2NH_2$	2.0
1b[a,d]	CH_2NH_2	4.0
12d[e]	$CH{=}CH_2$	4.3
1d[a,e]	Me	4.8
12m[f]	$CH{=}NOH$	7.9
1a[e]	CH_2OH	10.5
12i[d]	$C{\equiv}CH$	12
12c[e]	CHF_2	14
12a[e]	CH_2F	15
12e[e]	CH_2CH_2OH	33
12q[d]	*t*-$CH{=}CHCH_2OH$	45
12f[b,d]	$CH(OH)CH_2OH$	70
12p[d]	$C(=CH_2)CH_2NH_2$	78
12k[d]	8-$CH(OH)CH_2NH_2$(epimer 2)	110
12l[c,d]	$CH(NH_2)CH_2NH_2$	140
12j[d]	8-$CH(OH)CH_2NH_2$(epimer 1)	220
12o[f]	*t*-$CH{=}CHCH_2NH_2$	240
12n[e]	$CH{=}NOMe$	280
12b[f]	$CH_2OCH_2CH_2OMe$	760

[a] Ref. 1. [b] (Epimer 1)/(Epimer 2) = 6. [c] (Epimer 2)/(Epimer 1) = 6. [d] Free acid. [e] Ammonium salt. [f] Triethylammonium salt.



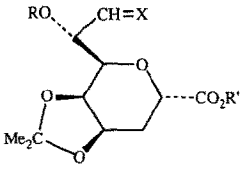
1 2

As the SEM group was reported to be subject to selective removal[3] with Bu_4NF in THF, the SEM alcohol **2e** was prepared and subjected to Swern oxidation to the aldehyde **3b**. The latter was readily converted into the oxime **13b**. Attempted removal of the SEM group of **13b** under the original conditions[3] was unsuccessful. We thus subjected **13b** to the action of $LiBF_4$ under the conditions of Ireland[8], which were also reported to cleave acetal groups, but the desired oxime could not be isolated. Instead, chromatography of the product gave a low yield of the methyl glycoside **14a**. As the $LiBF_4$ deprotection of **13b** was carried out in the absence of methanol, and the R_F value of the product detected by t.l.c. differed from that of **14a**, it was believed that formation of **14a** occurred on silica gel chromatography as a consequence of the presence of MeOH in the chromatography system. This suggested that $LiBF_4$ deprotection resulted in removal of the oxime group of **13b** as well as the SEM group and the isopropylidene group, and that the spot detected by t.l.c. of the product before chromatography was the deprotected aldehyde **15b** or its cyclic hemiacetal tautomer **14b**. Accordingly, the $LiBF_4$ deprotection was repeated, and the resulting solution was treated with hydroxylamine hydrochloride and pyridine. Chromatography of the resulting product gave the desired oxime methyl ester **11m**, which was converted into the oxime acid **12m** by hydrolysis with triethylamine in water.

The SEM aldehyde **3b** was readily converted into the *O*-methyl oxime **13c**. The recent report by Paquette[9] of selective removal of SEM groups with molten Bu_4NF suggested deprotection of **13c** using this methodology. Treatment of **13c** with fused Bu_4NF gave a new, polar product detected by t.l.c. which could not be isolated by column chromatography. As the polar nature of the product shown by t.l.c. suggested that ester cleavage had occurred, leading to the tetrabutylammonium salt **13d**, the melt containing the new product was dissolved in DMF and treated with benzyl bromide to yield the benzyl ester **13e** in 86% yield from the *O*-methyl oxime **13c**. The isopropylidene group of **13e** was removed on treatment with aqueous acetic acid, and the resulting benzyl ester **11n** was hydrolyzed with triethylamine in water to give the *O*-methyloxime acid **12n**.

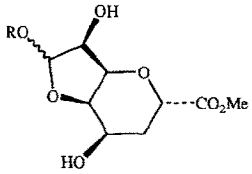
As among the most active analogs prepared were the 8-deoxy-9-amine **1c** and the 8,9-alkene **12d** (Table I), it seemed desirable to prepare analogs that possessed both a side chain amino group and an 8,9-double bond. Accordingly the allylic amines **12o** and **12p** were synthesized. The latter analog **12p** was of particular interest as it possessed both the C-9 amino group of **1c** and the terminal double bond of the alkene **12d**.

The synthesis of **12o** was initiated by reaction of the aldehyde **3a** with (triphenylphosphosphoranylidene)acetaldehyde to give the *trans*-α,β-unsaturated aldehyde **16**.



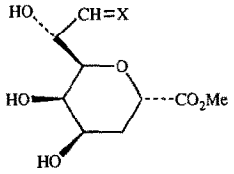
13

a. R = MEM, X = NOH, R' = Me
b. R = SEM, X = NOH, R' = Me
c. R = SEM, X = NOMe, R' = Me
d. R = H, X = NOMe, R' = NBu_4
e. R = H, X = NOMe, R' = Bn



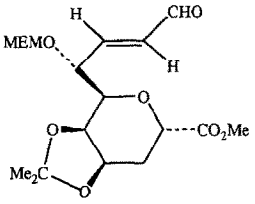
14

a. R = Me
b. R = H



15

a. X = NOH
b. X = O



16

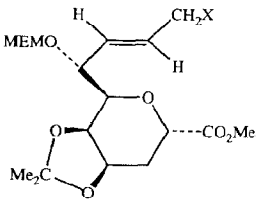
Reduction of **16** with $NaBH_3CN$ in methanol in the presence of acetic acid or with $NaBH_4$ in aqueous methanol gave the allylic alcohol **17a**, which was deprotected to give the analog **12q**.

The allylic alcohol **17a** was converted into the allylic azide **17b** with LiN_3 Ph_3P, and CBr_4 in DMF by the method of Hata, *et al.*[10]. Selective reduction of **17b** to the allylic amine **17c** was effected with Ph_3P in THF, followed by addition of water according to the method of Knouzi *et al.*[11].

Treatment of **17c** with 1:10 HCl–MeOH gave two products which were separated chromatographically. The major, less-polar product was not characterized, but was unaffected by further treatment with 1:10 HCl–MeOH as assayed by t.l.c. Ester hydrolysis of the more-polar product gave the desired amino acid **12o**.

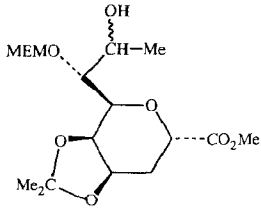
The first step in the synthesis of the allylic amine **12p** was the conversion of the aldehyde **3a** into a mixture of C-8 epimeric secondary alcohols **18** with Me_2CuLi. Swern oxidation of **18** gave the ketone **19a**. Attempts to effect methylenation of **19a** to form the alkene **19b** by means of the Wittig reaction were unsuccesful and led only to polar degradation-products. The conversion of **19a** into the alkene **19b** was effected with CH_2I_2–Zn–$TiCl_4$ by the method of Hibino, *et al.*[12]. Wohl–Ziegler bromination of **19b** gave a mixture of products containing the desired bromide **19c**. Treatment of the mixture with LiN_3 in DMF gave the allylic azide **19d**.

Because of the low yield obtained on acid hydrolysis of the protected, isomeric allylic amine **17c**, as just described, an alternative approach for the conversion of **19d**



17

a. X = OH
b. X = N_3
c. X = NH_2
d. X = Br



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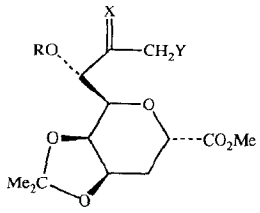
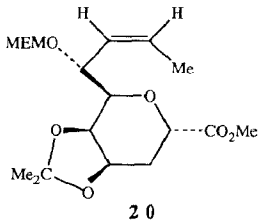


19

a. X = O, Y = H, R = MEM
b. X = CH_2, Y = H, R = MEM
c. X = CH_2, Y = Br, R = MEM
d. X = CH_2, Y = N_3, R = MEM
e. X = CH_2, Y = N_3, R = H
f. X = CH_2, Y = N_3, R = $SiBu^tMe_2$
g. X = CH_2, Y = NH_2, R = $SiBu^tMe_2$



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into the amino acid **12p** was desired. Accordingly, **19d** was hydrolyzed with 1:10 HCl–MeOH, but selective reduction of the azide group of the resulting allylic azide methyl ester **11r** with Lindlar catalyst by the method of Corey[13] was unsuccessful. Acid-catalyzed isopropylidenation of **11r** gave **19e**, which was converted into the 7-O-*tert*-butyldimethylsilyl ether **19f**. Reduction of **19f** to the amine **19g** was effected with Ph_3P followed by the addition of water in CH_2Cl_2. Cleavage of the *tert*-butyldimethylsilyl and isopropylidene groups of **19g** with 1:10 HCl–MeOH followed by hydrolysis with triethylamine in water gave the amino acid **12p**.

In an attempt to prepare the *cis* allylic amine **12s**, the aldehyde **3a** was converted into the *cis* alkene **20** by means of the Wittig reaction. Wohl–Ziegler bromination of **20**, however, gave rise to *cis–trans* interconversion of the double bond leading to the *trans* allylic bromide **17d**, as established by the coupling constant of the vinyl protons of **17d**. Treatment of the crude bromide **17d** with LiN_3 in DMF gave the *trans* allylic azide **17b**, identical with that prepared from the alcohol **17a** as already described.

CMP-Kdo synthetase inhibition. — The IC_{50} values of the 2-deoxy-Kdo analogs are recorded in Table I. The most active of the new analogs was the alkene **12d**, which was second in activity only to the most active analog, the 9-amino-8-deoxy-analog **1c**,

which was reported previously[1]. Disappointingly, both of the C-8-epimeric 8-hydroxy-9-amines (**12j** and **12k**) were much less active than **1c**.

EXPERIMENTAL

General methods. — N.m.r. spectra were determined with a General Electric GN 300 spectrometer at 300 MHz. High-resolution mass spectra were determined with a Kratos MS50 mass spectrometer. I.r. spectra were determined with a Perkin–Elmer model 283B i.r. spectrophotometer or a Nicolet 60 SX FT i.r. spectrometer. All compounds had absorptions characteristic of their chromophores present. Optical rotations were determined with a Perkin–Elmer model 241 digital polarimeter. Evaporations were performed under diminished pressure. Gravity chromatography was performed with Merck, Darmstadt 70–230 mesh silica gel. Flash chromatography was performed with Merck, Darmstadt 230–400 mesh silica gel. Extractions with $CHCl_3$ were carried out by shaking the mixtures or solutions with mixtures of $CHCl_3$ and 5% aq. $NaHCO_3$. The $CHCl_3$ solutions were separated and dried ($MgSO_4$), the $CHCl_3$ was evaporated under diminished pressure, and the residues were dried under high vacuum.

*Methyl 2,6-anhydro-8-*O*-benzoyl-3-deoxy-*D-glycero-D-talo-*octonate* (**1e**). — To a stirred solution of 4.07 g (0.017 mol) of the methyl ester[1] of **1a** in 125 mL of dry pyridine at 0°, was added over 0.5 h, 3.6 g (25 mmol) of BzCl. The mixture was stirred for 1.5 h at 0° and then overnight at room temperature. Methanol (5 mL) was added and the mixture was stirred for another 0.5 h. The pyridine was evaporated off. The residue was purified by flash chromatography on silica gel (EtOAc) to yield 3.0 g (51%) of the monobenzoate **1e**; m.p. 118–119°.

*Methyl 2,6-anhydro-8-*O*-benzoyl-3-deoxy-4,5-*O*-isopropylidene-*D-glycero-D-talo-*octonate* (**2a**). — To a stirred solution of 4.5 g (13 mmol) of **1e** in 166 mL of dry acetone was added 2.4 g of MeOH-washed Dowex 50W × 12(H^+) resin. The mixture was stirred for 2 h at room temperature. The resin was filtered and rinsed with $CHCl_3$. Extraction with $CHCl_3$ yielded 5.0 g (100%) of the isopropylidene derivative **2a**; ^{1}H-n.m.r. ($CDCl_3$): δ 1.26 and 1.39 (2 s, 6 H, CMe_2), 1.90 (m, 1 H, $J_{3a,3e}$ 16.8, $J_{3a,4}$ 12.6, $J_{3a,2e}$ 3, $J_{3e,4}$ or $J_{3e,2}$ 4.2 or 6.9 Hz, H-3*a*), 2.33 (m, 1 H, H-3*e*), 3.70 (s, 3 H, CO_2Me), and 7.41–8.1 (m, 5 H, ArH).

*Methyl 2,6-anhydro-8-*O*-benzoyl-3-deoxy-4,5-*O*-isopropylidene-7-*O*-[(2-methoxyethoxy)methyl]-*D-glycero-D-talo-*octonate* (**2b**). — To a stirred solution of 5.79 g (16 mmol) of **2a** and 10.54 g (82 mmol) of *N,N*-diisopropylethylamine in 170 mL of dry CH_2Cl_2 was added dropwise, 9.49 g (76 mmol) of chloro(2-methoxyethoxy)methane. The mixture was stirred for 48 h at room temperature. Methanol (24 mL) was added to the ice-cold mixture, which was then stirred for 1 h at room temperature. Extraction by $CHCl_3$ followed by flash chromatography (20:2:0.1 PhMe–EtOAc–Et_3N), yielded 5.4 g (72%) of **2b**; ^{1}H.n.m.r. ($CDCl_3$): δ 1.34 and 1.49 (2s, 6 H, CMe_2), 1.94 (m, 1 H, $J_{3a,3e}$ 15.6, $J_{3a,4}$ 11.4, $J_{3a,2}$ 3, $J_{3e,4}$ or $J_{3e,2}$ 3.9 or 6 Hz, H-3*a*), 2.27 (m, 1 H, H-3e), 3.35 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 4.88 (d, 1 H, J_{AB} 6.9 Hz, H_A) and 4.93 (d, 1 H, H_B) ($MeOCH_2CH_2OCH_AH_BO$), and 3.58 (s, 3 H, CO_2Me).

Anal. Calc. for $C_{23}H_{32}O_{10}$: C, 58.96; H, 6.88. Found: C, 58.81; H, 6.88.

*Methyl 2,6-anhydro-8-*O*-benzoyl-3-deoxy-4,5-*O*-isopropylidene-7-*O*-[2-trimethylsilyl) ethoxymethyl]-*D*-glycero-*D*-talo-octonate* (**2c**). — To a stirred solution of 3.8 g (10 mmol) of **2a** and 5.8 g (45 mmol) of *N,N*-diisopropylethylamine in 10 mL of dry CH_2Cl_2 was added, dropwise, 5.0 g (0.03 mol) of chloro-2-(trimethylsilyl)ethoxymethane. The mixture was stirred for 48 h at room temperature. Methanol (5 mL) was added to the ice-cold mixture, which was stirred for 0.5 h at room temperature. Extraction by $CHCl_3$ followed by flash chromatography on silica gel (20:2:0.1 PhMe–EtOAc–EtN_3) yielded 4.01 g (78%) of **2c**; ^{1}H-n.m.r. ($CDCl_3$): δ (m, 2 H, $Me_3SiCH_2CH_2O$), 1.42 and 1.56 (2s, 6 H, CMe_2), 2.0 (m, 1 H, $J_{3a,4}$ 15.0, $J_{3a,3e}$ 10.8, $J_{3a,2}$ 3, $J_{3e,4}$ or $J_{3e,2}$ 3.9 or 6.0 Hz, H-3*a*), 2.33 (m, 1 H, H-3*e*) 3.63 (s, 3 H, CO_2Me), 4.89 (d, 1 H, J_{AB} 6.9 Hz, H_A) and 4.93 (d, 1 H, H_B of) $Me_3SiCH_2CH_2OCH_AH_BO$), 7.48–8.18 (m, 5 H, ArH).

*Methyl2,6-anhydro-3-deoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-*D*-glycero-*D*-talo-octonate* (**2d**). — A mixture of 1.6 g (3.4 mmol) of **2b** in 14 mL of dry MeOH and 3.4 mL (0.86 mmol) of freshly prepared 0.25M NaOMe in MeOH was stirred for 17 h at room temperature. Extraction by $CHCl_3$ followed by flash chromatography on silica gel (1:1 PhMe–EtOAc) and then EtOAc gave 0.89 g (72%) of **2d**; ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 and 1.47 (2 s, 6 H, CMe_2), 1.81 (m, 1 H, $J_{3a,3e}$ 15.9, $J_{3a,4}$ 11.4, $J_{3a,2e}$ 2.7, $J_{3a,3e}$ 15.9 Hz, $J_{3e,2}$ or $J_{3e,4}$ 3.3 or 6.6 Hz, H-3*a*), 2.37 (m, 1 H, H-3*e*) 3.40 (s, 3 H, $CH_3OCH_2CH_2O$), 3.77 (s, 3 H, CO_2Me), and 4.84 (s, 2 H, $MeOCH_2CH_2OCH_2$).

*Methyl 2,6-anhydro-3-deoxy-4,5-*O*-isopropylidene-7-*O*-[2-(trimethylsilyl)ethoxymethyl]-*D*-glycero-*D*-talo-octonate* (**2e**). — This compound was prepared in 64% yield from **3c** according to the procedure used for **2b**; ^{1}H-n.m.r. ($CDCl_3$): δ 0.94 (m, 2 H, $Me_3SiCH_2CH_2O$), 1.33 and 1.45 (2 s, 6 H, CMe_2), 1.78 (m, 1 H, $J_{3a,4}$ 17.4, $J_{3a,3e}$ 11.7, $J_{3a,2}$ 3, $J_{3e,4}$ or $J_{3e,2}$ 3.6 or 6.9 Hz, H-3*a*), 2.34 (m, 1 H, H-3*e*) 3.74 (s, 3 H, CO_2Me), 4.74 (d, 1 H, J_{AB} 6.9 Hz, H_A), and 4.78 (d, 1 H, H_B of $Me_3SiCH_2CH_2OCH_AH_BO$).

*Methyl 2,6-anhydro-3,8-dideoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-8-oxo-*D*-glycero-*D*-talo-octonate** (**3a**). — Dimethyl sulfoxide (0.8 mL, 11.5 mmol) was added to a stirred solution of 0.75 mL (8.5 mmol) of oxalyl chloride in 10 mL of CH_2Cl_2, under N_2, cooled in a Dry Ice–$CHCl_3$ bath at -50 to $-60°$. The mixture was stirred for 10 min and a solution of 700 mg (1.9 mmol) of the alcohol **2d** in 14 mL of CH_2Cl_2 was added within 5 min; stirring was continued for an additional 15 min. Triethylamine (3.2 mL, 23 mmol) was added and the mixture was stirred for 10 min and then allowed to warm to room temperature. Water (2.4 mL) was added and the mixture was diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with ice-cold 0.5M HCl, then 5% $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated under diminished pressure to yield 696 mg (100%) of the aldehyde **3a**; $[\alpha]_D^{25}$ +17.6° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.35 and 1.51 (2 s, 6 H, CMe_2), 1.86 (m, 1 H, $J_{3a,3e}$ 17.7, $J_{3a,4}$ 11.7, $J_{3a,2}$ 3, $J_{3e,4}$ or $J_{3e,2}$ 3.3 or 6 Hz, H-3*a*), 2.33 (m, 1 H, H-3*e*), 3.38 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.72 (s, 3 H, CO_2Me), 4.78 (d, 1 H, J_{AB} 6.9 Hz, H_A), 4.83 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), and 9.86 (d, 1 H, $J_{7,8}$ 1.5 Hz, CHO).

*Methyl 2,6 anhydro-3,8-dideoxy-4,5-*O*-isopropylidene-7-*O*-[2-(trimethylsilyl)-*

ethoxymethyl]-8-oxo-D-glycero-D-talo-octonate* (**3b**). — This compound was prepared from **2e** according to the procedure of **3a** in 95% yield.

Methyl 2,6-anhydro-3-deoxy-4,5-di-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-glycero-D-talo-*octonate* (**2d**). — A freshly prepared solution of 37.8 mg (1 mmol) of $NaBH_4$ in 18 mL of H_2O was added to a stirred solution of 362 mg (1 mmol) of **3a** in 18 mL of MeOH at 0°. After 16 h, an additional amount of $NaBH_4$ (37.8 mg) in H_2O (18 mL) was added and the mixture was stirred for another 1.5 h at 0°. Acetone (1.8 mL) was added and the mixture was extracted with 5% $NaHCO_3$ and $CHCl_3$. Extraction with $CHCl_3$ followed by flash chromatography, eluting first with PhMe and then 2:1 EtOAc–PhMe, yielded 183 mg (50%) of **2d**.

Methyl 8-amino-2,6-anhydro-3,8-dideoxy-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-glycero-D-talo-*octonate* (**2f**). — A mixture of 178 mg (0.49 mmol) of **3a**, 472 mg (6.1 mmol) of NH_4OAc, and 42.5 mg (0.68 mmol) of $NaBH_3CN$ in 6 mL of dry MeOH was stirred for 16 h at room temperature. Extraction with $CHCl_3$ followed by chromatography (20:5:0.1 $CHCl_3$–MeOH–Et_3N) yielded 72 mg (40%) of **2f**; ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 and 1.47 (2 s, 6 H, CMe_2), 1.93 (m, 1 H, $J_{3a,3e}$ 17.4, $J_{3a,4}$ 11.1, $J_{3a,2}$ 2.7, $J_{3e,4}$ or $J_{3e,2}$ 3.6 or 5.4 Hz, H-3*a*), 2.33 (m, 1 H, H-3*e*) 3.38 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$); 3.73 (s, 3 H, CO_2Me), 4.85 (d, 1 H, J_{AB} 6 Hz, H_A), and 4.89 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$).

8-Amino-2,6-anhydro-3,8-dideoxy-D-glycero-D-talo-*octonic acid* (**1b**). — To a solution of 60 mg (0.16 mmol) of **2f** in 4 mL of MeOH was added 5 mL of saturated HCl in MeOH. The mixture was stirred for 2.5 h at room temperature and evaporated under diminished pressure. The deprotected methyl ester was hydrolyzed by stirring with 0.4 mL of Et_3N and 7.5 mL of H_2O for 19 h at room temperature. After evaporation under diminished pressure, the residue was chromatographed (4:6:3 $CHCl_3$–MeOH–NH_4OH) to give 13.6 mg (37%) of **1b** as a colorless solid.

Methyl 2,6-anhydro-dideoxy-8-fluoro-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-glycero-D-talo-*octonate* (**2g**) *and methyl 2,6-anhydro*-3,8-dideoxy-4,5-di-O-*isopropylidene-8-O-(2-methoxyethyl)*-D-glycero-D-talo-*octonate* (**2h**). — To a magnetically stirred solution of 609 mg (1.67 mmol) of the alcohol **2d** in 40 mL of dry (3 Å sieve) CH_2Cl_2, under nitrogen, cooled in a Dry Ice–acetone bath, was added 1.25 mL (9.5 mmol) of DAST. Stirring was continued with cooling for 0.5 h and then for 1.5 h at room temperature. Methanol (2.0 mL) was added to the stirred solution. The product was isolated by extraction with $CHCl_3$ and the residue was purified by flash chromatography (10:10:0.1 PhMe–EtOAc–Et_3N) giving 306 mg of a mixture of **2g** and **2h** characterized from their deprotected products **12a** and **12b** prepared as described next.

2,6-Anhydro-3,8-dideoxy-8-fluoro-D-glycero-D-talo-*octonic acid ammonium salt* (**12a**) *and 2,6-anhydro-3-deoxy-8-O-(2-methoxyethyl)*-D-glycero-D-talo-*octonic acid triethylammonium salt* (**12b**). — The foregoing mixture of **2g** and **2h** (306 mg) was stirred with 880 mg of MeOH-washed AG 50W × 8 (H^+) resin in 30 mL of dry MeOH for 5

* Compounds **3a** and **3b** are strictly octuronic acid derivatives; the nonsystematic names used here retain the substituent locants and configurational symbols of the other compounds in this paper.

days at room temperature. The mixture was filtered and the filtrate evaporated under diminished pressure. The crude product was chromatographed (1:20 MeOH–EtOAc) to give 118 mg of the deprotected ester **11a** and 96 mg of **11b**, which were hydrolyzed by aq. Et_3N to **12a** and **12b**, respectively, in quantitative yield according to the procedure of **1b**. For **12a**; $[\alpha]_D^{20}$ +66.7° (*c* 1, H_2O); ^{1}H-n.m.r. (D_2O) δ 2.03 (dt, 1 H, $J_{3a,4}$ $J_{3a,a}$ 12.9, $J_{3a,2}$ 6.3, $J_{3e,2}$ or $J_{3e,4}$ 5.4 Hz, H-3*a*), 2.20 (dd, 1 H, H-3*e*), and 4.36 (d, 1 H, $J_{4,5}$ 5.1 and $J_{5,6}$ 0.9 Hz, H-5); exact mass: calc. for $C_8H_{12}FO_6$ $(M-H)^-$ 223.0618; found 223.0628.

For **12b**; $[\alpha]_D^{25}$ +52.8° (*c* 1, H_2O): ^{1}H-n.m.r. (D_2O): δ 2.03 (dt, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 12.9, $J_{3a,2}$ 6.3 Hz, $J_{3e,2}$ or $J_{3e,4}$ 4.8 Hz, H-3*a*), 2.18 (dd, 1 H, H-3*e*), 3.40 (s, 3 H, OMe), and 4.34 (d, 1 H, $J_{4,5}$ 5,1 Hz, H-5); exact mass:calc. for $C_{11}H_{19}O_8$ $(M-H)^-$ 279.1080; found 279.1053.

*Methyl 2,6-anhydro-3,8-dideoxy-8,8-difluoro-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-*D*-glycero-*D*-galacto-octonate* (**4**). — To a magnetically stirred solution of the aldehyde **3a** [prepared immediately before use by Swern oxidation of 608.4 mg (1.67 mmol) of alcohol **2d**] in 45 mL of CH_2Cl_2, cooled under nitrogen in a Dry Ice–acetone bath, was added 2.5 mL of DAST. Stirring was continued for 20 min with cooling and then for 1 h at room temperature. The crude product (625 mg) was isolated by $CHCl_3$ extraction as an orange syrup. Chromatography with 5:1 PhMe–EtOAc gave 329 mg (51%) of **4** as a clear, pale-yellow syrup; $[\alpha]_D^{25}$ + 0.04° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.35 and 1.50 (2 s, 6 H, CMe_2), 1.86 (m, 1 H, $J_{3a,3e}$ 15, $J_{3a,4}$ 10.8, $J_{3a,2}$ 2.7, $J_{3a,3e}$ 15, $J_{3e,4}$ or $J_{3e,2}$ 3 or 6 Hz, H-3*a*), 2.32 (m, 1 H, H-3e), 3.39 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), and 3.73 (s, 3 H, CO_2Me).

Anal. Calc. for $C_{16}H_{26}F_2O_8$: C, 49.99; H, 6.82; F, 9.89. Found C, 49.52; H, 6.78; F, 10.25.

*2,6-Anhydro-3,8-dideoxy-8,8-difluoro-*D*-glycero-*D*-talo-octonic acid, ammonium salt* (**12c**). — This compound was obtained from **4** in 82% yield after chromatography (10:10:1 $CHCl_3$–MeOH–H_2O) according to the procedure for **12a**; $[\alpha]_D^{25}$ +62.5° (*c* 1, H_2O); ^{1}H-n.m.r. (D_2O): δ 2.04 (m, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 12.9, $J_{3a,2}$ 6.3, $J_{3e,2}$ or $J_{3e,4}$ 4.8 Hz, H-3*a*), 2.21 (m, 1 H, H-3*e*), 4.37 (d, 1 H, $J_{4,5}$ 5.1 Hz, H-5), and 6.18 (t, 1 H, J_{HF} 54.6 Hz, H-8); exact mass:calc. for $C_8H_{11}F_2O_6$ $(M-H)^-$ 241.0516; found 241.0517.

*Methyl 2,6-anhydro-3,8,9-trideoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-*D*-glycero-*D*-talo-non-8-enonate* (**5**). — Hexamethyldisilazane (1.1 mL, 5.2 mmol) was added to a stirred suspension of 0.55 g (4.8 mmol) of 35% KH in oil and 12 mL of 5:1 THF–Me_2SO under N_2, at 0°. After 1 h, 1.85 g (5.2 mmol) of methyltriphenylphosphonium bromide was added and stirring was continued for another hour at 0°. To the Wittig reagent, cooled to −78°, was added the aldehyde **3a** [prepared from 0.7 g (1.9 mmol) of the alcohol]. The mixture was stirred for 1 h at 78° and then overnight at room temperature. Acetone (1.0 mL) was added to the mixture at 0°, which was stirred for 0.5 h at 0° and 2 h at room temperature. Saturated aq. NH_4Cl (7.2 mL) was added to the stirred mixture, which was then extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with 0.5M HCl, saturated aq. $NaHSO_3$, water, saturated aq. $NaHCO_3$, dried ($MgSO_4$), and evaporated under diminished pressure. The residue was purified by flash chromatography eluting first with PhMe, and then 2:1 PhMe–EtOAc yielding 0.37 g

(53%) of **5**; ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 and 1.49 (2 s, 6 H, CMe_2); 1.89 (m, 1 H, $J_{3a,3e}$ 15.4, $J_{3a,4}$ 11.4, $J_{3a,2}$ 3.3, $J_{3a,3e}$ *15.4*. $J_{3e,2}$ or $J_{3e,4}$ 3.3 or 6 Hz, H-3*a*), 2.24 (m, 1 H, H-3*e*), 3.40 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.72 (s, 3 H, CO_2Me), 4.70 (d, 1 H, J_{AB} 6.9 Hz, H_A) and 4.82 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), 5.38 (m, 2 H, $CH=CH_2$), and 5.86 (m, 1 H, $CH=CH_2$).

2,6-Anhydro-3,8,9-trideoxy-D-glycero-D-talo-*non-8-enonic acid, ammonium salt* (**12d**). — This compound was prepared from **5** in 92% yield according to the procedure of **12h**; $[\alpha]_D^{20}$ +74.1° (*c* 0.1, H_2O); ^{1}H-n.m.r. (D_2O): δ 2.05 (m, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 12.6, $J_{3a,2}$ 6, $J_{3e,2}$ or $J_{3e,4}$ 5.4 Hz, H-3*a*), 4.33 (d, 1 H, $J_{4,5}$ 5.4 Hz, H-5, H-3*a*), 2.18 (m, 1 H, H-3*e*), 5.35 (m, 2 H, H-9), and 6.07 (m, 1 H, H-8); exact mass:calc. for $C_9H_{13}O_6$ $(M-H)^-$ 217.0712; found 217.0716.

Methyl 2,6-anhydro-3,8-dideoxy-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-glycero-D-talo-*nononate* (**6a**). — To a stirred solution of 406.2 mg (1.13 mmol) of the alkene **5** in 4.0 mL of THF, under nitrogen, was added 4.0 mL (2.0 mmol) of 9-BBN (0.05M in THF). Stirring was continued for 6 h and the reaction vessel was cooled in an ice–water bath. To the stirred, cooled solution was added 0.8 mL of 3M NaOH and then 0.8 mL of 30% H_2O_2. Stirring was continued with cooling for 1 h. The crude product (840.8 mg of clear, colorless syrup) was isolated by $CHCl_3$ extraction. Flash chromatography with EtOAc followed by gravity chromatography with 1:1 PhMe–EtOAc gave 224.2 mg (53%) of **6a** as a colorless syrup; $[\alpha]_D^{20}$ +0.18 (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 and 1.47 (2 s, 6 H, CMe_2), 1.88 (m, 1 H, $J_{3a,3e}$ 15.3, $J_{3a,4}$ 11.2, $J_{3a,2}$ 3, $J_{3e,4}$ or $J_{3e,2}$ 5.2 or 3.4 Hz, H-3*a*), 2.25 (m, 1 H, H-3e), 3.40 (s, 3 H, $CH_3OCH_2CH_2O$), 3.38 (s, 3 H, CO_2Me), 4.77 (d, 1 H, J_{AB} 2.2 Hz, H_A), and 4.92 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$).

Anal. Calc. for $C_{17}H_{30}O_9$: C, 53.95; H, 7.99. Found: C, 53.89; H, 7.83.

2,6-Anhydro-2,8-dideoxy-D-glycero-D-talo-*nononic acid, ammonium salt* (**12e**). — This compound was obtained from **6a** in 76% yield according to the procedure for **12h**. Compound **12e** had $[\alpha]_D^{20}$ +66.1° (*c* 1, H_2O); ^{1}H-n.m.r. (D_2O): δ 1.73 (m, 1 H, H-9A), 2.08 (m, 1 H, H-9B), 2.04 (m, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 12.9, $J_{3a,2}$ 6.6, $J_{3a,2}$ or $J_{3a,4}$ 4.5 Hz, H-3*a*), 2.20 (m, 1 H, H-3e), and 4.37 (1 H, $J_{4,5}$ 5.7 Hz, H-5); exact mass:calc. for $C_9H_{15}O_7$ $(M-H)^-$ 235.0818; found 235.0839.

The C-8 epimeric methyl 2,6-anhydro-3-deoxy-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-erythro(*and* L-threo)-D-talo-*nononates* (**6b** and **7a**). — To a stirred solution of 259.3 mg (2.21 mmol) of *N*-methylmorpholine *N*-oxide monohydrate in 2.2 mL of THF–*tert*-BuOH (1:2 v/v) was added 21 mL of water, 0.72 mL (0.07 mmol) of 2.5% OsO_4 in *tert*-BuOH, and then a solution of 524.4 mg (1.44 mmol) of the alkene **5** in 3.6 mL of THF. Stirring was continued for 3 h. To the resulting stirred solution was added 150.1 mg of Florisil, 78 mg of $NaHSO_3$, and 0.45 mL of water. After stirring for 15 min, the mixture was filtered through a Celite mat and the mat was washed with $CHCl_3$. The crude product (638.4 mg of a dark-brown syrup) was isolated by extraction with $CHCl_3$ from the combined organic solutions. Flash chromatography using 20:1 EtOAc–EtOH gave 496.9 mg (90%) of the mixture of **6b** and **7a**. Compound **6b** had $[\alpha]_D^{19}$ +9.8° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 and 1.47 (2 s, 6 H, CMe_2), 1.84 (m, 1 H,

$J_{3a,3e}$ 15.1, $J_{3a,4}$ 12, $J_{3a,2}$ 2.7, $J_{3e,2}$ or $J_{3e,4}$ 3.3 or 5.4 Hz, H-3*a*), 2.31 (m, 1 H, H-3*e*), 3.40 (s, 3 H, $CH_3OCH_2CH_2O$), and 3.77 (s, 3 H, CO_2Me).

2,6-Anhydro-3-deoxy-D-erythro(*and* L-threo)-D-talo-*nononic acid, ammonium salt* — (**12f**). — Compound **12f** was obtained from a mixture of **6b** and **7a** in 71% yield after chromatography (10:10:1 $CHCl_3$–MeOH–H_2O) according to the procedure for **12h**. Compound **12f** had $[\alpha]_D^{19}$ +56.4° (*c* 1, H_2O); ^{1}H-n.m.r. (D_2O): δ 2.04 (m, major + minor, H-3*a*) and 2.22 (m, major, H-3*e*) and 2.27 (m, minor, H-3*e*) ($J_{3a,3e}$ $J_{3a,4}$ 12.9, $J_{3a,2}$ 6.6, $J_{3e,2}$ or $J_{3e,4}$ 5.4 Hz) (major/minor > 10), and 4.37 (d, 1 H, H-5, $J_{4,5}$ 6 Hz); exact mass:calc. for $C_9H_{15}O_8$ $(M-H)^-$ 251.07669; found 251.0781.

*The C-8 epimeric methyl 2,6-anhydro-3-dideoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-9-*O*-p-tolylsulfonyl*-D-erythro(*and* L-threo)-D-talo-*nononates* (**6c** *and* **7b**). — To a stirred solution of 153.1 mg (0.39 mmol) of the mixture of **6b** and **7a**, prepared as just described, in 3.0 mL of pyridine, cooled in an ice–water bath, was added 97.6 mg (0.51 mmol) of *p*-toluenesulfonyl chloride. Stirring was continued with cooling for 0.5 h and then overnight at room temperature. The product was isolated by extraction with $CHCl_3$ yielding 207.4 mg (104%) of the mixture of **6c** and **7b**. Compound **6c** had ^{1}H-n.m.r. ($CDCl_3$): δ 1.62 (s, 6 H, CMe_2), 1.79 (m, 1 H, $J_{3a,3e}$ 14.9, $J_{3a,4}$ 11.3, $J_{3a,2}$ 2.7, $J_{3e,2}$ or $J_{3e,4}$ 3.5 or 6.07 Hz, H-3*a*), 2.29 (m, 1 H, H-3*e*), 2.44 (s, 3 H, ArMe), 3.38 (s, 3 H, CO_2Me), and 3.44 (s, 3 H, $MeOCH_2CH_2O$).

*The C-8 epimeric methyl 9-azido-2,6-anhydro-3,9-dideoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)*-D-erythro(*and* L-threo)-D-talo-*nononates* (**6d** *and* **7c**). — A solution of 644 mg (1.24 mmol) of the mixture of **6c** and **7b**, prepared as just described, 400.8 mg (6.17 mmol) of NaN_3, and 12 mL of Me_2SO was heated with stirring for 19 h at 100°. The crude product (364.9 mg of light-orange oil) was isolated by extraction with $CHCl_3$. Flash chromatography with 1:1 PhMe–EtOAc of 440.1 mg of material prepared in this manner from 827 mg (1.60 mmol) of the mixture of **6c** + **7b** gave 267.3 mg (40%) of **6d** and 27.8 mg (4%) of **7c**. Compound **6d** had $[\alpha]_D^{23}$ −4.06° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.34 and 1.47 (2 s, 6 H, CMe_2), 1.84 (m, 1 H, $J_{3a,3e}$ 14.9, $J_{3a,4}$ 11.3, $J_{3a,2}$ 2.7, $J_{3e,2}$ or $J_{3e,4}$ 3.56 or 6.08 Hz, H-3*a*), 2.33 (m, 1 H, H-3*e*), 3.40 (s, 3 H, $CH_3OCH_2CH_2O$), 3.77 (s, 3 H, CO_2Me), 4.80 (d, 1 H, J_{AB} 3.9 Hz, H_A), and 4.86 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$).

Anal. Calc. for $C_{27}H_{29}O_9N_3$: C, 48.68; H, 6.97; N, 10.02. Found: C, 48.62; H, 7.19; N, 9.93.

9-Azido-2,6-anhydro-3,9-dideoxy-D-erythro(*or* L-threo)-D-talo-*nononic acid* (**12g**). — Compound **12g** was obtained from **6d** in 65% yield after chromatography (1:1 $CHCl_3$–MeOH) according to the procedure for **12h**.

9-Amino-2,6-anhydro-3,9-dideoxy-D-erythro(*or* L-threo)-D-talo-*nononic acid* (**12j**). — Compound **12j** was obtained from **12g** in 75% yield according to the procedure for **12k**; $[\alpha]_D^{21}$ +52.5° (*c* 1, H_2O): ^{1}H-n.m.r. (D_2O): δ 2.04 (d, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 13.2, $J_{3a,2}$ 6.3, $J_{3e,2}$ or $J_{ee,4}$ 4.8 Hz), H-3*a*), 2.22 (d, 1 H, H-3*e*), and 4.37 (d, 1 H, $J_{4,5}$ 5.7 Hz, H-5); exact mass:calc. for $C_9H_{16}NO_7$ $(M-H)^-$ 250.0927; found 250.0948.

*Methyl 9-azido-2,6-anhydro-3,9-dideoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)*-D-erythro(*or*-L-threo)-D-talo-*nononate* (**7d**). — To a magnetically

stirred solution of 419.6 mg (1.0 mmol) of the hydroxy azide **6d** in 5 mL of pyridine, cooled in an ice bath, was added 0.23 mL (3.0 mmol) of $MeSO_2Cl$. Stirring was continued with cooling for 0.5 h, and then for 2.75 h at room temperature. Extraction with $CHCl_3$ gave the methanesulfonate **6e**. The latter was dissolved in 12 mL of DMF, treated with 650 mg of CsOAc, and the resulting solution was heated with stirring for 18 h. Extraction with $CHCl_3$ gave 282 mg of brown syrup which on flash chromatography with 1:1 PhMe–EtOAc gave 150 mg (33%) of **7d**; ^{1}H-n.m.r. ($CDCl_3$):δ 1.33 and 1.47 (2 s, 6 H, CMe_2), 1.92 (m, 1 H, $J_{3a,3e}$ 15, $J_{3a,4}$ 11, $J_{3a,2}$ 3, $J_{3e,2}$ or $J_{3e,4}$ 3.9 or 6 Hz, H-3*a*), 2.19 (m, 1 H, H-3*e*), 2.14 (s, 3 H, COMe), 3.39 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.72 (s, 3 H, CO_2Me), 4.82 (d, 1 H, J_{AB} 6.6 Hz, H_A), 4.98 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), and 5.28 (dt, 1 H, $J_{7,8}$ 3, $J_{8,9}$ 6.3 Hz, H-8).

9-Azido-2,6-anhydro-3,9-dideoxy-D-erythro(*or* L-threo)-D-talo-*nononic acid* (**12h**). — The method employed for deprotection of the non-basic, protected methyl esters is exemplified by the conversion of **7d** into **12h**. To a stirred solution of 142 mg (0.31 mmol) of **7d** in 14 mL of MeOH was added 461 mg of MeOH-washed AG 50WX8 (H^+) resin. The mixture was stirred for 4 days at room temperature. The resin was removed by filtration and the filtrate was evaporated under diminished pressure. The crude product was purified by chromatography (1:20 MeOH–EtOAc) to yield 56 mg (63%) of **11h**. A mixture of 56 mg (0.19 mmol) of **11h** in 6 mL of H_2O and 0.3 mL (2.1 mmol) of Et_3N was stirred for 17 h at room temperature. The solution was lyophilized and the residue was dissolved in 8 mL of H_2O, and was treated with AG 50WX8 (H^+) resin to pH 3. The solution was filtered through a Millipore filter (EH type) and the filtrate was lyophilized to yield 50 mg (94%) of **12h** as a colorless solid; ^{1}H-n.m.r. (D_2O): δ 2.09 (m, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 12.9, $J_{3a,2}$ 6.6, $J_{3e,2}$ or $J_{3e,4}$ 5.1 Hz, H-3*a*), 2.23 (m, 1 H, H-3*e*), and 4.62 (d, 1 H, $J_{4,5}$ 6.6 Hz, H-5).

9-Amino-2,6-anhydro-3,9-dideoxy-D-erythro(*or* L-threo)-D-talo-*nononic acid* (**12k**). — Catalytic hydrogenation of the deprotected azido acids to the amino acids is exemplified by the conversion of **12h** into **12k**. A solution of 50 mg (0.18 mmol) of **12h** in 20 mL of water with 50 mg of 20% Pd–C was hydrogenated in a Parr apparatus at 60 lb.in^{-2} for 4 h at room temperature. After removal of the catalyst, the solution was lyophilized. The residue was chromatographed on silica gel (2:4:1:1 $CHCl_3$–MeOH–H_2O–NH_4OH) to yield 25.7 mg (57%) of **12k** as a white solid; $[\alpha]_D^{21}$ +47.3° (*c* 1, H_2O); ^{1}H-n.m.r. (D_2O): δ 2.12 (m, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 10.5, $J_{3a,2}$ 5.7, $J_{3e,2}$ or $J_{3e,4}$ 4.2 Hz, H-3*a*), 2.33 (m, 1 H, H-3*e*), 4.07 (d, 1 H, $J_{7,8}$ 2.1 Hz, H-7), 4.3 (dt, 1 H, $J_{8,9}$ 6.9 Hz, H-8), and 4.46 (d, 1 H, $J_{4,5}$ 5.1 Hz, H-5); exact mass:calc. for $C_9H_{16}NO_7$ $(M-H)^-$ 250.0927; found 250.0919.

The C-8 epimeric methyl 8,9-diazido-2,6-anhydro-3,8,9-trideoxy-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-erythro(*and* L-threo)-D-talo-*nononates* (**6g** *and* **7f**). — To a stirred solution of 477.2 mg (1.21 mmol) of the mixture of diols **6b** and **7a**, prepared as just described, in 6 mL of pyridine, cooled in an ice bath, was added 0.38 mL (4.84 mmol) of $MeSO_2Cl$. Stirring was continued for 1 h with cooling and then for 2 h at room temperature. Extraction with $CHCl_3$ gave the mixture of disulfonates **6f** and **7e**. The latter mixture was immediately treated with 642.4 mg (9.88 mmol) of NaN_3 in 30 mL of Me_2SO and the resulting stirred mixture was heated for 26 h at 100°. Extraction

with $CHCl_3$ gave 306 mg of crude product. Flash chromatography of the latter with 5:1 PhMe–EtOAc gave 243.9 mg (45%) of a mixture of **6g** and **7f** in ratio of 6:1. Compound **6g** had $[\alpha]_D^{21} + 30.6°$ (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$); δ 1.33 and 1.46 (2 s, 6 H, CMe_2), 1.92 (m, 1 H, $J_{3a,3e}$ 18, $J_{3a,4}$ 11.1, $J_{3a,2}$ 3.6, $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 6 Hz, H-3*a*), 2.26 (m, 1 H, H-3*e*), 3.40 (major) and 3.41 (minor) (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.78 (major) and 3.77 (minor) (s, 3 H, CO_2Me), 4.75 (major) and 4.80 (minor) (d, 1 H, J_{AB} 6.9 Hz, H_A), and 4.98 (major) and 4.95 (minor) (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$).

Anal. Calc. for $C_{17}H_{28}N_6O_8$: C, 45.93; H, 6.35; N, 18.91. Found: C, 45.85; H, 6.54; N, 18.87.

8,9-Diamino-3,8,9-trideoxy-D-erythro(or L-threo)-D-talo-*nononic acid* (**12l**). — A mixture of 215 mg of **6g** and **76f** was deprotected according to the procedure for **12h** in 95% yield. The resulting diazido acid was hydrogenated according to the procedure for **12k** in 63% yield after chromatography (1:2:1 $CHCl_3$–MeOH–NH_4OH); $[\alpha]_D^{21} + 52.3°$ (*c* 1, H_2O); ^{1}H-n.m.r. (D_2O): δ 2.07 (m, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 13.2, $J_{3a,2}$ 7.2, $J_{3e,2}$ or $J_{3e,4}$ 4.8 Hz, H-3*a*), 2.26 (m, 1 H, H-3*e*), and 4.42 (d, 1 H, $J_{4,5}$ 6.6 Hz, H-5); exact mass:calc. for $C_9H_{17}N_2O_6$ $(M-H)^-$ 249.1087; found 249.1074.

Methyl 2,6-anhydro-8,8,9,9-tetradehydro-3,8,9-trideoxy-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-glycero-D-talo-*nononate* (**8**). A mixture of 1.09 g (2.2 mmol) of **6e**, 980 mg of Bu_4NCN (Fluka) and 21 mL of MeCN was stirred and heated for 6 h at 70°. After cooling, 385 mg of boric acid was added and the mixture was evaporated under diminished pressure. The residue was purified by flash chromatography (1:2 EtOAc–PhMe) yielding 164 mg of starting material and 176 mg (26%) of **8**; $[\alpha]_D^{25} -90.2°$ (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.27 and 1.40 (2 s, 6 H, CMe_2), 1.85 (m, 1 H, $J_{3a,3e}$ *15*, $J_{3a,4}$ 11.7, $J_{3a,2}$ 3 Hz, $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 6 Hz, H-3*a*), 2.23 (m, 1 H, H-3*e*), 2.40 (d, 1 H, $J_{7,9}$ 2.4 Hz, C≡CH), 3.33 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.68 (s, 3 H, CO_2Me), 4.70 (m, 1 H, J_{AB} 6.6 Hz, H_A), and 4.97 (m, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$); exact mass:calc. for $C_{17}H_{27}O_8$ MH^+ 359.1706; found 359.1714.

2,6-Anhydro-8,8,9,9-tetradehydro-3,8,9-trideoxy-D-glycero-D-talo-*nononic acid* (**12i**). — Compound **12i** was prepared from **8** in 62% yield according to the procedure for **12h**; **12i** had $[\alpha]_D^{23} + 51.3°$ (*c* 1, H_2O); ^{1}H-n.m.r. (D_2O); δ 2.07 (m, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 12.6, $J_{3a,2}$ 6.6, $J_{3e,2}$ or $J_{3e,4}$ 4.8 Hz, H-3*a*), 2.19 (m, 1 H, H-3*e*), and 2.88 (d, 1 H, $J_{7,9}$ 2.4 Hz, H-9); exact mass:calc. for $C_9H_{11}O_6$ $(M-H)^-$ 215.0556; found 215.0542.

Methyl 2,6-anhydro-3,8-dideoxy-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-8-oximino-D-glycero-D-talo-*octonate* (**13a**). — A mixture of 184.7 (0.51 mmol) of **3a**, 106 mg (1.5 mmol) of hydroxylamine hydrochloride and 1.5 mL of dry pyridine was stirred for 22 h at room temperature. Extraction with $CHCl_3$ yielded 185 mg (91%) of the oxime (**13a**); ^{1}H-n.m.r. ($CDCl_3$): δ 1.34 and 1.48 (2 s, 6 H, CMe_2), 1.87 (m, 1 H, $J_{3a,3e}$ 18, $J_{3a,4}$ 11.1, $J_{3a,2}$ 2, $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 6.3 Hz, H-3*a*), 2.30 (m, 1 H, H-3*e*), 3.39 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.73 (s, 3 H, CO_2Me), 4.74 (d, 1 H, J_{AB} 6.9 Hz, H_A), 4.83 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), and 7.47 (d, 1 H, $J_{7,8}$ 7.5 Hz, H-8).

Methyl (methyl 2,6-anydro-3-deoxy-D-glycero-D-talo-*8-aldo-octonate)*-5,8-furanoside* (**14a**) — (*a*) A mixture of **13a** (160 mg) was stirred with 460 mg of AG50 WX8

* Numbering of this aldaric acid derivative is reversed to retain homology with other compounds reported here.

(H^+) resin in 15 mL of dry MeOH for 3 days. Removal of the resin and evaporation yielded an oil, which was chromatographed (1:25 MeOH–EtOAc) affording 82 mg (65%) of **14a**; ^{1}H-n.m.r. ($CDCl_3$): δ 2.11 (m, 1 H, $J_{3a,3e}$ 13.5, $J_{3a,4}$ 10.2, $J_{3a,2}$ 6.3 Hz, $J_{3e,2}$ $J_{3e,4}$ 4.5 Hz, H-3*a*), 2.22 (m, 1 H, H-3*e*), 3.43 (s, 3 H, OMe), 3.77 (s, 3 H, CO_2Me), and 4.93 (d, 1 H, $J_{7,8}$ 3 Hz, H-8).

(*b*) A mixture of 590 mg (1.6 mmol) of **3a**, 1.8 g of AG 50WX8 (H^+) resin, and 60 mL of dry MeOH was stirred for 3 days at room temperature. Removal of the resin and evaporation of the filtrate gave 132 mg (33%) of **14a** after chromatography.

Methyl 2,6-anhydro-3,8-dideoxy-4,5-O-isopropylidene-7-O-[2-(trimethylsilyl)-ethoxymethyl]-8-oximino-D-glycero-D-talo-*octonate* (**13b**). — A mixture of 510 mg (1.26 mmol) of **3b**, 367 mg (5.3 mmol) of hydroxylamine hydrochloride, and 4.5 mL of dry pyridine was stirred for 21 h at room temperature. Extraction with $CHCl_3$ and chromatography (1:4 EtOAc–PhMe) yielded 405 mg (77%) of the oxime **13b**; ^{1}H-n.m.r. ($CDCl_3$): δ 0.93 (m, 2 H, $Me_3SiCH_2CH_2OCH_2O$), 1.33 and 1.47 (2 s, 6 H, CMe_2), 1.84 (m, 1 H, $J_{3a,3e}$ 17.7, $J_{3a,4}$ 10.8, $J_{3a,2}$ 3, $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 6 Hz, H-3*a*), 2.28 (m, 1 H, H-3*e*), 3.72 (s, 3 H, CO_2Me), 4.68 (d, 1 H, J_{AB} 6.9 Hz, H_A), 4.76 (d, 1 H, H_B of $Me_3SiCH_2CH_2OCH_AH_BO$), 6.76 (d, $J_{7,8}$ 8.1 Hz, H-8), (minor, *syn*-, trace), and 7.45 (d, 1 H, $J_{7,8}$ 7.5 Hz, H-8) (major, *anti*).

Methyl 2,6-anhydro-3,8-dideoxy-8-oximino-D-glycero-D-talo-*octonate* (**11m**). — A solution of M $LiBF_4$ in MeCN (1.4 mL, 1.4 mmol) was added to a stirred solution of **13b** (123 mg, 0.29 mmol) in 1.4 mL of 4% H_2O in MeCN. The mixture was stirred for 1 h at room temperature and then for 4 h at 50°. Hydroxylamine hydrochloride (408 mg, 0.58 mmol) and 2.8 mL of dry pyridine were added and the mixture was stirred for 16 h at room temperature. After evaporation, the residue was purified by chromatography (3:2 MeCN–EtOAc) yielding 171 mg (23%) of **11m**; ^{1}H-n.m.r. ($CDCl_3$):δ 2.10 (dt, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 12.3, $J_{3a,2}$ 6.6, $J_{3a,2}$ or $J_{3a,4}$ 5.4 Hz, H-3*a*), 2.23 (dd, 1 H, H-3*e*), 3.78 (s, 3 H, CO_2Me), 6.98 (d, trace, $J_{7,8}$ 7.2 Hz, *anti*-CH=NOH), and 7.57 (d, major, $J_{7,8}$ 7.2 Hz, *syn*-C*H*=NOH).

2,6-Anhydro-3,8-*dideoxy-8-oximino*-D-glycero-D-talo-*octonic acid, ammonium salt* (**12m**). — A solution of 17.4 mg (0.07 mmol) of **11m** in 4 mL of water and 0.1 mL (0.7 mmol) of Et_3N was stirred for 18 h at room temperature. The solution was lyophilized to yield 23.5 mg (100%) of **12m**; $[\alpha]_D^{25}$ +38.5° (*c* 0.25, H_2O); ^{1}H-n.m.r. (D_2O): δ 2.02 (dt, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 13.4, $J_{3a,2}$ 6.9, $J_{3e,2}$ or $J_{3e,4}$ 4.8 Hz, H-3*a*), 2.17 (dd, 1 H, H-3*e*), 7.03 (d, minor, $J_{7,8}$ 6.9 Hz, H-8 *syn*-oxime), and 7.60 (d, major, $J_{7,8}$ 7.2 Hz, H-8 *anti*-oxime) (*anti*/*syn* = 2.7); exact mass: calc. for $C_8H_{12}NO_7$ $(M-H)^-$ 234.0614; found 234.0627.

Methyl2,6-anhydro-3,8-*dideoxy-4,5*-O-*isopropylidene-8-methoxyimino-7*-O-*[2-(trimethylsilyl)ethoxymethyl]*-D-glycero-D-talo-*octonate* (**13c**). — A mixture of 460 mg (1.1 mmol) of **3b**, 480 mg (5.7 mmol) of methoxylamine hydrochloride, and 6.8 mL of dry pyridine was stirred for 17 h at room temperature. Extraction with $CHCl_3$ and chromatography (1:8 EtOAc–PhMe) yielded 386 mg (78%) of **13c**; ^{1}H-n.m.r. ($CDCl_3$): δ 0.96 (m, 2 H, $Me_3SiCH_2CH_2OCH_2O$), 1.34 and 1.48 (2 s, 6 H, CMe_2), 1.86 (m, 1 H, $J_{3a,3e}$ 17.7, $J_{3a,4}$ 11.1, $J_{3a,2}$ 3, $J_{3e,2}$ or $J_{3e,4}$ 6.3 or 3.6 Hz, H-3*a*), 2.29 (m, 1 H, H-3*e*), 3.73 (s, 3 H, NOMe), 3.88 (s, 3 H, CO_2Me), 4.72 (d, 1 H, J_{AB} 6.9 Hz, H_A), 4.78 (d, 1 H, H_B of $Me_3SiCH_2CH_2OCH_AH_BO$), and 7.40 (d, 1 H, $J_{7,8}$ 7.5 Hz, H-8).

*Benzyl 2,6-anhydro-3,8-dideoxy-4,5-*O*-isopropylidene-8-methoxyimino*-D-glycero-D-talo-*octonate* (**13e**). — A mixture of 386 mg (0.83 mmol) of **13c** and 6.7 mL (6.7 mmol) of M Bu_4NF in THF was evaporated to dryness under diminished pressure and the residue was heated for 20 h at 60°. The melt was dissolved in 18 mL of DMF and 2.1 mL (17.6 mmol) of $PhCH_2Br$ was added. After stirring for 21 h at room temperature, the solvent was removed by evaporation under diminished pressure. The crude product was purified by flash chromatography (1:3 EtOAc–PhMe) affording 290 mg (86%) of **13e**; $[\alpha]_D^{21}$ −34.6° (*c 1*, MeOH); ^{1}H-n.m.r. ($CDCl_3$): δ 1.38 and 1.50 (2 s, 6 H, CMe_2), 1.86 (m, 1 H, $J_{3a,3e}$ *18*, $J_{3a,4}$ 11.4 $J_{3a,2}$ 3, $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 6 Hz, H-3*a*), 2.31 (m, 1 H, H-3*e*), 3.88 (s, 3 H, NOMe), 5.18 (s, 2 H, CH_2Ph), 7.37 (m, 5 H, ArH), 7.69 (d, 1 H, $J_{7,8}$ 3.6 Hz, major, *cis* H-8), and 7.11 (d, 1 H, $J_{7,8}$ 4.5 Hz, *trans* H-8 minor), major/minor = 8; exact mass: calc. for $C_{19}H_{26}NO_7$ (M + 1)$^+$ 380.1709; found 380.1688.

Benzyl 2,6-anhydro-3,8-dideoxy-8-oximino-D-glycero-D-talo-*octonate* (**11n**). — Compound **13e** (290 mg) was heated with 15 mL of 2:1 AcOH–H_2O for 3 h at 60°. Solvent was evaporated under diminished pressure to yield **11n**; ^{1}H-n.m.r. ($CDCl_3$): δ 2.0 to 2.3 (m, 2 H, H-3*a* and H-3*e*), 3.86 (s, 3 H, NOMe), 5.19 (s, 2 H, CH_2Ph, 7.36 (m, 5 H, ArH), 7.57 (d, 1 H, $J_{7,8}$ 4.5, major, *cis* H-8), and 6.95 (d, 1 H, $J_{7,8}$ 4.5, minor, *trans* H-8), major/minor = 4.

2,6-Anhydro-3,8-dideoxy-8-methoxylmino-D-glycero-D-talo-*octonic* acid, *ammonium salt* (**12n**). — The foregoing benzyl ester (**11n**) was hydrolyzed by stirring with a mixture of 1.5 mL of triethylamine and 30 mL of H_2O for 48 h at room temperature. Chromatography (20:20:1) $CHCl_3$–MeOH–H_2O) followed by treatment of the product with M NH_4OH gave 109 mg (54%) of **12n**; $[\alpha]_D^{22}$ +48.6° (*c* 1, H_2O); ^{1}H-n.m.r. (D_2O): δ 2.05 (m, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 13.2, $J_{3a,2}$ 6.9, $J_{3e,2}$ or $J_{3e,4}$ 4.5 Hz, H-3*a*), 2.20 (m, 1 H, H-3*e*), 3.87 (s, 3 H, OMe), 7.05 (d, minor, $J_{7,8}$ 7.2 Hz, H-8 *syn*-oxime), and 7.63 (d, major, $J_{7,8}$ 6.9 Hz, H-8 *anti*-oxime,) (*anti*/*syn* = 6.4); exact mass: calc. for $C_9H_{16}NO_7MH^+$ 250.0927; found 250.0951.

(*E*)-*Methyl2,6-anhydro-3,8,9,10-tetradeoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-10-oxo*-D-glycero-D-talo-*dec-8-enonate* (**16**). — To a freshly prepared sample of the aldehyde **3a** [prepared from 391.8 mg (1.08 mmol) of the alcohol **2d**] in 10 mL of PhMe was added 396.3 mg (1.30 mmol) of 2-(triphenylphosphoranylidene-acetaldehyde. The resulting solution was flushed with nitrogen and heated for 4 h at 75° with stirring. An additional amount of 2-(triphenylphosphoranylidene)acetaldehyde (415.8 mg, 1.37 mmol) was added and stirring and heating were continued for 3 h. The solution was applied directly to a flash chromatography column. Elution with 2:1 PhMe–EtOAc gave 398.7 mg of crude product. Gravity chromatography of the latter using 2:1 PhMe–EtOAc gave 207.7 mg (50%) of **16** as a deep-yellow syrup; ^{1}H-n.m.r. ($CDCl_3$): δ 1.36 and 1.49 (2 s, 6 H, CMe_2), 1.85 (m, 1 H, $J_{3a,3e}$ 15.6, $J_{3a,4}$ 11.4, $J_{3a,2}$ 6, $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 6.0 Hz, H-3*a*), 2.28 (m, 1 H, H-3*e*), 3.38 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.72 (s, 3 H, CO_2Me), 4.76 (d, 1 H, J_{AB} 0.23 Hz, H_A) and 4.86 (d, 1 H, H_B of $MeOCH_2$ $CH_2OCH_AH_BO$), 6.39 (m, 1 H, $J_{8,9}$ 16.2, $J_{9,10}$ 7.8, $J_{7,9}$ 1.5, $J_{7,8}$ 5.4 Hz, H-9), 7.07 (m, 1 H, H 8), and 9.63 (m, 1 H, H-10).

(E)-Methyl 2,6-anhydro-3,8,9-trideoxy-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-*glycero*-D-talo-*dec-8-enonate* (**17a**). — (*a*) To a stirred solution of 331.6 mg (0.854 mmol) of the aldehyde **16** in 8.5 mL 1:4 MeOH–AcOH was added a freshly prepared solution of 144 mg (2.29 mmol) of $NaBH_3CN$ in water. Stirring was continued for 2 h. Extraction with $CHCl_3$ gave the crude product which on flash chromatography (EtOAc) gave 173.9 mg (52%) of **17a**; $[\alpha]_D^{22}$ −76° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$); δ 1.33 and 1.48 (2 s, 6 H, CMe_2), 1.87 (m, 1 H, $J_{3a,3e}$ 15, $J_{3a,4}$ 10.8, $J_{3a,2}$ 3, $J_{3e,2}$ or $J_{3e,4}$ 3.9 or 5.7 Hz, H-3*a*), 2.27 (m, 1 H, H-3*e*), 3.39 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.72 (s, 3 H, CO_2Me), 4.73 (d, 1 H, J_{AB} 7.5 Hz, H_A) and 4.81 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), 5.77 (m, 1 H, $J_{8,9}$ 15.9, $J_{7,8}$ 7.8, $J_{8,10}$ $J_{8,10'}$ 1.5, $J_{9,10}$ $J_{9,10'}$ 6 Hz, H-8), and 6.03 (m, 1 H, H-9).

(*b*) To a stirred solution of 435.7 mg (1.12 mmol) of the aldehyde **16** in 20 mL of MeOH, cooled in an ice–water bath, was added a freshly prepared solution of 42.6 mg (1.13 mmol) of $NaBH_4$ in 2.0 mL of water. Stirring was continued for 2 h and 1 mL of acetone was then added. Extraction with $CHCl_3$ gave 444.2 mg of a clear, yellow oil. Flash chromatography (EtOAc) gave 250 mg (57%) of **17a** identical with that prepared as just described.

(E)-2,6-Anhydro-3,8,9-trideoxy-D-glycero-D-talo-*dec-8-enonate* (**12q**). — This compound was prepared from **17a** in quantitative yield according to the procedure for **12h**; $[\alpha]_D^{22}$ +83.5° (*c* 0.5, H_2O); ^{1}H-n.m.r. (D_2O): δ 2.12 (dt, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 12.0, $J_{3a,2}$ 6.6, $J_{3e,2}$ or $J_{3e,4}$ 6.0 Hz, H-3*a*), 2.23 (dd, 1 H, H-3*e*), 5.87 (m, 1 H, $J_{8,9}$ 15.9, $J_{9,10}$ 4.8, $J_{7,8}$ 6.9 Hz, H-9), and 5.98 (m, 1 H, H-8); exact mass: calc. for $C_{10}H_{15}O_7$ $(M-H)^-$ 247.0817; found 247.0840.

(E)-Methyl 2,6-anhydro-10-azido-3,8,9,10-tetradeoxy-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-glycero-D-talo-*dec-8-enonate* (**17b**). — (*a*) A stirred solution of 241 mg (0.62 mmol) of the alcohol **17a** in 9 mL of DMF was cooled in an ice–water bath and purged with nitrogen. Triphenylphosphine (657 mg, 2.5 mmol) and 250 mg (5.11 mmol) of LiN_3 were added and stirring was continued with cooling for 15 min. Carbon tetrabromide (840 mg, 2.5 mmol) was added and stirring was continued with cooling for 15 min and then for 2 h at room temperature. The crude product (987 mg), obtained by $CHCl_3$ extraction was chromatographed using 1:2 EtOAc–PhMe to yield 182 mg (71%) of **17b**; $[\alpha]_D^{25}$ −71° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.34 and 1.48 (2 s, 6 H, CMe_2), 1.89 (m, 1 H, $J_{3a,3e}$ 15, $J_{3a,4}$ 11.1, $J_{3a,2}$ 3, $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 6 Hz, H-3*a*), 2.24 (m, 1 H, H-3*e*), 3.40 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.72 (s, 3 H, CO_2Me), 4.72 (d, 1 H, J_{AB} 7.2 Hz, H_A), 4.82 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), and 5.85 (m, 2 H, *trans* H-8 and H-9).

(*b*) To a stirred solution of 95 mg (0.21 mmol) of the bromide **17d** in 5 mL of DMF, under nitrogen, was added 41 mg (0.84 mmol) of LiN_3 and stirring was continued overnight. Chromatography of the crude product obtained by $CHCl_3$ extraction of the solution gave 52.4 mg (60%) of **17b**, identical with that prepared as just described.

(E)-Methyl 2,6-anhydro-10-amino-3,8,9,10-tetradeoxy-4,5-O-isopropylidene-7-O-(2-methoxyethoxymethyl)-D-glycero-D-talo-*dec-8-enonate* (**17c**). — To a stirred solution of 200 mg (0.48 mmol) of the azide **17b** in 10 mL of THF was added 317 mg (1.2 mmol) of Ph_3P and stirring was continued overnight. Extraction with $CHCl_3$ gave 504

mg of crude product which was chromatographed using 20:2:0.1 $CHCl_3$–MeOH–Et_3N to give 82.5 mg (44%) of **17c** as a colorless syrup; ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 and 1.48 (2 s, 6 H, CMe_2), 1.87 (m, 1 H, $J_{3a,3e}$ 15, $J_{3a,4}$ 11.7, $J_{3a,2}$ 2.7, $J_{3e,2}$ or $J_{3a,4}$ 3.6 or 6 Hz, H-3*a*) and 2.24 (m, 1 H, H-3*e*) 3.39 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.72 (s, 3 H, CO_2Me), 4.68 (d, 1 H, J_{AB} 6.9 Hz, H_A), 4.86 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), 5.78 (q, 1 H, H-8), and 6.02 (dt, 1 H, $J_{8,9}$ 15.9, $J_{9,10}$ $J_{9,10'}$ 6.3 Hz, H-9).

*(E)-Methyl 2,6-anhydro-10-bromo-3,8,9,10-tetradeoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-*D-glycero-D-talo-*dec-8-enonate* (**17d**). — A stirred solution of 122.7 mg (0.33 mmol) of the alkene **20** and 73.1 mg (0.41 mmol) of NBS was heated for 2 h at 75° with irradiation by a 150-watt floodlamp. The succinimide was removed by filtration through a Celite mat. Evaporation of the CCl_4 under diminished pressure left 103 mg (69%) of **17d**; ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 and 1.48 (2 s, 6 H, CMe_2), 1.90 (m, 1 H, $J_{3a,3e}$ 15.6 $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 5.7 Hz, H-3*a*), 2.24 (m, 1 H, H-3*e*), 3.40 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.74 (s, 3 H, CO_2Me), 4.73 (d, 1 H, J_{AB} 6.9 Hz, H_A) and 4.81 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), 5.83 (m, 1 H, H-8), and 6.05 (m, 1 H, $J_{8,9}$ 15.0, $J_{7,8}$ $J_{9,10}$ 7.5 Hz, H-9).

*(E)-10-Amino-2,6-anhydro-3,8,9,10-tetradeoxy-*D-glycero-D-talo-*dec-8-enonic acid, triethylammonium salt* (**12o**). — The method employed for deprotection of basic, protected methyl esters is exemplified by the conversion of **17c** into **12o**. A solution of 80.5 mg (0.2 mmol) of **17c** into 8 mL of 1:10 conc. HCl–MeOH was stirred for 5 h at room temperature. After evaporation under diminished pressure, the residue was chromatographed (10:20:0.2 $CHCl_3$–MeOH–Et_3N) to yield 16.4 mg (30%) of the deprotected methyl ester **11o** and 32 mg of an unidentified, less-polar product. Compound **11o** was hydrolyzed by stirring with 0.2 mL of Et_3N and 3.7 mL of H_2O for 24 h at room temperature. The solution was lyophilized to yield 18.4 mg (84%) of **12o**;$[\alpha]_D^{25}$ +73° (*c* 0.5, H_2O); ^{1}H-n.m.r. (D_2O): δ 1.28 (t, 9 H, *J* 6 Hz, CH_2CH_3), 2.05 (dt, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 10.5, $J_{3a,2}$ 5.4, $J_{3e,2}$ or $J_{3e,4}$ 4.2 Hz, H-3*a*), 2.20 (dd, 1 H, H-3*e*), 3.21 (q, 6 H, *J* 6 Hz, CH_2CH_3), 4.35 (d, 1 H, $J_{4,5}$ 4.8 Hz, H-5), 5.93 (m, 1 H, H-9), and 6.08 (m, 1 H, $J_{8,9}$ 13.2, $J_{9,10}$ 5.1, $J_{7,8}$ 5.7 Hz, H-8); exact mass: calc. for $C_{10}H_{16}NO_6$ $(M-H)^-$ 246.0978; found 246.0978.

*The C-8 epimeric methyl 2,6-anhydro-3,9-dideoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-*D-erythro (*and* L-threo)-D-talo-*nononates* (**18**). — To a stirred suspension of 2.33 g (12.2 mmol) of CuI in 40 mL of ether under nitrogen, cooled in an ice–water bath, was added 15.9 mL (22.3 mmol) of 1.4M MeLi in ether. The ice–water bath was replaced with a Dry Ice–acetone bath, and a solution of the freshly prepared aldehyde **3a** [prepared by Swern oxidation of 2.05 g (5.65 mmol) of alcohol **2d**] in 12 mL of ether was added dropwise. After the addition was complete, stirring was continued for 3 h with cooling. Methanol (9 mL) was then added to the stirred, cooled solution, which was allowed to warm to room temperature. Extraction with $CHCl_3$ in which the $CHCl_3$ solutions were washed first with 10% NH_4Cl and then 10% $NaHCO_3$ gave 882 mg of an orange syrup which on flash chromatography with EtOAc gave 794 mg (38%) of **18** as a mixture of 8-epimers; ^{1}H-n.m.r. ($CDCl_3$): δ 1.28 (d, 3 H, $J_{8,9}$ 6.9 Hz, 8-Me), 1.34 and 1.47 (2 s, 6 H, CMe_2), 1.83 (m, 1 H, $J_{3a,3e}$ 15.9, $J_{3a,4}$ 11.7, $J_{3a,2}$ 3, $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 6.9

Hz, H-3*a*), 2.34 (m, 1 H, H-3*e*), 3.39 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.77 (s, 3 H, CO_2Me), 4.77 (d, 1 H, J_{AB} 6.9 Hz, H_A), and 4.97 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$).

*Methyl 2,6-anhydro-3,8,9-trideoxy-8,8-didehydro-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-8-C-methylene-*D-glycero-D-talo-*octonates* (**19b**). — Swern oxidation of 857 mg of the alcohol **18** yielded 770 mg (90%) of the ketone **19a** as described in the preparation of **3a**. Diiodomethane (0.84 mL, 10.4 mmol) was added to a stirred suspension of 1.2 g (18.3 mmol) of zinc in 23 mL of THF at room temperature, under N_2. After 30 min, 2.05 mL (2.05 mmol) of M $TiCl_4$ in CH_2Cl_2 was added at 0° and the resulting mixture was stirred for 30 min at room temperature. A solution of 770 mg (2.04 mmol) of **19a** in 7 mL of THF was added dropwise at room temperature. After being stirred for 30 min, the mixture was diluted with CH_2Cl_2. The organic layer was washed with M HCl and then 5% $NaHCO_3$ solution. After evaporation, the crude product was purified by flash chromatography (1:5 EtOAc–PhMe) to give 358 mg (47%) of **19b**; $[\alpha]_D^{25}$ −79.2° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.34 and 1.49 (2 s, 6 H, CMe_2), 1.82 (s, 3 H, $J_{3a,4}$ 18.3, $J_{3a,3e}$ 10.5, $J_{3a,2}$ 3, $J_{3e,2}$ or $J_{3e,4}$ 3.6 or 5.7 Hz, 8-Me), 1.94 (m, 1 H, H-3*a*), 2.22 (m, 1 H, H-3*e*), 3.40 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.72 (s, 3 H, CO_2Me), 4.62 (d, 1 H, J_{AB} 6.6 Hz, H_A), 4.74 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), 5.08 (br s, 1 H, $=CH_2$), and 5.12 (t, 1 H, *J* 1.8 Hz, $=CH_2$); exact mass: calc. for $C_{18}H_{31}O_8$ MH^+ 375.2019; found 375.2028.

*Methyl2,6-anhydro-9-azido-*3,8,9-*trideoxy-8,8-didehydro-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-8-*C-*methylene-*D-glycero-D-talo-*nononate* (**19d**). — A stirred suspension of 345.6 mg (0.923 mmol) of the alkene **19b**, 214 mg (1.20 mmol) of NBS, and 17 mL of CCl_4 was irradiated with a 150-watt floodlamp and heated for 2 h at 75°. An additional portion (107 mg, 0.60 mmol) of NBS was added and heating and irradiation were continued for 1 h. Succinimide was removed by filtration through a Celite mat and the mat was washed thoroughly with CCl_4 The combined filtrate and washing were washed with 10% NaCl and dried ($MgSO_4$). Evaporation of the CCl_4 under diminished pressure gave the crude bromide **19c**, which was dissolved in 12 mL of DMF and heated with 142 mg (2.90 mmol) of LiN_3. The resulting solution was stirred overnight at room temperature. Extraction with $CHCl_3$ gave 425 mg of an orange syrup which on chromatography with 5:1 PhMe–EtOAc gave 97.5 mg (25%) of **19d** as a yellow syrup; ^{1}H-n.m.r. ($CDCl_3$): δ 1.34 and 1.48 (2s, 6 H, CMe_2), 1.90 (m, 1 H, $J_{3a,3e}$ 17.4, $J_{3a,4}$ 11.2, $J_{3a,2}$ 3, $J_{3e,2}$ $J_{3e,4}$ 3.6 or 5.7 Hz, H-3*a*), 2.24 (m, 1 H, H-3*e*), 3.39 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.72 (s, 3 H, CO_2Me), 4.67 (d, 1 H, J_{AB} 6.9 Hz, H_A), and 4.77 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), 5.37 (br s, 1 H, $=CH_2$), and 5.42 (br s, 1 H, $=CH_2$).

*9-Amino-2,6-anhydro-3,8,9-trideoxy-8,8-didehydro-8-*C*-methylene-*D-glycero-D-talo-*nononic acid* (**12p**). — A solution of 97.5 mg (0.23 mmol) of the allylic azide **19d** in 9.4 mL of 10:1 MeOH–conc. HCl was kept for 25 h at room temperature. The major portion of the solvent was evaporated under diminished pressure. Residual HCl was removed by co-distillation with MeOH under diminished pressure. The crude azide **11r** thus obtained was dissolved in 5 mL of acetone and treated with 111 mg of MeOH-

washed Dowex 50W × 12 (H^+) resin, and the resulting suspension was stirred for 2 h. The resin was removed by filtration and the acetone was evaporated. The residue was taken up in $CHCl_3$ and the extract was washed with 5% $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the $CHCl_3$ gave **19e** as a yellow syrup. The latter was dissolved in 4 mL of $CHCl_3$ and 0.123 mL (0.47 mmol) of *i*-Pr_2NH was added. The resulting solution was cooled in an ice bath and flushed with nitrogen. Dimethyl-*tert*-butylsilyl trifluoromethylsulfonate (0.108 mL, 0.47 mmol) was added and the resulting solution was stirred with cooling for 2 h. Extraction with $CHCl_3$ gave a residue which, on flash chromatography using 5:1 PhMe–EtOAc gave 65.4 mg (63%) of **19f**. To a magnetically stirred solution of the latter (0.148 mmol) in 3.2 mL of THF was added 99.5 mg (0.379 mmol) of Ph_3P. Stirring was continued overnight at room temperature. Water 0.4 mL was added and stirring was continued for 3 h. Extraction with $CHCl_3$ followed by chromatography with 20:2:0.1 $CHCl_3$–MeOH–Et_3N gave 29.1 mg of **19g** as a colorless syrup. A solution of the latter in 3.0 mL of 10:1 MeOH–conc. HCl was stirred at room temperature for 2.5 h. The major portion of the solvent was evaporated and residual HCl was removed by evaporation with MeOH under diminished pressure. Chromatography of the residue with 1:2:0.2 $CHCl_3$–MeOH–Et_3N gave 13.7 mg of **11p**. The latter was dissolved in 2.0 mL of water and treated with 0.1 mL of Et_3N. The resulting solution was kept overnight at room temperature. Solvent was removed by lyophilization. A second lyophilization from water gave 12.3 mg (34%) of **12p** as a white glass; $[\alpha]_D^{25}$ +50° (*c* 0.25, H_2O); ^{1}H-n.m.r. (D_2O): δ 2.08 (m, 1 H, $J_{3a,3e}$ $J_{3a,4}$ 12.6, $J_{3a,2}$ 6.6, $J_{3e,2}$ or $J_{3e,4}$ 4.8 Hz, H-3*a*), 2.23 (m, 1 H, H-3*e*), 5.51 (s, 1 H, H_A), and 5.60 (s, 1 H, H_B) ($H_AH_BC=C$); exact mass: calc. for $C_{10}H_{16}NO_6$ $(M-H)^-$ 246.0983; found 246.0978.

*(Z)-Methyl 2,6-anhydro-3,8,9,10-tetradeoxy-4,5-*O*-isopropylidene-7-*O*-(2-methoxyethoxymethyl)-*D-glycero-D-talo-*dec-8-enonate* (**20**). — A suspension of 564 mg (1.5 mmol) of $Ph_3PCH_2CH_3Br$ and 8 mL of 5:1 THF–Me_2SO was cooled in an ice–water bath and flushed with nitrogen. To the stirred, cooled solution was added 3.0 mL of a solution of 0.5M $(Me_3Si)_2NK$ in PhMe. After the addition was complete, stirring was continued for 1 h. The ice–water bath was replaced with a Dry Ice–acetone bath and a solution of the freshly prepared aldehyde **3a** [prepared by Swern oxidation of 424 mg (1.16 mmol) of the alcohol **2d**] in 3.0 mL of THF was added. Stirring was continued with cooling for 1 h and then overnight at room temperature. Extraction with $CHCl_3$ (washes with 10% NH_4Cl and then 5% $NaHCO_3$) gave a product which on flash chromatography with 4:1 PhMe–EtOAc gave 438 mg (62%) of **20**; ^{1}H-n.m.r. ($CDCl_3$): δ 1.35 and 1.50 (2 s, 6 H, CMe_2), 1.75 (d, 3 H, *J* 6 Hz, 9-Me), 1.90 (m, 1 H, $J_{3a,3e}$ 12.6, $J_{3a,4}$ 8.7, $J_{3a,2}$ 2.7, $J_{3e,2}$ $J_{3e,4}$ 4.2 Hz, H-3*a*), 2.24 (m, 1 H, H-3*e*), 3.41 (s, 3 H, $CH_3OCH_2CH_2OCH_2O$), 3.73 (s, 3 H, CO_2Me), 4.66 (d, 1 H, J_{AB} 6 Hz, H_A), 4.77 (d, 1 H, H_B of $MeOCH_2CH_2OCH_AH_BO$), 5.40 (br t, 1 H, $J_{7,8}$ $J_{8,9}$ 8.7 Hz, H-8), and 5.89 (m, 1 H, H-9).

CMP-Kdo synthetase assay. —CMP-Kdo synthetase was isolated from *Escherichia coli* by the method of Goldman and Kohlbrenner[14]. The reaction was monitored with a coupled assay performed at 30° in semi-micro cuvettes containing 50mM Hepes (pH 7.6), mM Kdo, 0.5mM $MgCl_2$, mM DTT, 1.8 mg of glycogen, 7.8 units of inorganic pyrophosphatase, 10 units of phosphorylase *a*, 13 units of phosphoglucomutase, 15

units of D-glucose 6-phosphate dehydrogenase, 0.36 mg of NADP, and CMP-Kdo synthetase in a final volume of 1 mL. After a 6-min pre-incubation period, the reaction was initiated by the addition of 10 μL of diluted CMP-Kdo synthetase. The change in absorption at 340 nm was measured with a Gilford Response spectrophotometer which was programmed to calculate reaction rates. The reaction was linear between 2 and 5 min. after CMP-Kdo synthetase addition. The apparent K_m of Kdo was 0.32mM.

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