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BRANCHED-CHAIN HALO- AND AMINO-CYCLITOLS: SYNTHESIS AND AN X-RAY CRYSTALLOGRAPHIC STUDY*†

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ABSTRACT

The base-catalyzed cyclizations of tri-*O*-acetyl-1,7-dibromo-1,7-dideoxy-*xylo*-2,6-heptodiulose (**2**), tri-*O*-acetyl-1,7-dichloro-1,7-dideoxy-*xylo*-2,6-heptodiulose (**3**), and tri-*O*-acetyl-1,7-di-*C*-azido-1,7-dideoxy-*xylo*-2,6-heptodiulose (**4**), to DL-4,5,6-tri-*O*-acetyl-2-*C*-bromo-3-*C*-(bromomethyl)-*2,3,4,6/5*-tetrahydroxycyclohexanone (**5**), DL-4,5,6-tri-*O*-acetyl-2-chloro-3-*C*-(chloromethyl)-*2,3,4,6/5*-tetrahydroxycyclohexanone (**6**), and DL-4,5,6-tri-*O*-acetyl-2-*C*-azido-3-*C*-(azidomethyl)-*2,3,4,6/5*-tetrahydroxycyclohexanone (**7**), respectively, are described. Reduction of the acetylated cycloses **5–7** by sodium borohydride proceeded with considerable stereoselectivity in producing branched *epi*-inositols, isolated as the tetraacetates **12, 13,** and **18.** These latter compounds were used to prepare the corresponding unprotected cyclitols **24, 25,** and **31,** and the branched amino-*epi*-inositols **27, 29, 30,** and **32.** The stereochemistry of the branched-chain cyclitols described appears to be the same as that of DL-1,4,5,6-tetra-*O*-acetyl-3-chloro-2-*C*-(chloromethyl)-*epi*-inositol (**13**), whose structure was confirmed by an X-ray crystallographic study.

INTRODUCTION

Some cyclitols isolated from natural sources contain side chains. Included among these branched cyclitols are the well-known, cyclitol carboxylic acids shikimic acid[3,4] and quinic acid[4], the *C*-methylinositols mytilitol (*C*-methyl-*scyllo*-inositol)[4,5] and (—)-laminitol (6-*C*-methyl-*myo*-inositol)[4,5], and the aminocyclitol, L-validamine. L-Validamine is a component of the validamycins, a class of *Streptomyces*-produced compounds structurally related to aminocyclitol antibiotics[7–9].

Syntheses of branched-chain cyclitols are often routed through one of the

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*Dedicated to Professor Stephen J. Angyal on the occasion of his retirement.
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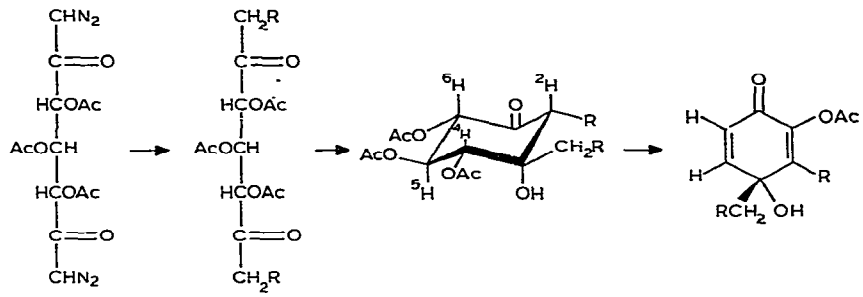
following reactions: addition of a carbon nucleophile to the carbonyl group of a suitably protected, cyclitol-derived cyclose; a Diels–Alder reaction; or cyclization of a nitro sugar. The synthesis of mytilitol, by the addition of a methyl Grignard reagent to penta-*O*-acetyl-*2,4,6/3,5*-pentahydroxycyclohexanone, illustrates the use of a cyclose in formation of a branched-chain cyclitol[10,11]. Applications of Diels–Alder reactions in preparing six-membered, branched carbocycles have been utilized in the syntheses of shikimic acid[3,4,13] and quinic acid[3,12]. Diels–Alder reactions have also led to several branched cyclohexanetetrols[14,15], and recently to validamine[16,17]. Construction from acyclic sugars of the cyclitol ring is achieved by the intramolecular cyclization of a nitro sugar or the condensation of a sugar dialdehyde and a nitroalkane[18–22]. This method for synthesis of cyclitols has been used extensively for the preparation of aminocyclitols[22]. Branched-chain aminocyclitols may also be prepared using the nitroalkane condensation, as evidenced by the synthesis of mytilamine (1-amino-1-deoxy-1-*C*-methyl-*scyllo*-inositol) from *xylo*-pentodialdose and nitroethane[23]. Cyclization of 6-deoxy-6-nitro-5-*C*-substituted hexoses to the corresponding branched nitrocyclitols has also been reported[24]. The carbon–carbon single-bond formation that occurs in the cyclization of a terminal deoxynitroaldose to a nitrocyclitol is a consequence of the strong electron-withdrawing ability of the nitro group. This group fosters abstraction of a proton from the terminal carbon atom and, in the basic medium, resonance-stabilizes the nitro carbanion once it has been formed. When the terminal methylene protons of an aldose or aldose derivative are activated by an adjacent ketone-carbonyl group, cyclization in a basic medium also occurs, the products being cycloses. This type of conversion is exemplified by the preparation of a mixture of inososes from D-*xylo*-hexos-5-ulose[25], and a mixture of inosose phosphates from the 6-phosphate of the same dicarbonyl sugar[26]. Ferrier reported a metal-ion catalyzed cyclization of a 5-ketohexose triester, derived from a 6-deoxy-5-enopyranoside, to a deoxycyclose[27].

Reports from this laboratory have described the conversions of the heptodiulose tri-*O*-acetyl-1,7-dibromo-1,7-dideoxy-*xylo*-2,6-heptodiulose[28,29] (**2**), under mildly basic conditions, into the unsaturated six-membered carbocycles. Here we describe the highly stereoselective cyclization of **2** and the 1,7-dichloro and 1,7-diazido analogs (**3** and **4**) of **2** to branched cycloses. These ring-forming reactions are the basis for a novel synthesis of branched-chain cyclitols.

RESULTS AND DISCUSSION

Branched-chain cycloses. — The protected dihalo-2,6-heptodiuloses **2** and **3** were conveniently prepared by bubbling the appropriate hydrogen halide through ethereal solutions of the bis(diazo)-2,6-heptodiulose[30] **1** (Scheme 1). When solutions of **2** and **3** in acetone were stirred with suspended, fused sodium acetate and each reaction monitored by ^{1}H-n.m.r. spectroscopy (90 MHz), it was observed that the dibromo- and dichloro-cycloses **5** and **6** were formed in a few h as the principal products of the respective reactions. Stirring the mixtures overnight led to complete dis-

appearance of the cycloses and to formation of the cross-conjugated ketones **8** and **9**. Given these results, it appears that the rate of cyclization is significantly greater than that of the elimination–rearrangement reaction that gives rise to the final unsaturated products. Ring formation to the cycloses most probably occurs by a simple, base-catalyzed, intramolecular aldol condensation, whereas the conversions of **5** into **8** and **6** into **9** are mechanistically more complex*. We initially attempted to monitor the cyclizations by t.l.c., but whereas **8** and **9** are well separated from the starting sugars, the cycloses **5** and **6** are chromatographically indistinguishable from these sugars.



1 | 2 R = Br, 3 R = Cl, 4 R = N_3 | 5 R = Br, 6 R = Cl, 7 R = N_3 | 8 R = Br, 9 R = Cl, 10 R = N_3

Scheme 1

When a solution of **2** in acetone was stirred with suspended sodium azide, **2** was converted into the amorphous diazidocyclose **7**. The course of this conversion was also monitored by ^{1}H-n.m.r. spectroscopy, with the focus being on the changes in the signals from the methylene protons of the acyclic starting-material (Fig. 1). After the mixture had been stirred for one h, the singlet at 4.4 p.p.m. from the terminal methylene protons of **2** had disappeared and a new singlet attributed to the terminal methylene protons of **4** developed. Corresponding changes in the signals at ~5.75 p.p.m., from the protons at C-3, C-4, and C-5 of **2**, were also observed. The diazido sugar **4** was not isolated, but rather the mixture was cooled to ~5° and kept without stirring. The reaction was monitored periodically, and after 3 h the spectrum showed a new, strong singlet at 4.65 p.p.m. and a very small peak from the terminal protons of unreacted **4**. The singlet at 4.65 p.p.m. is assigned to H-2 of **7**, with the rest of the ring protons clustered at 5.85 p.p.m. The diazidocyclohexadienone **10** was the apparent final product (*via* ^{1}H-n.m.r. only) after the reaction had been allowed to continue at 5°. As with **2** and **3**, the cyclization of **4** was significantly faster than the conversion of the cyclose (**7**) into the unsaturated, final product. An attempt to convert the dichlorodiketone (**3**) to **7** gave the dichlorocyclose **6**, but none of the desired product.

*The proposed mechanisms leading to the formation of **8** and **9** will be described elsewhere.

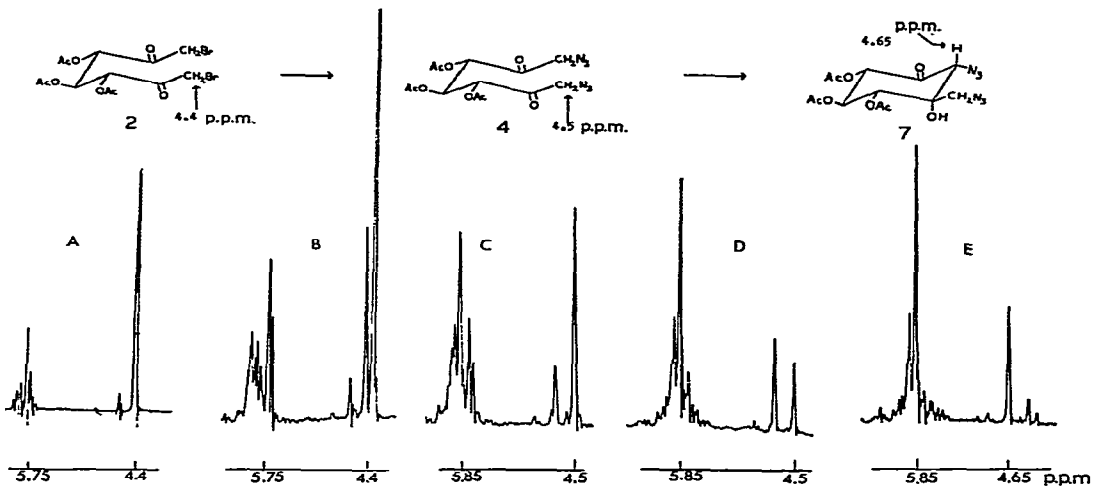
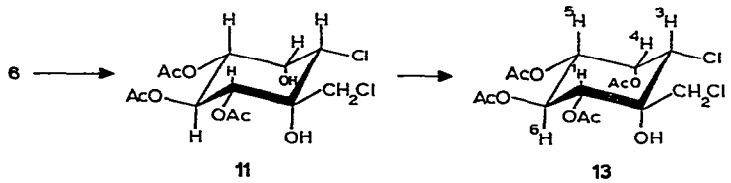


Fig. 1. 90-MHz, ^{1}H-n.m.r. spectra (non-acetyl region) from monitoring the reaction of **2** with sodium azide: spectrum A, compound **2**; spectra B and C, mixture after ~0.5 and 1 h; spectra D and E, mixture after ~2 and 3h. Reprinted with permission of the American Chemical Society; K. L. RINEHART, JR., (Ed.), *Aminocyclitol Antibiotics, ACS Symp. Ser.*, 1980, in press.

In summarizing the described cyclizations, it may be said that these reactions proceed under mild conditions with high-yield conversion to give single, racemic, branched-chain cycloses.

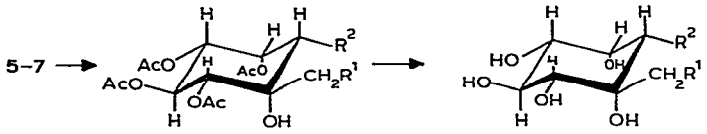
Branched-chain cyclitols. — Once formed, the dibromo and dichlorocycloses **5** and **6** were seen as convenient precursors to new branched-chain *epi*-inositols. Catalytic hydrogenation of **6** in acetic acid with platinum-black catalyst gave crystalline DL-1,5,6-tri-*O*-acetyl-3-chloro-2-*C*-(chloromethyl)-*epi*-inositol (**11**, Scheme 2). However, the dibromocyclose **5** resisted catalytic hydrogenation, and only small amounts of unidentified products were formed.



Scheme.2

Reduction of **5** and **6** was achieved in methanol–ether with sodium borohydride. The resultant cyclitols were then isolated as their tetraacetates **12** and **13** (Scheme 3). Deacetylation of **12** to the dibromocyclitol **24** and of **13** to the dichlorocyclitol **25** was effected with methanolic hydrogen chloride. Table I lists the branched, acetylated cyclitols (with the exception of compounds **11** and **23**) and free cyclitols described in this report.

The aminocyclitols **27**, **29**, and **30** were the first aminocyclitols prepared as a consequence of the cyclizations described. The synthesis of these molecules was



Scheme 3

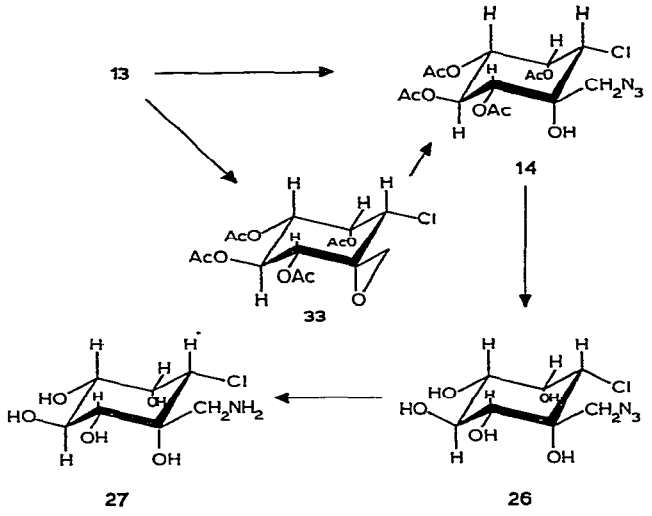
routed through the monoazido precursors **26** and **28**. The azidochlorocyclitol **26** was initially prepared by a two-step, nucleophilic-displacement sequence from the tetraacetate **13**. Compound **13** was converted into the spiroepoxide **33** with potassium *tert*-butoxide in *tert*-butyl alcohol (Scheme 4). The oxirane ring of unpurified **33** was then opened with sodium azide in the same alcohol solution, whereupon acetylation of the mixture gave the azidochlorocyclitol tetraacetate **14**. Synthesis of **14** from **13** was more conveniently achieved by conducting displacement of the exocyclic halogen with sodium azide in refluxing, aqueous 2-methoxyethanol, by a procedure described by Suami and co-workers for the preparation of acetylated azidocyclitols[31]. Deacetylation of **14** with sodium methoxide in methanol gave the free cyclitol **26**. This latter sequence was also used to convert the dibromocyclitol tetraacetate **12** into the azidobromocyclitol **28**.

Although catalytic hydrogenolysis of **26** in aqueous solution with platinum-black readily gave the branched aminochloro-*epi*-inositol **27**, the same hydrogenolysis procedure applied to **28** yielded the aminodeoxycyclitol **30** as the sole product (Scheme

TABLE I

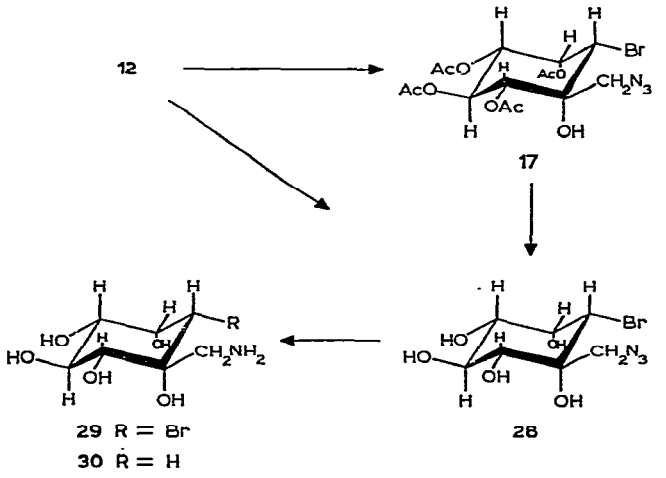
DL-2-*C*-*epi*-INOSITOLS AND ACETATES DERIVED FROM D-XYLOSE

Structure		*Structure*	
Compound	*Substituents*	*Compound*	*Substituents*
12	$R^1 = R^2 = Br$	**24**	$R^1 = R^2 = Br$
13	$R^1 = R^2 = Cl$	**25**	$R^1 = R^2 = Cl$
14	$R^1 = N_3$, $R^2 = Cl$	**26**	$R^1 = N_3$, $R^2 = Cl$
15	$R^1 = OAc$, $R^2 = Cl$	**27**	$R^1 = NH_2$, $R^2 = Cl$
16	$R^1 = I$, $R^2 = Cl$	**28**	$R^1 = N_3$, $R^2 = Br$
17	$R^1 = N_3$, $R^2 = Br$	**29**	$R^1 = NH_2$, $R^2 = Br$
18	$R^1 = R^2 = N_3$	**30**	$R^1 = NH_2$, $R^2 = H$
19	$R^1 = NHAc$, $R^2 = Cl$	**31**	$R^1 = R^2 = N_3$
20	$R^1 = NHAc$, $R^2 = Br$	**32**	$R^1 = R^2 = NH_2$
21	$R^1 = NHAc$, $R^2 = H$		
22	$R^1 = R^2 = NHAc$		

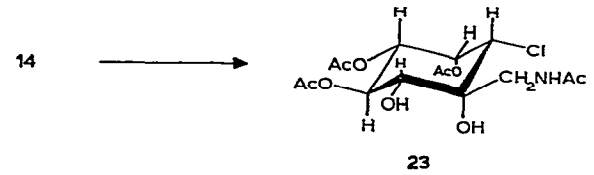


Scheme .4

5). Presumably, the slightly basic, aqueous solution generated by hydrogenolysis of the azido group fostered hydrogenolysis of the ring bromine atom as well. When the hydrogenolysis of **28** was performed in acetic acid solution, the bromine was not cleaved and the aminobromocyclitol **29** was formed. Hydrogenolysis of **14** to the corresponding amine was also achieved, but the reaction was accompanied by O→N acetyl migration to yield the *N*-acetyl cyclitol triacetate **23** as the only product (Scheme 6).



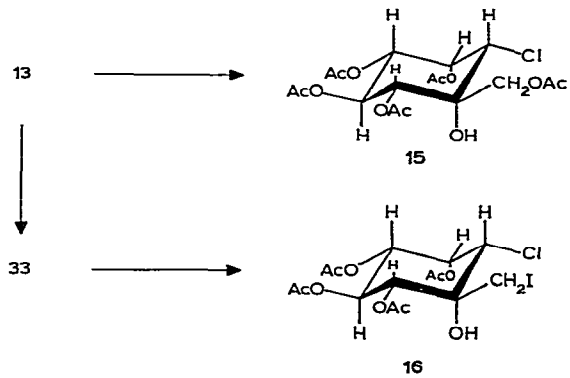
Scheme. 5



23

Scheme. 6

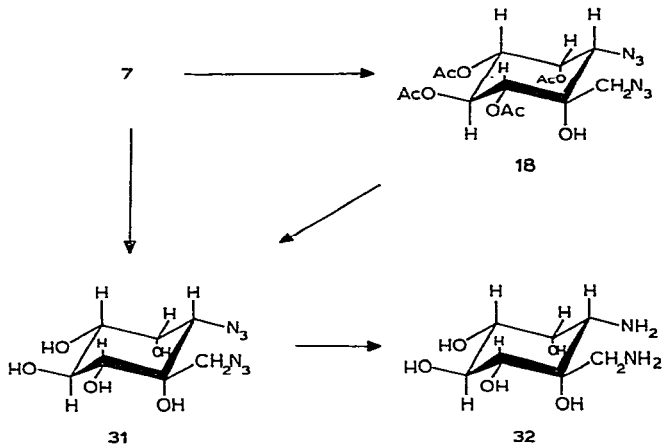
As stated, the exocyclic chlorine atom of **13** may be displaced by azide ion directly, or indirectly by opening the epoxide ring of **33**. A similar displacement from **13**, *via* the epoxide **33**, with sodium iodide, produced the chloroiodotetraacetate **16**. However, treatment of **13** with sodium iodide in aqueous 2-methoxyethanol, followed by acetylation of the crude product, gave the chlorocyclitol pentaacetate **15**. Apparently, iodide ion displaced the exocyclic chlorine atom from **13** but was in turn displaced during the acetylation (Scheme 7).



Scheme 7

Discovering that azide-displacement reactions of **12** and **13** led only to monoaminocyclitols, we turned our attention to the synthesis and cyclization of the diazidodiketone **4** in order to synthesize a ring system having two azido groups. The single-vessel preparation and cyclization of **4** as described earlier in this paper led to the desired, substituted ring-system. Crude **7** was then reduced with sodium borohydride and the product deacetylated to give the crystalline diazidocyclitol **31** (Scheme 8). Compound **31** was prepared in 64% yield from **2** when no attempt was made to isolate any of the intermediate products formed in the synthesis. The conversion of **31** into the diaminocyclitol **32** was then accomplished by catalytic hydrogenolysis. The crude, sodium borohydride reduction-product from **7** was acetylated to the diazidocyclitol tetraacetate **18** (64% from **2**), and this acetate was also readily converted into **32**.

Structural studies. — The stereochemistry at C-1, -4, -5, and -6 of **12** and **13** was confirmed from the ^{1}H-n.m.r. spectra of these molecules (Tables II and III). It was assumed that cyclization of the diketones **2**, **3**, and **4** rendered the least sterically-constrained cycloses **5**, **6**, and **7**, having the bulky C-2 halomethyl or azidomethyl and C-3 halo or azido substituents in equatorial positions. Formation of **14** from **13**



Scheme. 8

and **17** from **12** gave indirect support to this stereochemical hypothesis. Had the halogen at C-3 of **12** or **13** been axial, neighboring-group participation of the axial 4-acetoxyl group would have fostered introduction of an azido group at C-3 or C-4, resulting in the formation of diazidocyclitols. Introduction of an azido group at C-3 would also be anchimerically assisted by the hydroxyl group at C-2 had the hydroxyl group and the C-3 halogen atom been in a 1,2-*trans*-diaxial relationship.

The proposed stereochemistry of the dichlorocyclose **6** and the cyclitols derived from **6** was verified by an X-ray crystallographic study of crystalline DL-1,4,5,6-tetra-*O*-acetyl-3-chloro-2-*C*-(chloromethyl)-*epi*-inositol (**13**). The ORTEP drawing of **13** (Fig. 2) shows the molecule in a chair conformation having the 2-chloromethyl, 3-chloro, and 1-, 5-, and 6-acetoxyl groups in equatorial dispositions. The 2-hydroxyl group and 4-acetoxyl group are both axial. As the cycloses **5**, **6**, and **7** lead to similar arrays of cyclitols, the stereochemistry of each cyclose is the same, and the stereochemistry of the resultant cyclitols is the same.

EXPERIMENTAL

General methods. — Melting points were obtained with a Fisher–Johns melting-point apparatus and are uncorrected. Solutions were evaporated under diminished pressure. ^{1}H-N.m.r. spectra (Tables II and III) were recorded at 90 MHz with a Varian Model EM 390 spectrometer with *tert*-butyl alcohol (in D_2O) or tetramethylsilane as internal standards. The i.r. spectra (Table IV) were obtained with a Perkin–Elmer Model 283 grating i.r. spectrometer. Thin-layer chromatography was performed on plates coated with Silica Gel GF_{254} (E. Merck, Darmstadt), and components were detected by spraying with 20% sulfuric acid. The acid-form cation-exchange resin used was Dowex AG 50W-X2. Elemental analyses (Table IV) were performed by Atlantic Microlab. Inc., Atlanta, GA 30366.

TABLE II

^{1}H-N.M.R. PARAMETERS[a]

Compound	*Solvent*	*Chemical shifts (δ values)* *H-1*	*H-2*	*H-3a*	*H-4*	*H-5*	*H-6*	*OH*	*CH_2NH*	*CH_aH_b*	*CH_aH_b*	*Other*	*CH_3CO (number of protons)*
5	Me_2SO-d_6		5.85s		5.98d	5.45t	5.89d	6.73s		3.55d	3.36d		2.07(6), 1.97(3)
6	Me_2SO-d_6		5.69s		5.92d	5.43t	5.82d	6.68s		3.60s	3.60s		2.10(6), 2.00(3)
7	$CDCl_3$		4.32s		5.60m	5.60m	5.60m			3.65d	3.38d		2.17(3), 2.12(3), 2.03(3)
11	Me_2SO-d_6	5.28d		4.69d	4.24m	5.16dd	5.54t	6.55d 5.79s		3.63d	3.43d		2.06(3), 2.02(3), 1.97(3)
12	$CDCl_3$	5.49d		4.78d	5.76t	5.14dd	5.69t	3.40s		3.50d	3.31d		2.21(3), 2.13(3), 2.03(3), 2.00(3)
13	$CDCl_3$	5.46d		4.62d	5 82t	5.11dd	5.75t	3.14s		3.60d	3.33d		2.24(3), 2.17(3), 2.06(3), 2.03(3)
14	$CDCl_3$	5.19d		4.31d	5.73t	4.99dd	5.65t	2.94s		3.55d	3.25d		2.18(3), 2.12(3), 2.00(3), 1.96(3)
15	$CDCl_3$	5.21d		4.42d	5.76t	5.08dd	5.73t	3.05s		4.15d	3.90d		2.25(3), 2.10(6), 2.02(3)
16	$CDCl_3$	5.43d		4.65d	5.73t	5.07dd	5.66t	3.12s		3.40d	3.18d		2.18(3), 2.12(3), 2.00(3), 1.98(3)
17	$CDCl_3$	5.23d		4.42d	5.75t	5.02dd	5.68t	2.90s		3.56d	3.25d		2.23(3), 2.15(3), 2.02(3), 1.98(3)
18	$CDCl_3$	5.18d		3.68d	5.84t	5.03dd	5.67t	2.91s		3.56d	3.31d		2.20(3), 2.15(3), 2.02(3), 2.00(3)
19	$CDCl_3$	5.00d		4.22d	5.65t	4.96dd	5.69t	3.05s	6.19t	3.89dd	2.90dd		2.18(3), 2.14(3), 2.02(6), 1.97(3)
20	$CDCl_3$	5.03d		4.32d	5.68t	5.00dd	5.72t	2.98s	6.17t	3.88dd	2.92dd		2.22(3), 2.15(3), 2.02(6), 1.98(3)
21	$CDCl_3$	4.96d		2.28–1.77	5.50q	4.98dd	5.73t	2.90bs	6.20t	3.52dd	2.93dd	H-3e = 2.28–1.77	2.13(6), 2.02(6), 2.00(3)
22	Me_2SO-d_6	5.18d		4.50q	5.30t	5.10dd	5.55t	3.60s	7.16t	3.26dd	2.79dd	NH = 7.75d	2.10(3), 1.98(3), 1.93(3), 1.90(3), 1.83(3), 1.76(3)
23	$CDCl_3$	3.42q		4.12d	5.68d	4.91dd	5.58t	3.10s 4.62d	6.55t	3.71dd	3.22dd		2.17(3), 2.06(6), 1.97(3)
24	D_2O	3.72dd		4.53d	4.22t	3.60d	3.88t			3.63d	3.47d		
25	D_2O	3.66d		4.47d	4.25t	3.59dd	3.90t			3.69s	3.69s		
26	Me_2SO-d_6	3.13d		4.19d	3.94t	3.30dd	3.60t			3.52d	3.28d		
27[b]	D_2O	3.57d		4.27d	4.27q	3.62dd	3.90t			3.49d	3.29d		
28	Me_2SO-d_6	3.20d		4.40d	4.03t	3.37dd	3.65t			3.61d	3.28d		
29[b]	D_2O	3.66d		4.40d	4.32q	3.64dd	3.94t			3.52d	3.29d		
30[b]	D_2O	3.47d		2.10dd	4.18t	3.54dd	3.87t			3.30d	2.99d	H-3e = 7.75dd	
31	Me_2SO-d_6	3.07d		3.20d	4.15t	3.22dd	3.62t			3.50d	3.34d		
32[b]	D_2O	3.72d		3.30d	4.29t	3.54dd	3.90t			3.30s	3.30s		
33	$CDCl_3$	5.35d		4.51d	5.70t	5.11dd	5.62t			2.86d	2.47d		2.16(3), 2.05(3), 1.98(6)

[a]All spectra recorded in $CDCl_3$ or Me_2SO-d_6 used Me_4Si as internal standard. All spectra recorded in D_2O used *tert*-butyl alcohol as internal standard. Singlets are unmarked.
[b]The ^{1}H-n.m.r. spectra of compounds **27**, **29**, **30**, and **32** were obtained with their hydrochloride salts.

TABLE III

^{1}H-N.M.R. PARAMETERS[a]

Compound	*Solvent*	*Coupling constants (J values, Hz)* $J_{1,6}$	J_{NH,CH_aH_b}	J_{NH,CH_aH_b}	$J_{3a,4}$	$J_{4,5}$	$J_{5,6}$	J_{H_a,H_b}	*Other*
5	Me_2SO-d_6					10.0	10.0	9.9	
6	Me_2SO-d_6					9.8	10.0		
7	$CDCl_3$							12.3	
11	Me_2SO-d_6	10.3			2.4	3.2	10.5	11.7	$J_{4,OH}$ 6.3
12	$CDCl_3$	10.5			3.0	3.0	10.5	12.0	
13	$CDCl_3$	10.2			3.3	3.3	10.5	12.0	
14	$CDCl_3$	10.5			3.0	3.0	10.5	12.0	
15	$CDCl_3$	10.5			3.8	3.8	11.3	12.0	
16	$CDCl_3$	10.2			3.8	3.8	10.2	10.8	
17	$CDCl_3$	10.5			3.8	3.8	10.5	12.0	
18	$CDCl_3$	10.2			3.0	3.0	10.5	12.8	
19	$CDCl_3$	10.4	7.8	5.0	3.4	3.4	10.6	14.3	
20	$CDCl_3$	9.9	8.3	4.5	3.4	3.0	10.5	14.3	
21	$CDCl_3$	9.8	7.5	6.0	3.0	3.0	10.5	14.3	$J_{3e,4}$ 2.8, $J_{3e,3a}$ 17.1
22	Me_2SO-d_6	9.6	6.0	3.0	3.8	3.8	10.5	14.0	$J_{NH,3a}$ 6.6
23	$CDCl_3$	10.2	8.0	6.0	3.1	3.45	10.5	14.3	$J_{OH,1}$ 5.7
24	D_2O	9.0			3.0	3.0	9.0	10.5	
25	D_2O	9.0			3.0	3.0	9.0		
26	Me_2SO-d_6	9.0			3.0	3.0	9.0	12.0	
27	D_2O	9.0			3.0	3.0	9.0	13.5	
28	Me_2SO-d_6	9.8			3.0	3.0	9.8	12.0	
29	D_2O	7.5		3.4	3.0	2.3	11.3	13.5	
30	D_2O	9.8				3.3	9.8	13.5	$J_{3e,4}$ 3.0, $J_{3e,3a}$ 15.8
31	Me_2SO-d_6	9.6			3.0	3.0	9.6	12.0	
32	D_2O	9.0			3.5	3.0	9.0		
33	$CDCl_3$	10.0			3.0	3.0	10.0	6.0	

[a]The ^{1}H-n.m.r. spectra of compounds **27**, **29**, **30**, and **32** were obtained with their hydrochloride salts.

3,4,5-Tri-O-acetyl-1,7-dibromo-1,7-dideoxy-xylo-*2,6-heptodiulose* (**2**). — A suspension of 3,4,5-tri-*O*-acetyl-1,7-dideoxy-1,7-di-*C*-diazo-*xylo*-2,6-heptodiulose (**1**; 10.49 g, 29.6 mmol) in anhydrous ether (200 mL) was placed in a 500-mL Erlenmeyer flask equipped with a drying tube, a gas-inlet tube, and a magnetic stirrer. Anhydrous hydrogen bromide was slowly bubbled through the stirred suspension for ~1.5 h. The suspension was kept overnight without stirring at —20°, and the white solid removed by filtration and dried *in vacuo*, to give 10.12 g (74%) of **2**, m.p. 98.0–99.5°; ν_{max}^{KBr} 1770, 1755, and 1745 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$): δ 5.71 (m, 1 H, $J_{3,4}$ = $J_{4,5}$ = 4.03 Hz, H-4), 5.63 (m, 2 H, H-3 and H-5), 4.11 (s, 4 H, two equivalent CH_2Br), and 2.15 (s, 9 H, three equivalent CH_3CO_2 groups).*

*Theoretical ^{1}H-n.m.r. spectra were generated by using the ITRCAL program, Nicolet Instrument Corporation, Madison, WI. The ITRCAL program applies the LAOCOON III algorithm; see ref. 31a.

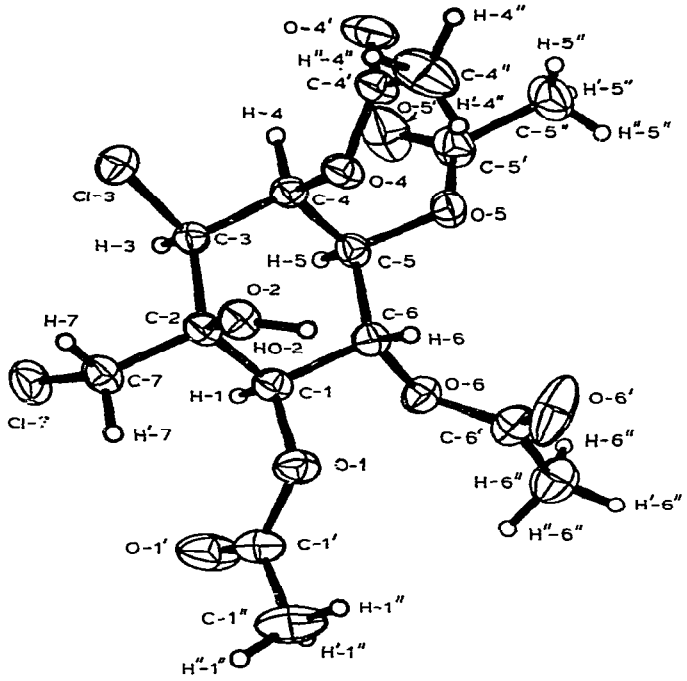


Fig. 2. ORTEP Drawing of **13**.

3,4,5-Tri-O-*acetyl-1,7-dichloro-1,7-dideoxy*-xylo-*2,6-heptodiulose* (**3**). — A suspension of **1** (11.30 g, 31.0 mmol) in anhydrous ether (300 mL) was treated with anhydrous hydrogen chloride (~1 h) as described for the preparation of **2**. The white product was filtered off and dried *in vacuo*, to give 11.09 g (94%) of **3**, m.p. 100–101°; ν_{max}^{KBr} 1765, 1755, and 1745 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$): δ 5.78 (m, 1 H, $J_{3,4} = J_{4,5} = 3.75$ Hz, H-4), 5.61 (m, 2 H, H-3 and H-5), 4.37 (s, 4 H, two equivalent CH_2Cl), 2.20 (s, 9 H, three equivalent CH_3CO_2 groups)*.

DL-(2,3,4,6/5)-*4,5,6-Tri*-O-*acetyl-2*-C-*bromo-3*-C-(*bromomethyl*)-*3,4,5,6-tetrahydroxycyclohexanone* (**5**). — To a solution containing **2** (4.9 g, 10.7 mmol) and dry acetone (50 mL, freshly distilled from potassium carbonate) was added fused sodium acetate (0.70 g, 8.5 mmol). The resulting mixture was kept for 3 h at room temperature with occasional stirring. The reaction was monitored by ^{1}H-n.m.r. (acetone) with the appearance of a singlet centered at 3.68 p.p.m. and with the corresponding disappearance of a 4-proton CH_2Br singlet centered at 4.43 p.p.m. The mixture was filtered and the filtrate treated with acid-form cation-exchange resin (10 mL). After 0.5 h, the resin was removed by filtration and the filtrate evaporated. The crude residue was crystallized from chloroform–hexane to give 2.97 g (60%) of **5**, m.p. 163–165°. Recrystallization from chloroform–hexane gave an analytical sample, m.p. 165–166°.

TABLE IV

ELEMENTAL ANALYSES[a] AND INFRARED SPECTRA[b]

Compound	*Molecular formula*	*Calculated*: *Found*:	*I.r. (cm^{-1})*
2	$C_{13}H_{16}Br_2O_8$	C, 33.94; H, 3.51; Br, 34.74 C, 34.06; H, 3.54; Br, 34.60	1770, 1755, 1745
3	$C_{13}H_{16}Cl_2O_8$	C, 42.07; H, 4.35; Cl, 19.10 C, 42.23; H, 4.37; Cl, 19.07	1765, 1755, 1745
5	$C_{13}H_{16}Br_2O_8$	C, 33.94; H, 3.51; Br, 34.74 C, 34.17; H, 3.61; Br, 34.81	3360, 1765, 1725
6	$C_{13}H_{16}Cl_2O_8$	C, 42.07; H, 4.35; Cl, 19.10 C, 41.96; H, 4.39; Cl, 19.39	3350, 1765, 1750, 1725
7	Not isolated		3420, 2100, 1740
11	$C_{13}H_{18}Cl_2O_8$	C, 41.84; H, 4.86; Cl, 19.00 C, 41.94; H, 4.87; Cl, 19.01	3460, 3420, 1755, 1730
12	$C_{15}H_{20}Br_2O_9$	C, 35.73; H, 4.00; Br, 31.70 C, 35.97; H, 4.07; Br, 31.87	3450, 1755, 1740
13	$C_{15}H_{20}Cl_2O_9$	C, 43.39; H, 4.86; Cl, 17.07 C, 43.27; H, 4.87; Cl, 16.98	3500, 1755, 1745
14	$C_{15}H_{20}ClN_3O_9$	C, 42.71; H, 4.78; Cl, 8.42 C, 42.47; H, 4.74; Cl, 8.55	3440, 2120, 1750, 1730
15	$C_{17}H_{20}ClO_{11}$	C, 46.53; H, 5.28; N, 8.08 C, 46.39; H, 5.33; N, 8.00	3420, 1750, 1740, 1720
16	$C_{15}H_{20}ClIO_9$	C, 35.56; H, 3.98; Cl, 7.00 C, 35.49; H, 3.98; Cl, 7.08	3400, 1755, 1720
17	$C_{15}H_{20}BrN_3O_9$	C, 38.64; H, 4.32; N, 9.01; Br, 17.14 C, 38.67; H, 4.34; N, 9.05; Br, 17.26	3360, 2150, 1750, 1735
18	$C_{15}H_{20}N_6O_9$	C, 42.06; H, 4.71; N, 19.62 C, 42.14; H, 4.76; N, 19.56	3450, 2110, 1750
19	$C_{17}H_{24}ClNO_{10}$	C, 46.63; H, 5.52; N, 3.20; Cl, 8.09 C, 46.76; H, 5.58; N, 3.18; Cl, 8.04	3530, 3355, 1745, 1650, 1540
20	$C_{17}H_{24}BrNO_{10}$	C, 42.34; H, 5.02; N, 2.90; Br, 16.57 C, 42.54; H, 5.05; N, 2.90; Br, 16.46	3525, 3360, 1755, 1745, 1655, 1550
21	$C_{17}H_{25}NO_{10}$	C, 50.62; H, 6.25; N, 3.47 C, 50.58; H, 6.25; N, 3.48	3560, 3340, 1750, 1660, 1570
22	$C_{19}H_{28}N_2O_{11}$	C, 49.56; H, 6.13; N, 6.08 C, 49.60; H, 6.15; N, 6.03	3440, 2270, 1750, 1660, 1550
23	$C_{15}H_{22}ClNO_9$	C, 45.52; H, 5.60; N, 3.54; Cl, 8.97 C, 45.42; H, 5.64; N, 3.53; Cl, 9.00	3560, 3470, 3380, 1740, 1665, 1545
24	$C_7H_{12}Br_2O_5$	C, 25.02; H, 3.60; Br, 47.57 C, 25.09; H, 3.63; Br, 47.46	3430, 3320
25	$C_7H_{12}Cl_2O_5$	C, 34.03; H, 4.90; Cl, 28.70 C, 34.04; H, 4.90; Cl, 28.63	3460, 3380, 3280
26	$C_7H_{12}ClN_3O_5$	C, 33.15; H, 4.79; N, 16.57; Cl, 13.98 C, 33.19; H, 4.81; N, 16.56; Cl, 14.01	3440, 3360, 2220(sh), 2115
27	$C_{13}H_{17}ClN_4O_{12}$	C, 34.19; H, 3.75; N, 12.27; Cl, 7.76 C, 34.42; H, 3.85; N, 12.13; Cl, 7.68	3420, 1585
28	$C_7H_{12}BrN_3O_5$	C, 28.20; H, 4.06; N, 14.10; Br, 26.81 C, 28.39; H, 4.09; N, 14.10; Br, 26.85	3450, 3370, 2120, 2230(sh)
29	$C_{13}H_{17}BrN_4O_{12}$	C, 31.15; H, 3.42; N, 11.18; Br, 15.94 C, 31.29; H, 3.45; N, 11.21; Br, 15.78	3400, 1600
30	$C_{13}H_{18}N_4O_{12}$	C, 36.97; H, 4.30; N, 13.27 C, 36.72; H, 4.30; N, 13.16	3400, 1580
31	$C_7H_{12}N_6O_5$	C, 32.31; H, 4.65; N, 32.30 C, 32.35; H, 4.70; N, 32.20	3400, 3250, 2230(sh), 2100
32	$C_{19}H_{22}N_8O_{19}$	C, 34.24; H, 3.33; N, 16.81 C, 34.44; H, 3.42; N, 16.64	3400, 1580

[a]Compounds **27**, **29**, **30**, and **32** were characterized as their picric acid salts. [b]The i.r. spectra of compounds **27**, **29**, **30**, and **32** were obtained with the free amines. All of the i.r. spectra were recorded for potassium bromide discs.

DL-(2,3,4,6/5)-*4,5,6-Tri*-O-*acetyl-2-chloro-3*-C-(*chloromethyl*)-*3,4,5,6-tetrahydroxycyclohexanone* (**6**). — To a solution containing **3** (10.1 g, 27.2 mmol) and dry acetone (165 mL, freshly distilled from anhydrous potassium carbonate) was added fused sodium acetate (1.60 g, 19.5 mmol). The resulting suspension was kept for 5 h at room temperature with occasional stirring. The reaction was monitored by ^{1}H-n.m.r. (acetone) with the appearance of a singlet at δ 3.76 (exocyclic CH_2Cl) and with the corresponding disappearance of a singlet centered at δ —4.65 (-COCH_2Cl). The mixture was filtered and the filtrate treated with acid-form cation-exchange resin (25 mL). After 0.5 h, the resin was removed by filtration and the filtrate evaporated to give 10.0 g of crude **6**. Crystallization of the product from 2:1 chloroform–hexane (300 mL) gave 7.48 g (74%) of **6**, m.p. 185–187°. Recrystallization from chloroform–hexane gave an analytical sample, m.p. 186–187°.

DL-(2,3,4,6/5)-*4,5,6-Tri*-O-*acetyl-2-azido-3*-C-(*azidomethyl*)-*3,4,5,6-tetrahydroxycyclohexanone* (**7**). — To a solution containing **2** (10.63 g, 23.1 mmol) and dry acetone (100 mL) was added finely divided sodium azide (6.18 g, 95.0 mmol). The reaction was monitored by ^{1}H-n.m.r. The stirred mixture was kept at room temperature until the peak at 4.4 p.p.m. (-CH_2Br) disappeared and a peak at 4.5 p.p.m. (-CH_2N$_3$) appeared. The mixture was refrigerated for 3 h at 5° until the peak at δ 4.5 disappeared and a peak at δ 4.65 (-CHN$_3$) appeared. The mixture was filtered and the filtrate treated with acid-form cation-exchange resin (40 mL). After 0.5 h, the resin was filtered off and washed with acetone. The combined filtrates were evaporated to give 9.23 g of a crude, glassy solid (**7**), which was used without purification for the preparation of **18**.

DL-*1,5,6-Tri*-O-*acetyl-3-chloro-2*-C-(*chloromethyl*)-*3-deoxy*-epi-*inositol* (**11**). — A solution of **6** (104 mg, 0.28 mmol) in acetic acid (6 mL) was hydrogenated in the presence of platinum oxide (100 mg, Matheson, Coleman and Bell) in a Parr shaker for 20 h at 80° under 3.4 atm of hydrogen. The catalyst was removed by filtration and the acetic acid by freeze drying. The resulting white solid was crystallized from ether–hexane, to give 74.6 mg (72%) of **11**, m.p. 169–171°. Recrystallization from ether–hexane gave an analytical sample, m.p. 175–177°.

DL-*1,4,5,6-Tetra*-O-*acetyl-3-chloro-2*-C-(*chloromethyl*)-*3-deoxy*-epi-*inositol* (**13**). — *Method A. From* DL-*1,5,6-tri*-O-*acetyl-3-chloro-2*-C-(*chloromethyl*)-*3-deoxy*-epi-*inositol* (**11**). A solution of **11** (99 mg, 0.26 mmol) in acetic anhydride (6 mL) containing fused sodium acetate (80 mg) was stirred overnight at room temperature. The solution was evaporated at 50° and the residue, in acetone (20 mL), was stirred for 0.5 h with acid-form cation-exchange resin (10 mL). The resin was removed by filtration, washed with acetone, and the combined filtrate and washings evaporated to give an amorphous, white solid. Crystallization of the solid from chloroform–hexane gave 57.3 mg (52%) of **13**, m.p. 150–152°. Recrystallization from the same solvent gave an analytical sample, m.p. 156–158° followed by resolidification and a second m.p. at 182–184°.

Method B. From DL-(2,3,4,6/5)-*4,5,6-tri*-O-*acetyl-2-chloro-3*-C-(*chloromethyl*)-*3,4,5,6-tetrahydroxycyclohexanone* (**6**). Sodium borohydride (4.19 g, 110.6 mmol)

was added to a stirred solution of **6** (8.00 g, 21.6 mmol) in 1:1 methanol–ether (640 mL) at −10°. The temperature was kept below 0° during the addition and at 10° for 3 h after the addition. The solution was treated with acid-form cation-exchange resin (190 mL) and then separated from the resin by filtration. The filtrate was evaporated to give a residue that was repeatedly dissolved in methanol and evaporated to remove boric acid as its methyl ester. The resulting solid was treated overnight at room temperature with acetic anhydride (200 mL) and pyridine (2 mL). The solution was evaporated at 50° and residual pyridine removed from the crude product by azeotropic evaporation of several portions of toluene (total volume 100 mL). The amorphous product (7.74 g, 86%) was crystallized from ethyl acetate–hexane, to give 5.65 g (63%) of **13**, m.p. 178–180°, identical in all respects with product obtained by method *A*.

DL-*3-Chloro-2*-C-(*chloromethyl*)-*3-deoxy*-epi-*inositol* (**25**). — To abs. methanol (3 mL) containing 4 drops of acetyl chloride was added **13** (207 mg, 0.50 mmol). The resulting solution was boiled for 15 h under reflux. The solution crystallized on being kept, to give **25** (105 mg, 85%), m.p. 218–220°. Recrystallization from ethanol–water gave an analytical sample, m.p. 222–223°.

DL-*1,4,5,6-Tetra*-O-*acetyl-3-bromo-2*-C-(*bromomethyl*)-*3-deoxy*-epi-*inositol*(**12**). — Sodium borohydride (4.19 g, 110.7 mmol) was slowly added to a solution of the crude cyclose **5** (9.94 g, 21.6 mmol) in 1:1 methanol–ether (500 mL) at −10°. The temperature was kept between 5 and 10° during the addition. After the addition had been completed, the stirred solution was cooled to 0° and over a 2-h period the mixture was allowed to warm to room temperature. The resulting solution was deionized with acid-form cation-exchange resin (200 mL) and the boric acid removed conventionally as methyl borate. The solid product was treated overnight with acetic anhydride (150 mL) and pyridine (1.5 mL) at room temperature and the mixture evaporated at 50°. Pyridine was removed from the product by azeotropic evaporation of toluene (total volume 100 mL). The resulting, amorphous solid (8.8 g) was crystallized from toluene (100 mL), to give 4.75 g (44%) of **12**, m.p. 156–159 and 167–171°. Recrystallization from ethyl acetate–hexane gave an analytical sample, m.p. 160–161.5 and 170–171.5°.

DL-*3-Bromo-2*-C-(*bromomethyl*)-*3-deoxy*-epi-*inositol* (**24**). — To a solution containing abs. methanol (2 mL) and 3–4 drops of acetyl chloride, was added **12** (129 mg, 0.256 mmol). The resulting solution was gently boiled under reflux for 10 h and then evaporated to give 85 mg of **24**, a light-pink solid, m.p. 220–228° (dec.). Recrystallization from ethanol–water gave an analytical sample, m.p. 230–231° (dec.).

DL-*1,4,5,6-Tetra*-O-*acetyl-3-azido-2*-C-(*azidomethyl*)-*3-deoxy*-epi-*inositol* (**18**). — To a solution of the crude, glassy compound **7** (9.23 g, 10.6 mmol) in 1:1 methanol–ether (500 mL) at −5° was added sodium borohydride (5.88 g, 155.4 mmol). The temperature was kept between 5 and 10° during the addition. The mixture was stirred for 2 h, allowed to warm to room temperature, and then deionized with acid-form cation-exchange resin (250 mL). The resin was removed by filtration and the filtrate evaporated to give a crude residue that was twice dissolved in methanol

(100 mL) and evaporated, giving an amorphous solid. This solid was treated overnight at room temperature with acetic anhydride (150 mL) and pyridine (1 mL) and the solution was then evaporated at 50°. Toluene (100 mL) was used to remove residual pyridine from the residue by azeotropic evaporation, and the amorphous product **18** was obtained in 92% yield (9.17 g). Crystallization of the product from ethyl acetate–hexane gave 6.29 g (64%) of **18**, m.p. 138–140°. Recrystallization from ethyl acetate–hexane gave an analytical sample, m.p. 142–143°.

DL-*3-Azido-2-C-(azidomethyl)-3-deoxy*-epi-*inositol* (**30**). — A solution of **18** (852 mg, 1.99 mmol) in abs. methanol (25 mL) was treated with sodium methoxide (14.4 mg, 0.27 mmol) in methanol (1 mL). The mixture was stirred for 1 h and then made neutral with acid-form cation-exchange resin (2 mL). The resin was filtered off and the filtrate evaporated to give 516 mg (100%) of **30**, m.p. 157–159°. Recrystallization from ethanol–water gave an analytical sample, m.p. 160–161°.

DL-*1,4,5,6-Tetra-O-acetyl-2,2'-anhydro-3-chloro-3-deoxy-2-C-(hydroxymethyl)*-epi-*inositol* (**33**). — A solution of potassium *tert*-butoxide (45 mg, 0.40 mmol) in *tert*-butyl alcohol (1 mL) was added to a stirred solution of **13** (124 mg, 0.30 mmol) in *tert*-butyl alcohol (8 mL). The mixture was stirred for 0.5 h, whereupon t.l.c. (1:1 benzene–ether) showed the disappearance of a spot at R_F 0.43 (**13**) and the appearance of a product spot at R_F 0.54. The mixture was stirred for 0.5 h with an excess of powdered, dry ammonium chloride (to neutralize the excess of base) and then evaporated. The residue was triturated with dichloromethane, inorganic salts were removed by filtration, and the filtrate was evaporated to give syrupy **33**; ν_{max}^{film} 1760 cm^{-1} (C=O). The product **33** was homogeneous (t.l.c.) and was used without purification for the preparation of **14**.

DL-*1,4,5,6-Tetra*-O-*acetyl-2*-C-(*azidomethyl*)-*3-chloro-3-deoxy*-epi-*inositol* (**14**). — *Method A. From* **13** *in* N,N-*dimethylformamide solution.* A solution of **13** (680 mg, 1.48 mmol) and sodium azide (618 mg, 9.5 mmol) in 90% aqueous *N,N*-dimethylformamide (40 mL) was boiled gently overnight under reflux. The mixture was evaporated and the residue treated with acetic anhydride (30 mL) and pyridine (5 drops) overnight at room temperature. The insoluble material was removed by filtration and the filtrate evaporated. The crude residue was suspended in dichloromethane (50 mL) and the suspension washed twice with water (25 mL). The organic layer was dried (magnesium sulfate) and evaporated to give 596 mg (94%) of crude **14**. Crystallization of the product from chloroform–hexane gave 436 mg (68%) of **14**, m.p. 145–148°. Recrystallization from chloroform–hexane gave an analytical sample, m.p. 150–151.5°.

Method B. From **13** *in 2-methoxyethanol solution.* A solution of **13** (196 mg, 0.472 mmol) and sodium azide (200 mg, 3.08 mmol) in 90% aqueous 2-methoxyethanol (10 mL) was boiled for 60 h under reflux. The mixture was evaporated and the crude residue treated at room temperature overnight with acetic anhydride (20 mL) containing 5 drops of pyridine. The solution was evaporated and the crude residue suspended in ethyl ether (50 mL), washed with water (25 mL), and dried (magnesium sulfate). Removal of the solvent gave 215 mg of crude product. Crystallization from

chloroform–hexane gave 146 mg (73%) of **14**, m.p. 149–151.5°, spectrally identical with a sample obtained by method *A*.

Method C. From DL-*1,4,5,6-tetra*-O-*acetyl-2,2'-anhydro-3-chloro-3-deoxy-2*-C-(*hydroxymethyl*)-epi-*inositol* (**33**). — A solution of potassium *tert*-butoxide (45 mg, 0.40 mmol) in *tert*-butyl alcohol (1 mL) was added to a stirred solution of **13** (124 mg, 0.30 mmol) in *tert*-butyl alcohol (8 mL). T.l.c. (1:1 benzene–ether) showed the disappearance of the starting material (R_F 0.43) and the appearance of the product **33** (R_F 0.54). Sodium azide (134.4 mg, 2.06 mmol) and ammonium chloride (193.2 mg, 3.61 mmol) were added to the mixture, which was stirred overnight at room temperature. The solvent was removed and the residue treated with acetic anhydride and pyridine overnight. The mixture was evaporated and the residue suspended in dichloromethane (50 mL). The suspension was washed twice with water (50 mL), and the organic layer was dried (magnesium sulfate). The solution was evaporated to give a crude residue (117.4 mg) that was crystallized from chloroform–hexane to give 75 mg (60%) of **14**, m.p. 147–150°, spectrally identical with a sample prepared by method *A*.

DL-*2*-C-(*Acetoxymethyl*)-*1,4,5,6-tetra*-O-*acetyl-3-chloro-3-deoxy*-epi-*inositol* (**15**). — A solution of **13** (250 mg, 0.60 mmol) and sodium iodide (533 mg, 3.56 mmol) in 90% aqueous 2-methoxyethanol (10 mL) was boiled for 60 h under reflux. The mixture was evaporated and the resulting, crude residue treated with acetic anhydride (20 mL) and pyridine (1 mL) overnight at room temperature. Solvents were removed from the mixture and the residue was suspended in water (50 mL) and extracted twice with dichloromethane (50 mL). The combined extracts were washed with 1% sodium thiosulfate, dried (magnesium sulfate), and evaporated to a syrup that was crystallized from ethyl acetate–hexane, to give 159 mg (60%) of **15**, m.p. 145–147°.

DL-(*1,4,5,6-Tetra*-O-*acetyl-3-chloro-3-deoxy-2*-C-(*iodomethyl*)-epi-*inositol* (**16**). — A solution of potassium *tert*-butoxide (79.6 mg, 0.67 mmol) in *tert*-butyl alcohol (8 mL) was added to a solution of **13** (162 mg, 0.39 mmol) in 1,2-dimethoxyethane (4 mL). The stirred mixture was monitored by t.l.c. (1:1 benzene–ether), showing R_F 0.55 for **33**. The stirred mixture was treated with anhydrous ammonium sulfate (315 mg, 2.38 mmol) and sodium iodide (176 mg, 1.17 mmol) for 3 h at room temperature and then evaporated. The crude residue was suspended in water (50 mL) and extracted twice with dichloromethane (50 mL). The combined extracts were washed with 10% sodium thiosulfate, dried (magnesium sulfate), and evaporated, to give 164.4 mg of an amorphous solid. Crystallization of the solid from toluene gave an analytical sample, m.p. 151–152°.

DL-*2*-C-(*Azidomethyl*)-*3-chloro-3-deoxy*-epi-*inositol* (**26**). — A solution of **14** (820 mg, 1.94 mmol) in abs. methanol (25 mL) was treated with sodium methoxide (16 mg, 0.3 mmol) in methanol (1 mL). After stirring for 1 h, the mixture was made neutral with acid-form cation-exchange resin (2 mL). The resin was filtered off, and a solid crystallized from the solution overnight (205 mg of **26**); m.p. 210.5–211.5° (dec.). The methanol solution was evaporated and the resultant syrup crystallized from ethanol, to give 190 mg (81% combined yield) of **26**, m.p. 207–209° (dec.).

Recrystallization from ethanol–water gave an analytical sample, m.p. 208–210° (dec.).

DL-*4,5,6-Tri*-O-*acetyl-2*-C-(*acetamidomethyl*)-*3-chloro-3-deoxy*-epi-*inositol* (**23**). — A solution of **14** (290 mg, 0.69 mmol) in ethanol (10 mL) was hydrogenated in the presence of platinum oxide (30 mg) in a Parr shaker for 20 h at room temperature. The mixture was filtered and the filtrate evaporated, to give 247 mg (80%) of **23**, m.p. 110–112 and 205–209°. Recrystallization from ethyl acetate–hexane gave an analytical sample, m.p. 213–215°.

DL-*2*-C-(*Aminomethyl*)-*3-chloro-3-deoxy*-epi-*inositol* (**27**). — A solution of **26** (100 mg, 0.39 mmol) in water (5 mL) was hydrogenated for 4 h at room temperature in the presence of platinum oxide (11.5 mg) under 1 atm of hydrogen. The mixture was filtered and the water lyophilized to give a grey solid that was dissolved in ethanol (5 mL), and the flocculent, black residue was filtered off. The solvent was evaporated to give a glassy solid that was dissolved in water and freeze dried, to give 92.9 mg of **27** as a white solid. The picrate of **27** was prepared by adding a saturated solution of picric acid in ethanol (1.5 mL) to a solution containing **27** (44 mg, 0.193 mmol) in ethanol (5 mL). The picrate of **27** (85 mg, 97%) crystallized from the solution; m.p. 225° (dec.).

DL-*1,4,5,6-Tetra*-O-*acetyl-2*-C-(*acetamidomethyl*)-*3-chloro-3-deoxy*-epi-*inositol* (**19**). — A solution containing acetic anhydride (4 mL), pyridine (4 mL), and **27** (103 mg, 0.45 mmol) was stirred overnight at room temperature. The mixture was evaporated to give a solid residue. Residual pyridine was azeotropically removed with carbon tetrachloride, yielding 193 mg (97%) of **19**, m.p. 100–105 and 169–174°. Crystallization from ethyl acetate–hexane gave an analytical sample, m.p. 100–105 and 175.5–177.5°.

DL-*1,4,5,6-Tetra*-O-*acetyl-2*-C-(*azidomethyl*)-*3-bromo-3-deoxy*-epi-*inositol* (**17**). — A mixture of **12** (104 mg, 0.21 mmol), sodium azide (104 mg, 1.6 mmol), and 90% 2-methoxyethanol (10 mL) was boiled for 60 h under reflux. The mixture was evaporated and the residue treated overnight at room temperature with acetic anhydride (10 mL) containing two drops of pyridine. The mixture was evaporated and the crude residue suspended in ethyl acetate (30 mL), washed twice with water (20 mL), and dried (magnesium sulfate). Removal of solvent gave 82 mg (84%) of a crude product that was crystallized from chloroform–hexane to give 43 mg (44%) of **17**, m.p. 140–143°. Recrystallization from chloroform–hexane gave an analytical sample, m.p. 144.5–146°.

DL-*2*-C-(*Azidomethyl*)-*3-bromo-3-deoxy*-epi-*inositol* (**28**). — *Method A. From 1,4,5,6-tetra*-O-*acetyl-2*-C-(*azidomethyl*)-*3-bromo-3-deoxy*-epi-*inositol* (**17**). A solution of **17** (509 mg, 1.09 mmol) in abs. methanol (25 mL) was treated with sodium methoxide (6.2 mg, 0.12 mmol) in methanol (1 mL). After stirring for 1 h, the mixture was made neutral with acid-form cation-exchange resin (2 mL). The resin was removed by filtration and the solution evaporated, to give 318 mg (98%) of **28**, m.p. 204–210° (dec.). Recrystallization from ethanol–water gave an analytical sample, m.p. 211–214° (dec.).

Method B. From DL-*1,4,5,6-tetra*-O-*acetyl-3-bromo-2*-C-(*bromomethyl-3-deoxy-*

epi-*inositol* (**12**). A mixture of **12** (5.03 g, 9.98 mmol), sodium azide (5.00 g, 76.9 mmol) and 90% 2-methoxyethanol (200 mL) was boiled for 60 h under reflux and the mixture was evaporated. The residue was suspended in water (100 mL) and the suspension cooled (~5°) to give 1.40 g (47%) of **28** as a light-brown solid, m.p. 206–210° (dec.). The aqueous solution was treated with acid-form cation-exchange resin (150 mL), the resin removed by filtration, and the filtrate evaporated. The resulting residue was crystallized from ethanol–water, to give 494 mg (17%) of **28**, m.p. 211–215° (dec.), spectrally identical with the product obtained by method *A*.

DL-*2*-C-(*Aminomethyl*)-*3-deoxy*-epi-*inositol* (**30**). — A solution of **28** (252 mg, 0.845 mmol) in water (30 mL) was stirred in the presence of platinum oxide (25 mg) and hydrogen at 1 atm for 5 h at room temperature. The mixture was filtered and the solvent freeze-dried, to give 234.4 mg of the hydrobromide of **30**. This salt was dissolved in water (5 mL) and the solution passed through a column of hydroxide-form anion-exchange resin (18 mL, Dowex AG 1-X2 OH^- resin). The water was removed by freeze-drying to give 161 mg (98%) of **30**. The picrate of **30** was prepared in 91% yield [m.p. 205–207° (dec.)] by a procedure similar to that described for the preparation of the picrate of **27**. Recrystallization of the picrate of **30** from ethanol–water gave an analytical sample, m.p. 204–206° (dec.).

DL-*1,4,5,6-Tetra*-O-*acetyl-2*-C-(*acetamidomethyl*)-*3-deoxy*-epi-*inositol* (**21**). — Compound **21** was prepared in 98% yield by a procedure similar to that described for the preparation of **19**. Crystallization from ethyl acetate–hexane gave an analytical sample of **21**, m.p. 184–186°.

DL-*2*-C-(*Aminomethyl*)-*3-bromo-3-deoxy*-epi-*inositol* (**29**). — A solution of **28** (444 mg, 1.49 mmol) in acetic acid (60 mL) and water (12 mL) was stirred for 9 h at room temperature in the presence of platinum oxide (40 mg) under hydrogen at 1 atm. The catalyst was removed by filtration and the solvent freeze-dried, to give 603 mg of the acetic acid salt of **29**, a very hygroscopic solid. The salt (in aqueous solution) was converted into the free base **29** on a column of hydroxide-form anion-exchange resin (15 mL, Dowex AG 1-X2 OH^- resin). Lyophilization of the water gave 272 mg of **29** (100%).

The picrate of **29** was prepared in 55% yield by a procedure similar to that described for the preparation of the picrate of **27**. Recrystallization of the picrate of **29** from ethanol–water gave an analytical sample, m.p. 225–228° (dec.).

DL-*1,4,5,6-Tetra*-O-*acetyl-2*-C-(*acetamidomethyl*)-*3-bromo-3-deoxy*-epi-*inositol* (**20**). — Compound **20** was prepared in 83% yield by a procedure similar to that described for the preparation of **19**. Crystallization from ethyl acetate–hexane gave an analytical sample of **20**, m.p. 184–186 and 193–195°.

DL-*3-Amino-2*-C-(*aminomethyl*)-*3-deoxy*-epi-*inositol* (**32**). — A solution of **30** (120 mg, 0.46 mmol) in water (5 mL) was stirred for 4 h at room temperature in the presence of platinum oxide (10 mg) under hydrogen at 1 atm. The mixture was filtered and the filtrate freeze-dried, to give 98.2 mg of **32**.

The dipicrate of **32** was prepared in 90% yield by a procedure similar to that

described for the preparation of the picrate of **27**. Recrystallization of the dipicrate of **32** from ethanol–water gave an analytical sample, m.p. 243–245° (dec.).

DL-*1,4,5,6-Tetra*-O-*acetyl-3-acetamido-2*-C-(*acetamidomethyl*)-*3-deoxy*-epi-*inositol* (**22**). — Compound **22** was prepared in 90% yield (m.p. 225–234°) by a procedure similar to that described for the preparation of **19**. Crystallization from ethyl acetate–hexane gave an analytical sample of **22**, m.p. 233–235°.

X-Ray crystallographic study of **13**. — Crystals of **13** were obtained at room temperature from a mixture of chloroform and hexane as clear, rectangular prisms. Weissenberg and oscillation photographs showed the crystals to be monoclinic, space group $P2_1/c$ (systematic absences: hOl with l odd, OkO with k odd). A crystal measuring ~0.3 × 0.3 × 0.5 mm and mounted approximately parallel to its a axis was used for data collection on a Picker FACS-1 diffractometer. Cell dimensions of $a = 9.801$ (2), $b = 21.209$ (4), $c = 10.465$ (1) Å, and $\beta = 115.40$ (2)° were determined by least-squares analysis of 2θ values for 15 reflections (CuKα, $\lambda = 1.5418$ Å). Intensity data were collected with nickel-filtered copper radiation, a scintillation counter, and a $\theta - 2\theta$ scanning technique. A scanning speed of 2°/min and a background sampling-time of 20 s at each scan terminus were used to measure the intensities of each of the 3231 unique reflections having $2\theta \leq 127°$. The intensities of three reflections (040, 304, and 330) that were monitored periodically during data collection showed no significant decrease or fluctuation. Intensities were assigned variances, $\sigma^2(I)$, according to counting-statistics, plus an additional term, $(0.03S)^2$, S being the scan count. Intensities and variances were corrected for Lorentz and polarization effects, absorption corrections were applied by means of the computer program ORABS[32], and data were scaled with a Wilson[33] plot.

A complete non-hydrogen-atom trial structure was obtained by use of the computer program MULTAN[34]. All hydrogen-atoms were located in a difference Fourier map calculated after several cycles of least-squares refinement of the trial model, including anisotropic thermal-parameters. The calculated density of 1.403 g.cm^{-3} may be compared with a value of 1.397 g.cm^{-3} measured by flotation in a mixture of organic solvents. Hydrogen atoms were included in subsequent structure-factor calculations, with isotropic temperature-factors corresponding to those of atoms to which they are bonded, but these factors were not refined. Final refinement used a modified version of the full-matrix, least-squares program ORFLS[35,36] and minimized $\sum w(F_0^2 - F_C^2/k^2)^2$, where k is a scale factor and $w = 1/\sigma^2(F_0)$. As limited core-storage prevented simultaneous variations of all parameters, two subsets of approximately equal numbers of parameters were refined in alternate cycles. Scattering factors and anomalous-dispersion corrections were taken from Tables 2.2A, 2.2C, and 2.3.1 of Vol. IV of the *International Tables for X-ray Crystallography*[37]. Also refined was an isotropic extinction-parameter (g of Zachariasen[38] as formulated by Coppens and Hamilton[39]). The final R index $(\sum||F_0|-|F_c||/|F_0|)$ was 0.049, and the goodness-of-fit $\{[\sum w(F_0^2 - F_C^2/k^2)^2/(m-s)]^{1/2}$, where m is the number of reflections used and s is the number of parameters refined$\}$ was 1.94. A drawing of the molecule, prepared with the aid of the computer program ORTEP[40], is shown as Fig. 2. Atomic

TABLE V

COORDINATES FOR DL-1,4,5,6-TETRA-*O*-ACETYL-3-CHLORO-2-*C*-(CHLOROMETHYL)-*epi*-INOSITOL (13)

(a) *Non-hydrogen-atom positional parameters* ($\times 10^4$). *E.s.d. values given in parentheses*				(b) *Hydrogen-atom positional parameters* ($\times 10^3$, *not refined*)			
Atom	X	Y	Z	*Atom*	X	Y	Z
Cl-3	−141(1)	3124(1)	3414(1)	H-1	326	392	731
Cl-7	372(1)	3604(1)	7113(1)	H-1″	348	595	743
C-1	3145(3)	4174(1)	6510(2)	H′-1′	254	593	830
C-2	1573(3)	4034(1)	5302(2)	H″-1″	380	570	860
C-3	1599(3)	3345(1)	4856(2)	H-3	117	307	564
C-4	2894(3)	3184(1)	4489(2)	H-4	287	274	427
C-5	4387(3)	3339(1)	5709(2)	H-4″	277	342	31
C-6	4455(3)	4021(1)	6145(2)	H′-4′	150	365	39
C-7	323(3)	4140(1)	5786(3)	H″-4″	300	405	133
C-1′	3290(3)	5020(1)	8091(3)	H-5	454	308	651
C-1″	3355(5)	5725(2)	8196(4)	H-5″	777	290	490
C-4′	2853(3)	3220(1)	2203(3)	H′-5″	792	230	535
C-4″	2607(5)	3641(2)	999(3)	H″-5″	670	260	385
C-5′	6093(3)	2634(1)	5375(3)	H-6	444	431	543
C-5″	7161(4)	2564(2)	4733(4)	H-6″	880	410	910
C-6′	6867(3)	4512(1)	7401(3)	H′-6″	889	483	877
C-6″	8220(4)	4515(2)	8784(4)	H″-6″	788	462	950
O-1	3235(2)	4837(1)	6818(2)	H-7	−64	411	497
O-1′	3260(3)	4666(1)	8948(2)	H′-7	39	457	613
O-2	1178(2)	4453(1)	4152(2)	HO-2	190	470	397
O-4	2753(2)	3540(1)	3269(2)				
O-4′	3151(3)	2669(1)	2287(2)				
O-5	5586(2)	3235(1)	5283(2)				
O-5′	5671(3)	2221(1)	5881(3)				
O-6	5829(2)	4106(1)	7422(2)				
O-6′	6700(3)	4820(1)	6404(3)				

TABLE VI

NON-HYDROGEN-ATOM BOND-DISTANCES

Bond	*Distance*[a] *(Å)*	*Bond*	*Distance (Å)*
C-1–C-2	1.546	C-6–O-6	1.444
C-1–C-6	1.524	C-1′–O-1	1.366
C-1–O-1	1.437	C-1′–O-1′	1.179
C-2–C-3	1.536	C-1′–C-1″	1.498
C-2–C-7	1.529	C-4′–O-4	1.344
C-2–O-2	1.411	C-4′–O-4′	1.200
C-7–Cl-7	1.780	C-4′–C-4″	1.476
C-3–Cl-3	1.787	C-5′–O-5	1.355
C-3–C-4	1.515	C-5′–O-5′	1.187
C-4–C-5	1.509	C-5′–C-5″	1.475
C-4–O-4	1.438	C-6′–O-6	1.340
C-5–C-6	1.509	C-6′–O-6′	1.182
C-5–O-5	1.442	C-6′–C-6″	1.485

positional parameters are given in Table V, and bond lengths between atoms other than hydrogen are presented in Table VI. Table VII gives hydrogen and non-hydrogen thermal parameters*.

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*Supplementary data: Hydrogen and non-hydrogen thermal parameters (Table VII) can be obtained from Elsevier Scientific Publishing Company, BBA Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/142/*Carbohydr. Res.*, 82 (1980) 303–324.

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