Table III. Anhydrous Fluoroantimonic Acid Catalyzed Alkylation of Benzene with Alkylbenzene–Alkane Mixtures

Alkylbenzene	Alkane	Temp, °C	Time	Alkylated benzene
tert-Butylbenzene	Isopentane	20	1 hr	18% pentylbenzenes (mostly 2-methyl-3-phenylbutane and some 2-methyl-2-phenylbutane)
2-Methyl-3-phenylbutane	Isobutane	20	30 min	7% *tert*-butylbenzene
			1 hr	8.5% *tert*-butylbenzene

Whereas our present studies were carried out, in order to be able to directly compare results of alkylation of benzene by alkanes, with alkane–alkene and tertiary alkylbenzene–alkane mixtures, with the superacidic fluoroantimonic acid as catalyst, the alkene promoted alkylations and transalkylations with alkanes can also be carried out using conventional Friedel–Crafts catalysts, such as aluminum chloride.

Experimental Section

Spectroscopic grade benzene (Mallinkrodt) was further purified by shaking with concentrated H_2SO_4, then with H_2O, dilute NaOH, and H_2O, followed by drying over 4X Linde molecular sieves and then fractionation from CaH_2. The benzene thus obtained was analyzed by gas–liquid chromatography and showed no detectable impurities. Ultra high purity methane (Matheson) was used which had a minimum purity of 99.95 mol %. Analysis by GLC showed no other detectable hydrocarbons. Ethane, propane, butane, and isobutane (Matheson) were all CP grade, i.e., >99% pure. Isopentane (Phillips) had a minimum purity of 99.5 mol %.

Gas–liquid chromatographic analyses were carried out on a Perkin-Elmer Model 226 chromatograph, equipped with 15.0 × 0.01 stainless steel open tubular Golay column, stationery phase: *m*-bis(*m*-phenoxyphenoxy)benzene + apiezon L, 100°, 30 psi helium pressure. Isolated products (Varian Aerograph Autoprep) were also identified by ^1H NMR spectroscopy (Varian A-56/60) and when needed by mass spectrometry.

Alkylation of Benzene with Alkanes. Reactions with C_1–C_4 alkanes as alkylating agents were carried out in 200-ml monel bombs, with a molar ratio of alkane:benzene:HF-SbF_5 of 20:2:1, at 25°, in case of methane, at 80°. The reaction with isopentane was carried out at atmospheric pressure at 25°. The reaction times are shown in Table I. After depressurizing, reaction mixtures were quenched with ice–water, washed with Na_2CO_3 solution, and dried over $MgSO_4$. The products were then analyzed by gas–liquid chromatography and mass spectrometry.

Alkylation of Benzene with Alkane–Alkene Mixtures. Benzene (0.2 mol) and 0.1 mol of isoalkane (isobutane or isopentane) were cooled to +5°. Anhydrous fluoroantimonic acid (0.01 mol) was added to the well-stirred mixture and then 0.1 mol of alkene (2-methylpropene or 2-methyl-butene-2) introduced while continuing the stirring. Samples were taken periodically, quenched, washed, and analyzed by gas–liquid chromatography.

Alkylation of Benzene with Alkylbenzene–Alkane Mixtures. The corresponding alkylbenzene (0.1 mol), 0.1 mol of benzene, and 0.2 mol of the isoalkane were mixed and cooled to −20°, 0.01 mol of anhydrous fluoroantimonic acid was added, and the stirred mixture was allowed to warm up to 20°, where it was stirred for 1 hr. Samples taken were quenched, neutralized, washed, and analyzed by gas–liquid chromatography.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

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A Chemical Model for the Cyclization Step in the Biosynthesis of L-*myo*-Inositol 1-Phosphate

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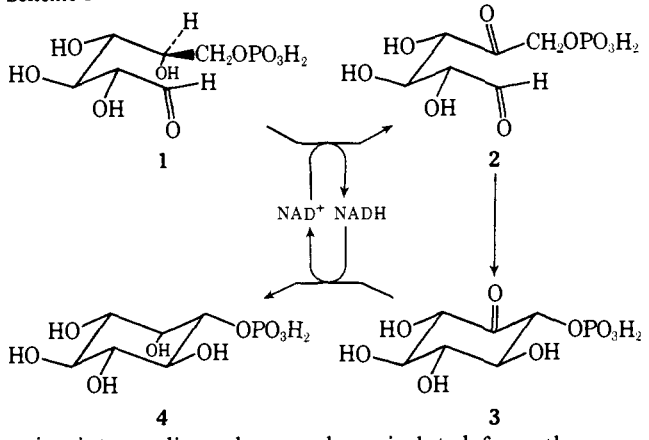
Abstract: Base treatment of D-*xylo*-hexos-5-ulose 6-phosphate (**2**) yielded, as the predominant products, two cyclose phosphates which, after reduction with sodium borohydride, gave a mixture of the cyclitol monophosphates L-*myo*-inositol 1-phosphate (**4**) and *epi*-inositol 3-phosphate (**8**). Compounds **4** and **8** were characterized as their trimethylsilyl derivatives by GC–MS. The parent cyclitols, after dephosphorylation of **4** and **8**, were identified in the same manner. The conversion of **2** to one of the cyclose phosphates, D-2,4,6/3,5-pentahydroxycyclohexanone 2-phosphate (**3**), represents a chemical model for the cyclization step in the biosynthesis of L-*myo*-inositol 1-phosphate (**4**).

The NAD-dependent conversion of D-glucose 6-phosphate (**1**) to L-*myo*-inositol 1-phosphate (**4**) has been observed in preparations from higher and lower plants as well as mammals.[1] In each system, L-*myo*-inositol 1-phosphate is considered to result from the cyclization of a δ-dicarbonyl monosaccharide derivative, D-*xylo*-hexos-5-ulose 6-phos-

phate (**2**, "5-keto-D-glucose 6-phosphate") by the enzyme L-*myo*-inositol 1-phosphate synthase. This intermediate is thought to undergo an enzyme-induced intramolecular aldol condensation to the isomeric cyclose phosphate, D-2,4,6/3,5-pentahydroxycyclohexanone 2-phosphate[2] (**3**), a reduction of which gives **4** (Scheme I). Neither of these pu-

Scheme I



tative intermediates has yet been isolated from the enzymatic transformation. However, this has been rationalized by the observations of Sherman et al.[3] who carried out a mass spectrometric study on the mechanism of the enzyme reaction and concluded that the intermediates must be tightly bound to the enzyme during the transformation. More recently Barnett and coworkers[4] have strengthened the validity of this proposed pathway in their study wherein a charcoal treated cyclase preparation from rat testis catalyzed the [4-^{3}H]-NADH reduction of **2** to [5-^{3}H]glucose 6-phosphate and, to a lesser extent, [^{3}H]*myo*-inositol 1-phosphate.

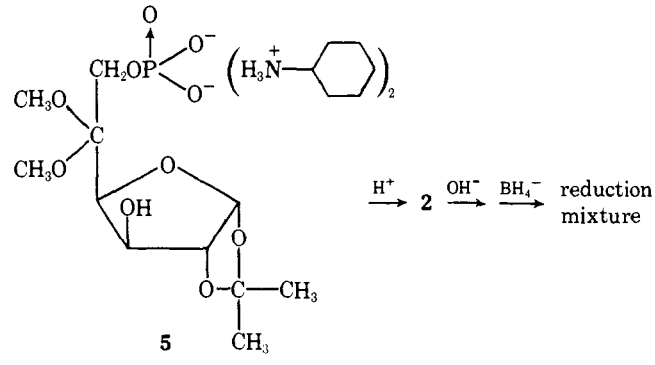
In this paper, we describe the base catalyzed cyclization of **2**, a reaction which mimics the proposed ring-forming step in the biogenesis of **4**.

Results

The use of a simple, unsubstituted, monosaccharide as a substrate for the generation of cyclitols by a base catalyzed aldol condensation was first realized by Kiely and Fletcher.[5] They demonstrated that D-*xylo*-hexos-5-ulose ("5-keto-D-glucose"), in aqueous hydroxide, gave the all-trans cyclose 2,4,6/3,5-pentahydroxycyclohexanone as the predominant product. This reaction served as the basis for a synthesis of the cyclitol-ring system from D-glucose and was, as well, a chemical model for the cyclization step in the biosynthesis of *myo*-inositol. Using essentially the same approach, we set out to refine the model for the cyclization by using the phosphate **2** as the substrate for base treatment, in closer analogy to the supposed biochemical process.

The experimental procedure was initiated by deblocking the phosphate salt **5** in order to generate **2**[6] (Scheme II).

Scheme II



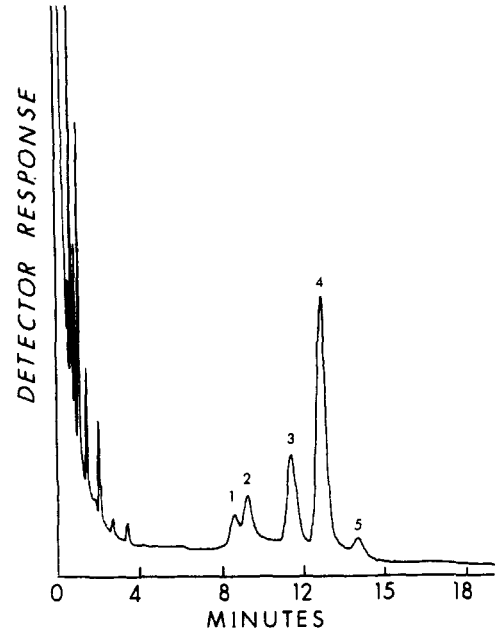


Figure 1. Total ion current monitor gas chromatogram (SE-30) of the trimethylsilylated reduction products obtained after base treatment of **2**. The numbered peaks are predominantly Me_3Si inositol phosphates.

An aqueous 0.1 *N* sodium hydroxide solution of **2** was prepared and, after 2 min at room temperature, quickly neutralized with an acid-form cation exchange resin. The reaction mixture was then treated with sodium borohydride in order to reduce residual aldehydo or keto carbonyl groups. The components of the mixture were analyzed as their trimethylsilyl (Me_3Si) derivatives by gas chromatography-mass spectrometry (GC-MS, Figure 1). The mixture contained two major components (peaks 3 and 4) and several minor components (including peaks 1, 2, and 5) of comparable retention times. The component that gave peak 3 was found to be gas chromatographically indistinguishable from the Me_3Si derivative of *myo*-inositol 1-phosphate. A comparison of the mass spectrum of the unknown compound with that of the authentic Me_3Si derivative of **4**[3] showed that the compounds were the same. The component giving peak 5 was identified as the Me_3Si derivative of *myo*-inositol 2-phosphate, again by a GC-MS comparison with authentic material. The retention times of the Me_3Si alditol phosphates, under the conditions used in this separation, are comparable to those of the Me_3Si cyclitol phosphates. However, the absence of characteristic alditol phosphate mass spectral peaks in the region of the chromatogram covered by components 1-5 implies that the base catalyzed reactions of **2** are rapid and that, after 2 min, no starting material remains in the reaction mixture.

The mass spectra of the remaining components (peaks 1, 2, and 4) were also characteristic for the Me_3Si derivatives of cyclitol monophosphates.[3,7] For example, the major component in the mixture (peak 4) gave a mass spectrum (Figure 2) which is, in all ways, typical of a Me_3Si cyclitol monophosphate. We give evidence below which leads us to conclude that Figure 2 is the spectrum of *epi*-inositol 3-phosphate (**8**).

The structures of two of the cyclitol monophosphates in the mixture were determined indirectly. A portion of the mixture was preparatively gas chromatographed, and two fractions were collected (fraction I, peaks 1 and 2 from Figure 1; fraction II, peaks 3-5 from Figure 1). The Me_3Si groups were then removed by solvolysis in hot methanol and the phosphates cleaved with an alkaline phosphatase. The resulting neutral cyclitols were subjected to GC-MS analy-

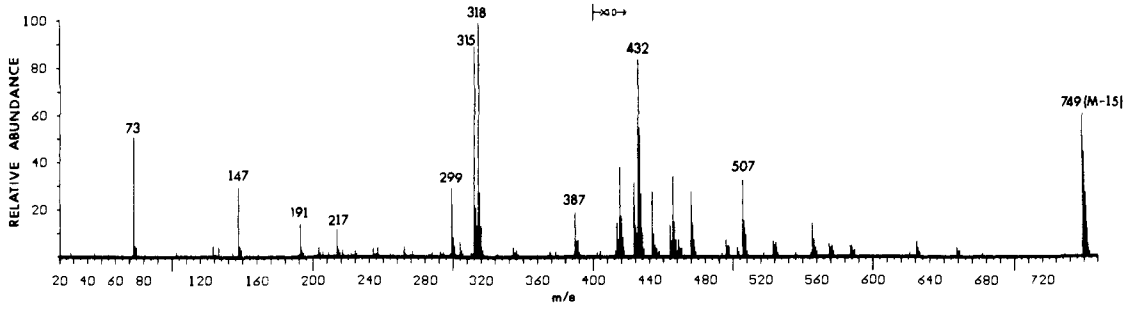


Figure 2. The 70-eV mass spectrum of peak 4, in Figure 1, assigned the structure heptakis(trimethylsilyl)-*epi*-inositol 3-phosphate (**8**). Spectrum obtained by GC–MS.

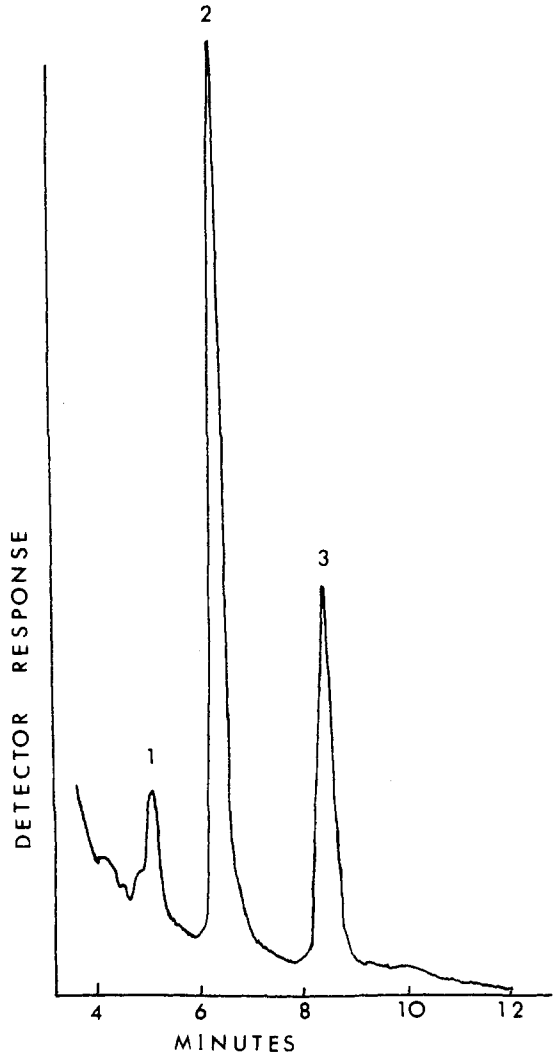


Figure 3. Gas chromatogram (SE-30) of fraction II after detrimethylsilylation and dephosphorylation. The peaks, identified by retention time[W. R. Sherman, S. L. Goodwin, and K. D. Gunnell, *Biochemistry*, **10**, 3491, (1971)] and by GC–MS [W. R. Sherman, N. C. Eilers, and S. L. Goodwin, *Org. Mass Spectrom.*, **3**, 829 (1970)] are: 1, Me_3Si *chiro*-inositol; 2, Me_3Si *epi*-inositol; 3, Me_3Si *myo*-inositol.

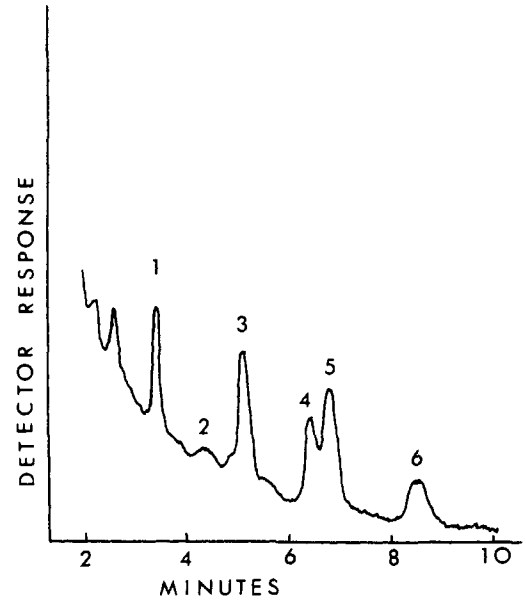


Figure 4. Gas chromatogram (SE-30) of fraction I after detrimethylsilylation and dephosphorylation. The peaks, identified by retention time (see references, Figure 3) are: 1, Me_3Si *allo*-inositol plus a comparable amount of an unknown; 2, Me_3Si *muco*-inositol as a minor component; 3, Me_3Si *chiro*-inositol; 4, Me_3Si *epi*-inositol; 5, Me_3Si *scyllo*-inositol; 6, Me_3Si *myo*-inositol.

sis as their Me_3Si ethers and identified by comparison with authentic samples.

Three cyclitols were identified in fraction II: *chiro*-, *epi*-, and *myo*-inositol (Figure 3). Since *epi*-inositol was the predominant cyclitol in this mixture, it must have been formed from the principal component (peak 4, Figure 1) in the phosphate mixture. The second most abundant cyclitol in this fraction was *myo*-inositol, presumably derived from the Me_3Si derivatives of its 1- and 2-phosphates (peaks 3 and 5, Figure 1). The component in least abundance was *chiro*-inositol, resulting from contamination by peak 2, Figure 1. This cross-contamination is usual in the preparative GC of Me_3Si phosphorylated sugars and seems related to other, presumably adsorption-based, effects seen with this class of compounds.[8]

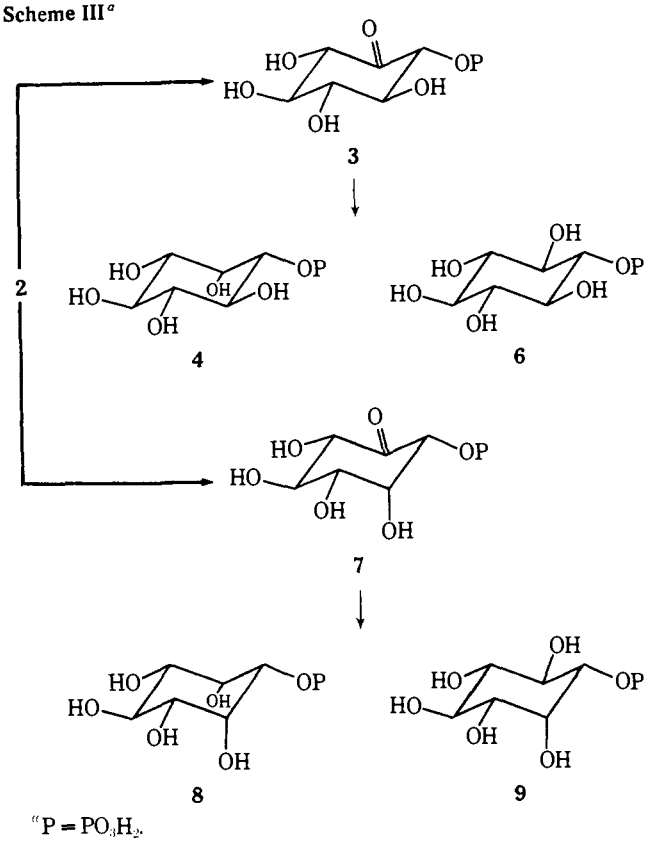
The dephosphorylation of fraction I gave six inositols (Figure 4), identified by their mass spectra and retention times as *allo*-, *muco*-, *chiro*-, *epi*-, *scyllo*-, and *myo*-inositols. Of these, *epi*- and *myo*- are contaminants from fraction II.

Discussion

When **2** is treated with base, it undergoes a simple intramolecular aldol condensation to give, as the principal products, the cyclose phosphates **3** and **7** (Scheme III). These compounds are, in turn, reduced stereoselectively with hydride ion to L-*myo*-inositol 1-phosphate (**4**) and *epi*-inositol 3-phosphate (**8**). The phosphate **4**, as its Me_3Si derivative, was identified directly by GC–MS. Compound **8** was identified as the cyclitol monophosphate that, when hydrolyzed, gave *epi*-inositol. The configurations of **4** and **8** have been assigned as shown since the reactions leading to these compounds proceed without isomerization occurring and originate from a compound (**2**) of known configuration.

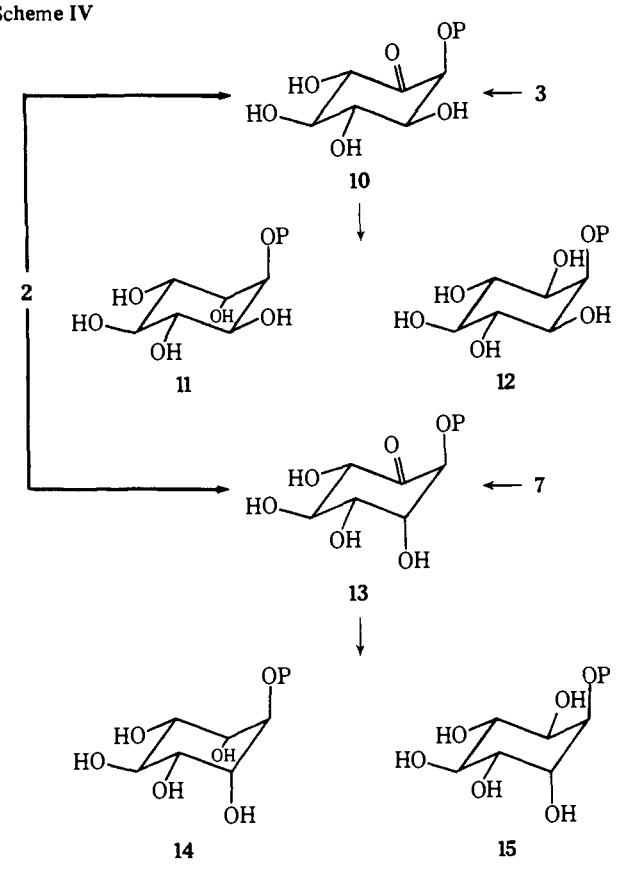
The preferred course of the cyclization of **2** in base, as contrasted with the enzyme-induced transformation, is the

Scheme III[a]

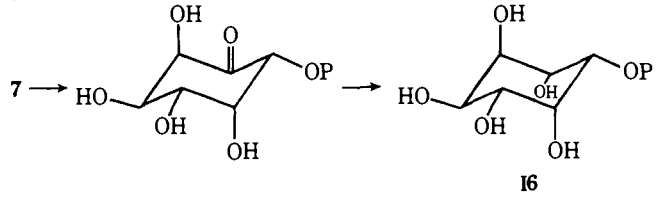


[a] P = PO_3H_2.

Scheme IV



Scheme V



one that generates the cyclose phosphate **7** with an axial hydroxyl at the new chiral center. This is shown by the greater abundance of both the cyclitol phosphate **8** (peak 4, Figure 1) and its dephosphorylation product, *epi*-inositol (peak 2, Figure 3). These results imply that, in the biogenesis of **4**, the orientation of the C-3 hydroxyl of the cyclose phosphate is under strict enzymatic control.

Of the minor abundance inositol phosphates observed in the hydride reduction mixture, only *myo*-inositol 2-phosphate (**12**) has been identified (peak 5, Figure 1). As shown in Scheme IV, this product may be the minor reduction product of the axially phosphorylated cyclose phosphate **10** (2,3,5/4,6-pentahydroxycyclohexanone 2-phosphate) produced directly by cyclization of **2**, or by epimerization at the phosphate center of **3**. The major reduction product from this sequence would be *chiro*-inositol 1-phosphate (**11**). The counterpart of this reaction sequence, i.e., formation of 2,4,5/3,6-pentahydroxycyclohexanone 6-phosphate (**13**) by way of epimerization of **7** at C-2 or by a simple ring closure of **2**, would give *muco*-inositol 3-phosphate (**14**, axial product) and *chiro*-inositol 1-phosphate (**15**, equatorial product). The finding of *chiro*- and *muco*-inositols among the products following phosphate hydrolysis is consistent with the occurrence of these minor pathways.

Our finding *allo*-inositol (peak 1, Figure 4) among the hydrolysis products of the reduced phosphates is evidence that epimerization at a hydroxylated carbon α to a carbonyl group of a cyclose phosphate occurs, to a degree, prior to reduction. The most likely source of *allo*-inositol is its 3-phosphate (**16**, Scheme V), generated by inversion at the α-hydroxyl of **7** followed by axial reduction. A less efficient route to *allo*-inositol would be from α-hydroxyl epimerization of **13** and then reduction to the equatorial product.

Summary

The chemically induced transformation of **2** to L-myo-inositol 1-phosphate (**4**) is a chemical model for the enzymatic formation of this common cyclitol phosphate. The cyclization of **2** is not as stereospecific as the biological reaction: thus we observe both stereoisomers of the hydroxyl produced in the aldol condensation as well as both epimers of the phosphate group. We also find evidence of isomerization of groups α to the cyclose carbonyl. These products underscore the degree of control exerted by the enzyme on the putative intermediate D-*xylo*-hexos-5-ulose 6-phosphate. Moreover, this is a further illustration of the propensity that δ-dicarbonyl monosaccharides have for undergoing ring closure to the six-membered carbocyclic ring system.[9,10]

Experimental Section

Analytical and preparative GC was carried out with a Beckman Model GC-5 gas chromatograph equipped with flame ionization detectors. Two different columns were used in the analytical separation: an 0.187 in. o.d. × 6 ft stainless steel column containing 1.5% SE-30 on 80–100 mesh Gas Chrom Q; and a column of the same dimensions packed with 3% SE-30. All preparative separations were accomplished on the former column. The gas chromatograph was fitted with a 10:1 effluent gas stream splitter for preparative GC separations, the fractions being collected in disposable pipets stuffed lightly with silanized glass wool. All column packing materials were purchased from Applied Science Laboratories, Inc., State College, Pa.

Cyclization of D-*xylo*-Hexos-5-ulose 6-Phosphate (2) in Aqueous Sodium Hydroxide Solution. The free sugar phosphate **2** was prepared by the method of Kiely and Fletcher.[6] In a typical experiment, a solution of di(cyclohexylammonium) 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-5-ulose dimethyl acetal 6-phosphate

(5, 11 mg or ca. 0.02 mmol) in water (0.05 ml) was kept at 40° with 0.5 ml of acid-form cation exchange resin [Rexyn 101 (H^+)]. The resin was removed by filtration, and a stream of nitrogen was passed through the combined filtrate and washings (1.35 ml), for 15 min, in order to deoxygenate the solution. To this solution was added a similarily deoxygenated solution of 1.0 *N* sodium hydroxide (0.15 ml), therefore making the reaction mixture 0.1 *N* in sodium hydroxide. The reaction mixture was immediately agitated to ensure adequate mixing and after 2 min was neutralized with an acid-form resin (1 ml). During the course of the reaction, the color of the solution went from colorless, to light yellow, to light green. Neutralization with the resin rendered the solution colorless once again.

Reduction of the Products from Alkali Treatment of 2. Sodium borohydride (12 mg) was added to the neutralized aqueous reaction mixture (2.5 ml) and the resulting solution kept at room temperature for 6 hr. This solution was treated with acid-form resin until hydrogen evolution ceased, the resin was removed by filtration, and the filtrate was freeze-dried to give a white fluffy mass. Boric acid was removed from the mixture as trimethyl borate in vacuo at 35°. A solution of the residue in water (0.5 ml) was transferred to a 3-ml centrifuge tube and the water removed by freeze-drying. The amorphous product from the reduction, after being treated with 300 μl of trimethylsilylating reagent,[11,12] gave a mixture that was gently warmed for several minutes and then kept at room temperature for an additional 2 hr before subjecting it to GC.

Preparative GC of the Reduction Products from 2. For preparative GC, 20-μl aliquots of the trimethylsilylation mixture were injected into the gas chromatograph. Two semisolid fractions were collected, fraction I corresponding to peaks 1 and 2, and fraction II, to peaks 3–5 (Figure 1). The fractions were eluted from the collection tubes with methanol, and then an aliquot of each was concentrated to dryness under a stream of nitrogen, trimethylsilylated, and analyzed by GC. Although fractions I and II were somewhat cross-contaminated, neither of the fractions contained any component other than those corresponding to peaks 1–5.

Dephosphorylation and GC of Fractions I and II. Fractions I and II were dissolved in deionized water (0.3 ml), and tris(hydroxymethyl)aminomethane-Mg^{2+} buffer (1 ml) was added. The buffer was prepared by the addition of $MgCl_2 \cdot 0.6\ H_2O$ (406 mg) to 50 ml of 1 *M* tris(hydroxymethyl)aminomethane hydrochloride (pH 7.4). The solutions were then incubated with alkaline phosphatase (Miles Laboratories, Inc., Kankakee, Ill.) (50 μl) for 2.5 hr at 40° and subsequently deionized with a mixed-bed resin (1:1, v/v, Amberlite IR 120 H^+:IRA 400 OH^-). The resin was filtered off and the combined filtrate and washings (ca. 10 ml) freeze-dried. The residues were then treated with the trimethylsilylating reagent (25 μl) and gas chromatographed at 170° on the 3% SE-30 column.

Gas Chromatography–Mass Spectrometry. An LKB-9000 gas chromatograph–mass spectrometer—PDP-12 computer system[13] was used to obtain all spectra. The GC conditions were: 0.25 in. o.d. × 4 ft glass column (3% SE-30 on 80–100 mesh Gas Chrom Q) operated at 30 ml of He/min and temperatures appropriate to the experiment. The MS was operated with 70-eV electron beam ionization energy, while the source and separator temperatures were 270 and 240°, respectively.

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Melochinone, a Novel Quinolinone from *Melochia tomentosa* L.[1a,b]

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Abstract: Melochinone ($C_{22}H_{21}NO_2$) from the tumorogenic plant *Melochia tomentosa* has been found to have the quinolinone structure II containing a fused seven-membered ring. The structure was obtained by X-ray crystallography using direct methods.

Decoctions of certain plants used as folk remedies by natives of Curacao have been implicated in their relatively high local rate of esophageal cancer.[3] *Melochia tomentosa*[4] is one such plant, roots of which have been used to relieve throat inflammation; in earlier studies, an extract of roots of this plant was indeed reported[7] to be tumorogenic. A benzene extract, obtained while fractionating the root constituents in search of this principal, gave a positive Dragendorff test and subsequent chromatography on silicic acid afforded a small amount of crystalline product, mp 316–318°,