Pergamon

Tetrahedron Vol. 50, No. 23, pp. 6783-6796, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $7.00+0.00

0040-4020(94)E0321-J

The Chemistry of Glucal Halohydrins: The Effect of the Halide on Epoxide Formation

Cecilia H. Marzabadi, Christopher D. Spilling* and Lisa M. Tyler

Department of Chemistry, University of Missouri-St. Louis, 8001 Natural Bridge Road, St. Louis, MO 63121

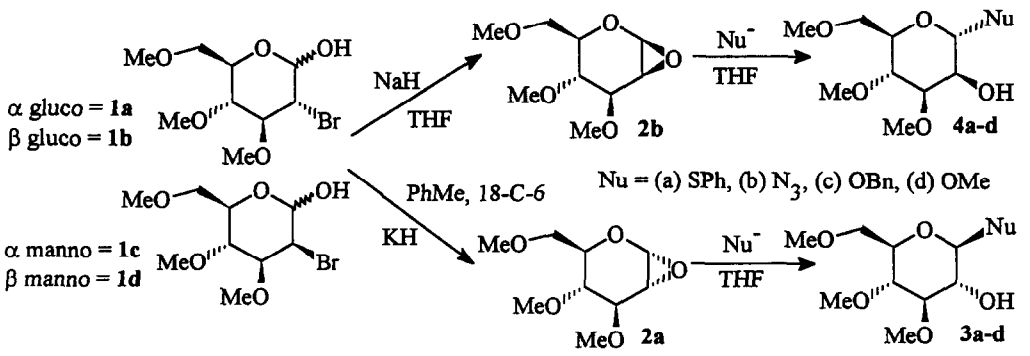
Abstract: Chlorohydrins, bromohydrins, and iodohydrins, formed by hydroxyhalogenation of tri-O-methyl glucal, undergo base induced cyclization to give glucal epoxides. The mechanism of the cyclization reaction was probed using ^{1}H NMR and deuterium incorporation studies. Cyclization and *in situ* trapping with Cs_2CO_3 in MeOD gave deuterated methyl 3,4,6-tri-O-methyl-α-D-mannoside and methyl 3,4,6-tri-O-methyl-β-D-glucoside, and an unsaturated aldehyde. These studies led to optimized stereoselectivity for the epoxide formation. Reaction of gluco bromohydrins with NaH or LiHMDS in THF at 5 °C gave β-epoxide, and reaction of manno iodohydrins with KH and 18-crown-6 in toluene at -70 °C gave α-epoxide. The epoxides were opened by reaction with sodium phenylthiolate to give phenyl 3,4,6-tri-O-methyl-1-thio-α-D-mannopyranoside (single isomer), and phenyl 3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside (>18:1), respectively.

INTRODUCTION

We recently reported an alternative approach to the stereoselective formation of 1,2-anhydro sugars (glycal epoxides) involving the formation and cyclization of bromohydrins.[1] We observed that either the α or β epoxides can be formed with moderate selectivity depending upon the cyclization conditions (Scheme 1). A diastereomeric mixture of bromohydrins **1**, prepared from tri-O-methyl-D-glucal and NBA in 10 % aqueous THF (manno : gluco, 2:1), reacted with KH in toluene and 18-crown-6 at -72 °C to give predominantly the α-epoxide **2a**. Trapping of the intermediate epoxide with a variety of nucleophiles (SPh, N_3, OBn, OMe) gave the β-glucosides **3** as the major product (1:10, α-manno : β-gluco). Conversely, reaction of the bromohydrin mixture with NaH in THF at 5 °C gave predominantly the β-epoxide **2b**, and trapping with nucleophiles gave the α-mannosides **4** as the major product (3:1, α-manno : β-gluco). The distribution of anomers obtained from trapping with nucleophiles was not that expected from a 2:1 ratio of manno and gluco bromohydrins. Epoxide formation would be expected to proceed with inversion of C-2 stereochemistry, and the subsequent ring opening[2] with inversion of configuration at C-1. Thus, one would predict that bromohydrins with a manno:gluco ratio of 2:1 would produce α and β epoxides in a ratio of 2:1, and the products of nucleophilic attack in a ratio of 1:2 (manno:gluco). To account for the observed product ratios, it seemed probable that a pathway existed which permits interconversion of the four isomeric bromohydrins. We proposed[1] a reaction

mechanism involving stereochemical scrambling at C-2 prior to the cyclization step. To support this proposal, a careful study of the reaction was performed using ^1H NMR spectroscopy, deuterium incorporation, and by observing the effect of changing halide.

Scheme 1



RESULTS

Formation of the Halohydrins. In general, diastereomeric mixtures of chlorohydrins **6**, iodohydrins **7**, and bromohydrins **1** were prepared by reaction of tri-O-methyl glucal with a halogenating agent in aqueous solvent (Scheme 2). Chlorohydrins **6a-d** were prepared using N-chlorosuccinimide in 10% aqueous THF and consisted of predominantly gluco diastereoisomers (1 : 2.3, manno:gluco). Iodohydrins **7a-d** were prepared using N-iodosuccinimide in 10% aqueous THF and consisted of predominantly the manno diastereoisomers (3.7 : 1, manno:gluco). Several experiments were performed to determine the effect of solvent and halogen source on the selectivity of the hydroxyhalogenation reaction (see experimental section, Table 2). In general, there were only small variations in the product ratios. Chlorination tended to favor gluco, and iodination and bromination tended to favor manno.[3] Optimized selectivity for the gluco bromohydrins **1** (93% overall yield, manno:gluco ratio, 1:2) was achieved by dibromination of tri-O-methyl glucal with bromine in CCl_4 and hydrolysis of the anomeric bromide with silver carbonate in aqueous THF (Table, entry 8).[4] The pure α-gluco bromohydrin **1a** was isolated in low yield (15%) by recrystallization from Et_2O and hexanes. The manno iodohydrins **7c** and **7d** were prepared with high selectivity (>18:1 manno:gluco by ^1H NMR, entry 12) using a variation on glycosidation conditions (NIS/ 10% aqueous propionitrile/-78° C) recently reported by Roush and co-workers.[5]

^1H NMR Spectroscopy: Monitoring the Cyclization Reaction of the Bromohydrins. Glucal epoxides are relatively labile and are not easily isolated. Since the ratio of substituted glycosides **3** and **4** are easily determined, it was necessary to ascertain that the ratio of these glycosides was indeed the same as the ratio of epoxides. This would allow a correlation of the ratio of the glycosides formed with the ratio of the intermediate epoxides. Therefore, the course of the cyclization reaction was followed using low temperature ^1H NMR to observe the epoxide formation *in situ*. NaH was added to the bromohydrin mixture in THF-d_8 at -60° C, and

^{1}H NMR spectra were obtained periodically until the reaction was complete. The spectra (Figure 1) clearly show the clean conversion of the bromohydrins into two new compounds with resonances at δ 4.82 (br s) and 4.79 ppm (d, J = 2.7 Hz) in a 3:1 ratio. The chemical shifts are consistent with those expected for a glucal epoxide,[2] and they were assigned as the α and β epoxides, respectively. The addition of an excess of sodium phenyl thiolate to the reaction resulted in the appearance of two new resonances (not shown) in the anomeric region at δ 5.59 (d, J = 1.5 Hz) and 4.47 (d, J = 9.6 Hz) in a 3:1 ratio corresponding to the known[1] α and β phenyl thioglycosides **4a** and **3a**, respectively. Reaction of the α-gluco bromohydrin **1a** was also studied by low temperature ^{1}H NMR (Figure 2). Addition of NaH to a THF-d_8 solution of the α-gluco bromohydrin **1a** led to a rapid equilibration to an α/β mixture of gluco bromohydrins, as evidenced by the new broad peak at δ 4.77 (Fig.2, spectrum b). In addition, a resonance at δ 9.6 ppm (not shown), assigned the open chain aldehyde, was observed. The resonances due to the anomeric protons of the bromohydrins slowly decreased while a new resonance at δ 4.79 ppm, assigned to the β epoxide, grew in.

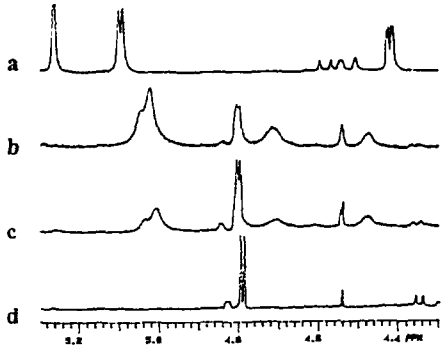


Figure 1: ^{1}H NMR spectra (δ 4.3-5.3 ppm) of the reaction of bromohydrins 1a-d with NaH in THF-d_8 a) Bromohydrins 4a-d in THF; b) NaH added, time =45 mins., temp. = 0 °C; c) time = 60 mins, temp. = 0 °C; d) time = 4 hrs, temp. =22 °C

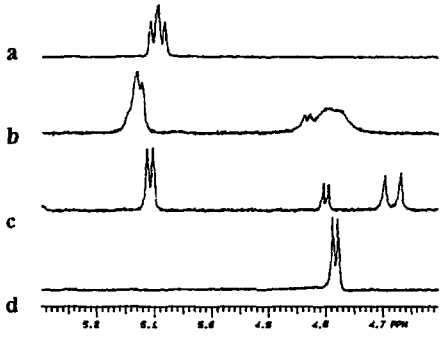


Figure 2: ^{1}H NMR spectra (δ 4.6-5.3 ppm) of the reaction of the α-gluco bromohydrin 1a with NaH in THF-d_8
a) α-gluco bromohydrin in THF (coupling to O-H observed), b) NaH added, time = 15 mins., temp. = -38 °C; c) time = 50 mins., temp. = 1 °C; d) time = 22 hrs., temp. = 24 °C.

It was apparent that a similar study on the manno bromohydrins **1c** and **1d** was necessary. The crude bromohydrin mixture was converted into the corresponding anomeric acetates, which were easily separated by chromatography on silica gel. Hydrolysis of the α-manno bromohydrin acetate with aqueous HCl in THF gave a mixture of the α and β manno bromohydrins **1c** and **1d**. NaHMDS was added to a mixture of the manno bromohydrins in THF-d_8 and the reaction was followed by ^{1}H NMR (spectra not shown). A clean conversion to the α and β epoxides was again observed. However, integration of the epoxide anomeric resonances gave a ratio of 1.4 : 1. Unfortunately, all efforts to perform a complimentary series of ^{1}H NMR experiments on the KH system, which is selective for the α-epoxide, failed. The spectra suffered from severe line broadening and a poor signal to noise ratio, and could not be interpreted.

Reaction of Halohydrins with Cesium Carbonate in MeOD. We had reported that the epoxides could be formed and trapped *in situ* by reaction of the bromohydrins **1a-d** in methanol solution.[1,6] Methyl glycosides **3d** and **4d** were formed by the *in situ* reaction (Scheme 2) of bromohydrins **1** with Cs_2CO_3 or $NaOCH_3$ in methanol (1:3, α-manno : β-gluco). In addition, an α,β-unsaturated aldehyde **5** was also isolated in up to 24 % yield from these *in situ* reactions. If substantial enolization was occurring under the cyclization conditions, then reactions performed in MeOD should result in the incorporation of deuterium in the glycoside products. Thus, the halohydrins **1**, **6**, and **7** were reacted with Cs_2CO_3 in methanol-d_1 (Scheme 2). Deuterated methyl glycosides **8a** and **8b** were isolated by column chromatography on silica gel and their yields determined (Table 1). Deuterium incorporation was confirmed with ^2H NMR spectroscopy. The extent of deuterium incorporation was then determined by acetylation of the methylglycosides **8** with acetic anhydride-d_6 in pyridine. The purified acetates **9a** and **9b** were examined by ^2H NMR, and a comparison of the areas of the C-2 resonance versus the acetate-d_3 resonance afforded a means of quantifying the extent of incorporation.

Scheme 2

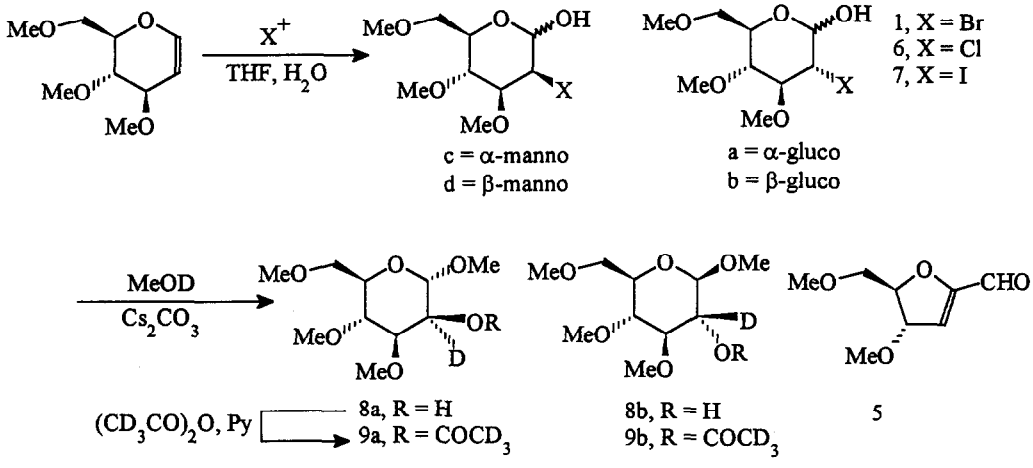


Table 1: % ^2H-Incorporation Into Methyl Glycosides Derived from 2-Halo-2-deoxy Sugars

Entry	Halohydrin	Starting Ratio manno : gluco	Reaction time	Yield **5**	Yield **8a+8b**	Product Ratio manno : gluco	% ^2H α-manno	% ^2H β-gluco
1	Cl	1:2.3	4 days	trace	49 %	1:7	88 %	79 %
2	Br	1.8:1	18 hrs	24%	37 %	1:4	71 %	20 %
3	I	3.7:1	42 hrs	13%	37 %	1:3	59 %	14 %

Reaction of the chlorohydrins in MeOD (Table 1, entry 1) led to a substantial amount of deuterium incorporation in both the α-methyl mannoside **8a** (88%), and the β-methyl glucoside **8b** (79%) and only trace quantities of aldehyde **5**. In addition, the change in ratio from the chlorohydrins (manno:gluco, 1:2.3) to the methyl glycosides (1:7), indicated considerable C-2 epimerization. The bromohydrins (entry 2) gave α-methyl

mannoside with high deuterium content (71%), and β-methyl glucoside with low incorporation (20%). Again, the ratio of methyl glycosides formed required some C-2 epimerization. Reaction of the iodohydrins (entry 3) in MeOD resulted in α-methyl mannoside and β-methyl glucoside with much lower levels of deuterium, 59% and 14% respectively. The ratio of methyl glycosides (manno:gluco, 3:1) was close to that expected based on a simple S_N2 mechanism (1:3.7). The bromohydrins **1** and iodohydrins **7** both yielded significant quantities (up to 24%) of aldehyde **5**.

DISCUSSION

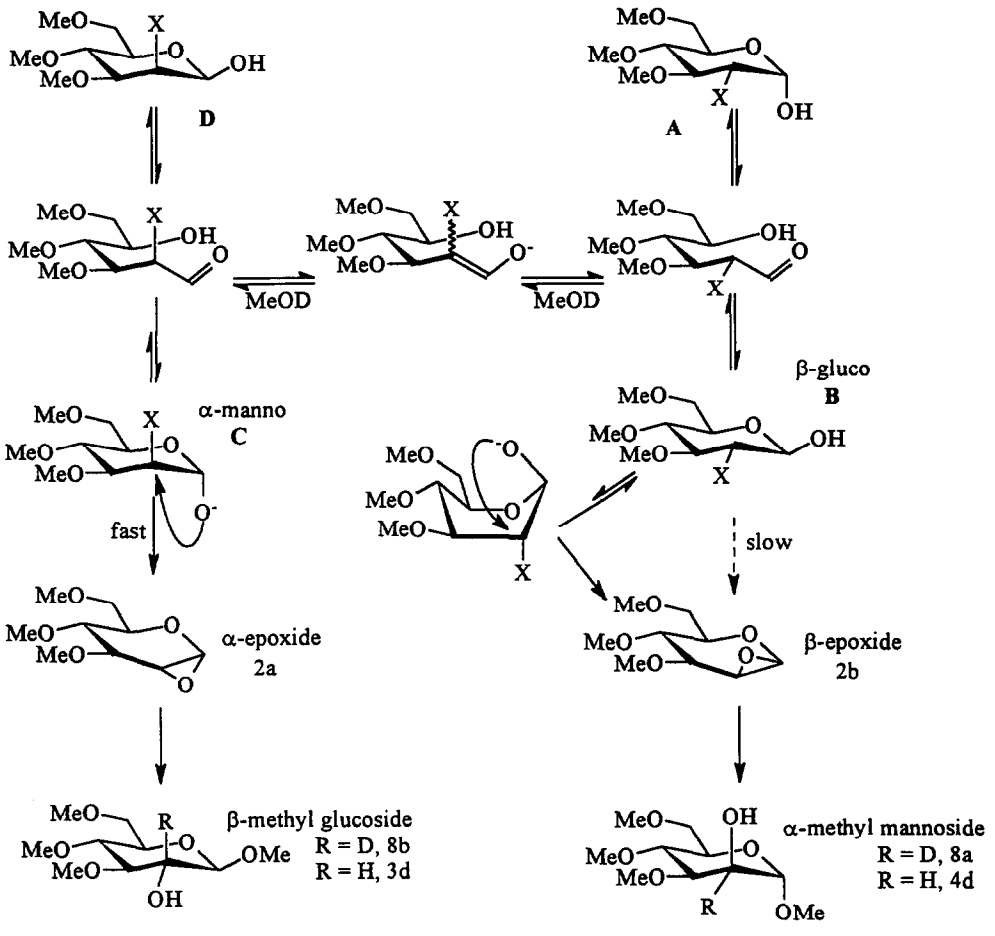
As stated earlier, epoxide formation would be expected to proceed with inversion of C-2 stereochemistry, and the subsequent ring opening[2] with inversion of configuration at C-1. Thus, one would predict that the halohydrin ratio would be reflected in the products of nucleophilic attack. Since cyclization of the halohydrins generally proceeds *via* an S_N2 mechanism, the geometry requirements of the reaction are met when the substituents have a trans relationship.

^1H NMR Experiments. The NMR spectra obtained from the reaction of bromohydrins **1a-d** with NaH in THF (Figure 1) showed clean conversion of the bromohydrins to both the α epoxide (δ 4.82 ppm) and β epoxide (δ 4.79 ppm). The ratio of epoxides was the same as the ratio of glycoside formed by addition of sodium phenyl thiolate. The gluco bromohydrins (Figure 2) cleanly converted to only the β epoxide, and therefore did not undergo epimerization at C-2. Whereas the manno bromohydrins gave both the α-epoxide and the β epoxide in a 1.4:1 ratio. Thus, with sodium as the counter ion only the manno isomers undergo epimerization at C-2. It is probable, based on the product ratios (1:10, manno:gluco), that reaction of the bromohydrin mixture with KH in toluene and 18-crown-6 results in C-2 epimerization for the gluco isomers.[1] The reactions appear to proceed via formation of an open-chain α-bromo aldehyde intermediate which closes to give appropriate 1,2 trans stereochemistry required for epoxide formation, as seen by the conversion of α-gluco to β-gluco in Figure 2.

Deuterium Incorporation. The product ratios (Table 1) indicate that a significant amount of methyl glucoside is formed via initial C-2 epimerization of the gluco halohydrin. In addition, the methyl mannoside consistently has the highest deuterium content, and is the minor product. Only in the cyclization of the chlorohydrins is the methyl glucoside also formed with high deuterium incorporation. The diaxial α-manno halohydrin **C**, leading to the methyl glucoside **8b**, is expected to react more rapidly than the diequatorial β-gluco halohydrin **B**, which leads to the methyl mannoside **8a** (Scheme 3). The rate difference is because a higher energy boat conformation is required for cyclization of the diequatorial (β-gluco) halohydrin. A study of the effects of conformation on halohydrin cyclization in steroids was conducted by Barton and coworkers.[7] The diaxial 2β-hydroxy-3α-bromo cholestane reacted 10^4 times faster the than the diequatorial 2α-bromo-3β-hydroxy cholestane under similar conditions. The α-manno halohydrin has the correct conformation for a efficient cyclization (anti periplanar) and probably cyclizes rapidly upon formation (Scheme 3) with little chance for equilibration. In comparison, cyclization of β-gluco halohydrin is slow and equilibration via the aldehyde is competitive. Thus, the cyclizing gluco halohydrin will have had ample opportunity for deuterium incorporation, accounting for the higher deuterium content of the methyl mannosides.

The epimerization of sugar derivatives at C-2 under basic conditions is a well known process which is generally considered to proceed through enolization of the acyclic aldehyde.[8] Recently, Roush and coworkers reported significant amounts of C-2 epimerization when attempting to form a trichloroacetamide from a 2-deoxy-2-thiophenyl glucose with sodium hydride and trichloroacetonitrile.[9] The base-catalyzed C-2 epimerization of N-acetylglucosamine has been studied by deuterium incorporation with NaOD in D_2O.[10] An enolization pathway was proposed to account for incorporation of deuterium at C-2 A significant feature of both the N-acetylglucosamine and the thioglucose experiments was the lack of observed β elimination (loss of the C-3 oxygen). Therefore, a rational explanation for the epimerization at C-2 observed with bromohydrins is an enolization of the acyclic α-bromo aldehyde.

Scheme 3



The Effect of Halide. In general, the amount of deuterium incorporation in the methylmannoside increases in the order; iodide < bromide < chloride. Only in the cyclization of the chlorohydrins is the methyl glucoside also formed with high deuterium incorporation. The effect of the halide on deuterium incorporation can also be explained by a comparison of relative reaction rates. Chloride, of the three halides examined, is the least reactive in substitution reactions, whereas iodide is the most reactive. Therefore, reaction of the chlorohydrin, is slow, even for the favored diaxial α-manno isomer. Thus equilibration, and deuterium incorporation becomes competitive for both the gluco and manno chlorohydrins giving high deuterium content in both methyl glycosides. The bromides and iodides also yield significant quantities of aldehyde **5**. Unsaturated aldehyde **5** is formed by attack of the C-5 OH on the α-haloaldehyde and subsequent elimination of the C-3 alkoxy, indicating a significant concentration of the ring open aldehyde.

A Generalized Reaction Mechanism. The data obtained from the deuterium experiments in MeOD also give some indication of the factors which are responsible for the diastereoselective formation of glycal epoxides in non-protic solvent (THF and PhMe). However, there are major differences between these reaction conditions since the alkoxide formation is essentially irreversible in a non protic solvent. Whereas, the metal counter ion (Cs vs Na) showed little effect on product distribution in methanol solution, changing the metal ion in non protic solvents has a dramatic effect on product ratios.[1] Under such circumstances the metal ion must play a critical role in selecting the reaction pathway and thus controlling the resulting stereochemistry. Metal ion as well as solvent have been shown to have large effects on the stereoselectivity of both acylation[11] and alkylation[12] of anomeric alkoxides. A change in relative reactivity of the anomeric alkoxides was proposed for acylation using BuLi in either THF or benzene. Similarly, in the alkylation of glucopyranose sodium alkoxides the preference for the β-anomer at higher temperature was attributed to increased nucleophilicity of the β-alkoxide relative to the α-alkoxide. Added crown ether showed little effect on the product distribution, but in the alkylation of the anomeric sodium alkoxides derived from furanose derivatives, added crown ether gave the α-product, and without crown ether the β-anomer was produced. Non-chelated versus chelated intermediates were proposed. We have previously observed[1] that addition of 15-crown-5 to the NaH/THF system caused a change in selectivity (from 3:1 to 1:1, manno : gluco) for cyclization of the bromohydrins **1**. Addition of 18-crown-6 to the cyclization of bromohydrins **1** with KH in THF also caused a change in selectivity. The alkoxide formed from KH and 18-crown-6 is extremely reactive and thus a kinetic pathway should be favored. The antiperiplanar conformation of the α-manno halohydrin is much more reactive than the competitive cyclization through the β-gluco halohydrin, which must adopt the boat conformation to react. Thus, the selectivity can be partially attributed to rate differences between the two competing cyclizations. In addition, the "naked" nature of the alkoxide could amplify the anomeric effect and favor the α-anomer.[9] In contrast, the alkoxide formed from NaH in THF is cyclizing through the slower, diequatorial reaction pathway. The sodium ion is strongly associated with the alkoxide oxygen and may be coordinated to other oxygen atoms in the carbohydrate. This arrangement probably favors an equatorial alkoxide (β) which can only react in the gluco form and therefore effectively blocks the alternative pathway. Coordination may also stabilize the boat conformation.

Optimization of the Stereoselectivity . If coordination were important in formation of the β-epoxide, then lithium alkoxides should be more selective than sodium alkoxides through stronger coordination. While LiH was unreactive towards bromohydrins **1a-d**, and n-BuLi resulted in decomposition, LiHMDS reacted rapidly at 5 °C with bromohydrins **1** (2:1 manno : gluco) in THF to form epoxide **2**. Addition of sodium phenylthiolate to the epoxide **2** gave α-phenylthio mannoside **4a** and β-phenylthio glucoside **3a** in a ratio of 10 : 1, an improvement over the results obtained with NaH or NaHMDS (3:1). It was clear from the NMR and deuterium experiments that the reaction of the pure gluco bromohydrins **1a,1b** with NaH or LiHMDS in THF would give a high selectivity for the β epoxide. Also, reaction of the pure diaxial manno iodohydrins **7c,7d** with potassium hydride in toluene and 18-crown-6 would give a high selectivity for the α-epoxide. Thus, either the α or β epoxide can be formed selectively by careful choice of halohydrin and reaction conditions. Reaction of the gluco bromohydrin **1a** with NaH in THF and trapping the epoxide with sodium phenylthiolate gave the α-thiophenyl mannoside (38%) as the only isolable product. Cyclization of the manno iodohydrins with KH/18-Crown-6 in $PhCH_3$ at -78° C, and trapping of the intermediate epoxides with nucleophiles (SPh, N_3) gave high selectivities for the β anomers (>1:18 α:β) in modest yields (35-40%). Reaction of the manno iodohydrins with Cs_2CO_3 in methanol gave slightly higher yields (43% glycosides and 19% aldehyde), but only a 1:6 ratio of α and β methyl glycosides **4d** and **3d**.

EXPERIMENTAL

^1H and ^{13}C spectra were recorded in $CDCl_3$ solution on a Varian XL-300 spectrometer at 300 and 75 MHz, respectively. ^1H chemical shifts are reported in ppm downfield from Me_4Si. The ^{13}C chemical shifts are reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). ^2H NMR spectra were recorded in $CHCl_3$ at 46 MHz, and chemical shifts are reported relative to $CDCl_3$ (7.24 ppm). Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Mass spectra were determined on a Varian Mat 331A spectrometer, and microanalyses were performed by Atlantic Microlab Inc. Optical rotations were recorded on an Autopol III polarimeter (Rudolph Research) under standard conditions. THF was distilled from sodium-benzophenone ketyl and CH_2Cl_2 was distilled from CaH_2. Methanol was distilled from Mg. The reactions were performed under argon. Column chromatography was performed on SiO_2 (Merck; 230-400 mesh) eluting with Et_2O/ hexanes mixtures. Tri-O-methyl -D-glucal[13] was prepared from tri-O-acetyl-D-glucal by methanolysis (MeONa, MeOH) and methylation (NaH, DMF, MeI).

General Procedure for Hydroxyhalogenation of 3,4,6-Tri-O-Methyl-D-Glucal. A solution of 3,4,6-Tri-O-methyl-D-glucal (1.3 g, 6.9 mmol) in 10 % aqueous THF (26 mL) was cooled to 5° C, and the halogenating reagent (7.6 mmol) was added. The reaction progress was followed by thin layer chromatography (SiO_2, 1:1 hexanes/Et_2O) until consumption of trimethyl glucal was indicated. The mixture was diluted with water (30 mL) and extracted with Et_2O (3x30 mL). The combined Et_2O extracts were washed with water (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a diastereomeric mixture of halohydrins.

Table 2. Experimental Variation in the Hydroxyhalogenation of Tri-O-methyl-D-Glucal

	Halogen Source	Temperature °C	Solvent	Time	Yield %	Ratio manno : gluco
1	NBS	5	DMF	4 hrs	96	2.8 : 1
2	NBS	5	CH_3CN	1 hr	92	4.2 : 1
3	NBS	5	THF	1 hr	36	3.5 : 1
4	NBS	5	Et_2O	2.5 hrs	52	5.2 : 1
5	NBA	5	DMF	overnight	92	2.5 : 1
6	**NBA**	**5**	**THF**	4 hr	**84**	**1.9 : 1**
7	NBA	room temp.	Et_2O	46 hrs	56	2.5 : 1
8	**Br_2 then Ag_2CO_3**	**room temp. room temp.**	**CCl_4 THF, H_2O**	**1 hr 20 hrs**	**100 97**	**1 : 2.1 1 : 2.1**
9	NIS	5	DMF	4.5 hrs	85	4.2 : 1
10	NIS	5	CH_3CN	25 mins	85	9 : 1
11	NIS	-20	CH_3CN	75 mins	91	18 : 1
12	**NIS**	**-70 to room temp.**	**CH_3CH_2CN**	**overnight**	**71**	**>18 : 1**
13	**NIS**	**room temp.**	**THF**	**1 hr**	**89**	**3.7 : 1**
14	NIS	5	Et_2O	1.25 hrs	60	2.4 : 1
15	NCS	room temp.	DMF	3 days	91	1 : 1
16	NCS	room temp.	CH_3CN	4 days	30	1 : 2.1
17	**NCS**	**room temp.**	**THF**	**6 days**	**89**	**1 : 2.3**
18	NCS	45	THF	3 days	88	1: 2.4
19	NCS	room temp.	Et_2O	24 hrs	38	1 : 1

Products from the entries in bold (6, 8, 12, 13, 17) were used for epoxide formation.

Bromohydrins 1a-d. 3,4,6-Tri-O-Methyl -D-glucal (1.3 g, 6.9 mmol) in 10 % aqueous THF (26 mL) and N-bromoacetamide (1.0 g, 7.6 mmol) gave a diastereomeric mixture of bromohydrins **4a-d** (1.7 g, 5.8 mmol, 84 %): ^{1}H NMR (anomeric protons) δ 5.45(s) **4c** (α-manno), 5.30 (d, J = 3.0 Hz) **4a** (α-gluco) , 4.75 (d, J = 8.6 Hz) **4b** (β-gluco), 4.58 (d, J = 1.5 Hz) **4d** (β-manno). Repeated recrystallization (3x, Et_2O/hexanes) produced a single diastereoisomer, **2-bromo-2-deoxy-3,4,6-tri-O-methyl-α-D-glucopyranose (1a):** mp 149-149.5 °C; $[\alpha]_D$ +145.2° (c = 1.00, $CHCl_3$); IR (KBr) 3401, 2992, 2917, 2842, 1451, 1379, 1189, 1128, 1048, and 1013 cm^{-1}; ^{1}H NMR δ 5.32 (t, 1H, J = 3.3 Hz), 4.04-3.99 (m, 1H), 3.80-3.69 (m, 2H), 3.68 (s, 3H), 3.66-3.57 (m, 2H), 3.55 (s, 3H), 3.41 (s, 3H), 3.15 (t, 1H, J = 9 Hz); ^{13}C NMR δ 92.9, 83.0, 81.4, 71.3, 70.4, 61.2, 60.6, 59.2, 51.9; MS (DP/CI) *m/z* 286, 284, 173, 141, 113, 101, 87, 71. Anal. Calcd. for $C_9H_{17}O_5Br$: C, 37.91; H, 6.01. Found: C, 38.00; H, 5.96. Acetylation of the bromohydrin mixture (**1a-d**) with Ac_2O in pyridine and CH_2Cl_2 at 5 °C gave a mixture of acetates (74 %). Column chromatography (SiO_2, EtOAc:hexanes, 1:4)) gave: **1-O-acetyl-2-bromo-2-deoxy-3,4,6-tri-O-methyl-α-D-mannopyranose** as an oil (13 %); IR ($CHCl_3$) 3010, 2932, 2836, 1749, 1373, 1149 and 1110 cm^{-1}; ^{1}H NMR δ 6.32 (d, 1 H, J = 1.9 Hz), 4.37 (dd, 1 H, J = 3.3, 1.8 Hz), 3.81-3.77 (m, 1 H), 3.71-3.52 (m, 4 H), 3.56 (s, 3 H), 3.47 (s, 3 H), 3.43 (s, 3 H), 2.11 (s, 3 H); ^{13}C NMR δ 168.3, 93.9, 78.7, 75.8, 74.3, 71.1, 61.0, 59.5, 57.0, 49.1, 21.0; MS (DP/CI) *m/z* 327, 325, 269, 267, 237, 235, 155, 89. Further elution yielded **1-O-acetyl-2-bromo-2-deoxy-3,4,6-tri-O-methyl-β-D-**

glucopyranose as a crystalline solid (16 %): m.p. 82-85 °C; IR ($CHCl_3$) 3011, 2937, 2839, 1759, 1117, 1102 and 1061 cm^{-1}; ^1H NMR δ 5.68 (d, 1 H, J = 9 Hz), 3.79-3.67 (m, 1 H), 3.70 (s, 3 H), 3.64-3.59 (m, 2 H), 3.56 (s, 3 H), 3.47-3.42 (m, 1 H), 3.41-3.29 (m, 2 H), 3.39 (s, 3 H), 2.13 (s, 3 H); ^{13}C NMR δ 168.7, 93.3, 86.7, 79.9, 75.4, 70.1, 61.3, 60.4, 59.2, 50.9, 20.8; MS (DP/CI) *m/z* 237, 235 (100).

Hydrolysis of 1-O-acetyl-2-bromo-2-deoxy-3,4,6-tri-O-methyl-α-D-mannopyranose. To the acetate (0.0271 g) in THF (5 mL) was added 1M aqueous HCl (1 mL). The mixture was stirred for 4 hrs and then additional aq. HCl (1 mL) was added. The mixture was heated to reflux for 10 hrs, it was then cooled and diluted with Et_2O (25ml). The organic solvents were washed with saturated aq. $NaHCO_3$ (2x25 mL) and H_2O (25 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a mixture of the manno bromohydrins **1c, 1d** (0.017 g, 72%).

Chlorohydrins 6-d. 3,4,6-tri-O-methyl-D-glucal (1.0 g, 5.3 mmol) in 10% aqueous THF (22 mL) and N-chlorosuccinimide (0.78 g, 5.9 mmol) gave chlorohydrins **6a-d** (1.14 g, 4.7 mmol, 89%) as a waxy solid: ^1H NMR (anomeric protons) δ 5.36 (d, J = 0.9 Hz) **6c** (α-manno), 5.27 (d, J = 3.3 Hz) **6a** (α-gluco), 4.67 (d, J = 8.1 Hz) **6b** (β-gluco), 4.47 (dd, J = 3.0, 1.5 Hz) **6d** (β-manno). Repeated recrystallization (3x, Et_2O/hexanes) produced a single diastereoisomer, **2-chloro-2-deoxy-3,4,6-tri-O-methyl-α-D-glucopyranose (6a)**: mp 149.3-150.0 °C; $[\alpha]_D$ +125.3° (c = 0.49, $CHCl_3$); IR ($CHCl_3$) 3407, 2989, 2919, 2841, 1448, 1379, 1188, 1131, 1100, 1052, and 1020 cm^{-1}; ^1H NMR δ 5.27 (t, 1H, J = 3.6 Hz), 4.04-3.98 (m, 1H), 3.78 (dd, 1H, J = 3.3, 1.2 Hz), 3.75-3.73 (m, 1H) , 3.68 (s, 3H), 3.63-3.53 (m, 3H), 3.55 (s, 3H), 3.41 (s, 3H), 3.14 (dd, 1H, J = 10.2, 8.7 Hz); ^{13}C NMR δ 92.7, 83.1, 80.8, 71.3, 70.2, 61.3, 60.6, 60.4, 59.2; MS (DP/CI) *m/z* 242, 240, 162, 105, 102, 101, 88, 87, 71, 45, 43; Anal. Calcd. for $C_9H_{17}O_5Cl$: C, 44.91; H, 7.12. Found: C, 44.97; H, 7.15.

Iodohydrins 7a-d. 3,4,6-tri-O-methyl-D-glucal (0.64 g, 3.4 mmol) in 10% aqueous THF (17 mL) and N-iodosuccinimide (0.84 g, 3.7 mmol) gave a diastereomeric mixture of iodohydrins **7a-d** (1.0 g, 89 %): ^1H NMR (anomeric protons) δ 5.59 (br s) **7c** (α-manno), 5.33 (br s) **7a** (α-gluco), 4.85 (d, J = 9 Hz) **7b** (β-gluco), 4.73 (d, J = 2.1 Hz) **7d** (β-manno). MS (DP/EI) *m/z* 332, 300, 197, 173, 127, 113, 101, 87, 71, 45. Acetylation of the iodohydrin mixture (**7a-d**) with Ac_2O in pyridine and CH_2Cl_2 at 5 °C gave a mixture of acetates (52 %). Column chromatography (SiO_2, Et_2O/hexanes, 2:3) gave **1-O-acetyl-2-deoxy-2-iodo-3,4,6-tri-O-methyl-α-D-mannopyranose** as an oil (22 %): $[\alpha]_D$ + 19.3° (c = 1.00, $CHCl_3$); IR (neat) 2929, 2831, 1749, 1456, 1373, 1297, 1220, 1141, 1112, 1046, 1001 cm^{-1}; ^1H NMR δ 6.39 (d, 1H, J = 1.5 Hz), 4.47 (dd, 1H, J = 4.5, 1.5 Hz), 3.86-3.80 (m, 1H), 3.67-3.57 (m, 2H), 3.56 (s, 3H), 3.55-3.47 (m, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 2.85 (dd, 1H, J = 8.1, 4.2 Hz), 2.10 (s, 3H); ^{13}C NMR δ 168.2, 95.3, 78.1, 76.4, 74.3, 71.1, 60.8, 59.4, 56.5, 30.3, 20.8; Anal. Calcd. for $C_{11}H_{19}O_6I$: C, 35.31; H, 5.12. Found: C, 35.44; H, 5.13. Further elution yielded **1-O-acetyl-2-deoxy-2-iodo-3,4,6-tri-O-methyl-β-D-glucopyranose** (13 %): mp 108-109 °C; $[\alpha]_D$ + 57.4° (c = 0.54, $CHCl_3$); ^1H NMR δ 5.74 (d, 1H, J = 9.3 Hz), 3.82 (t, 1H, J = 10.2 Hz), 3.69 (s, 3H), 3.65-3.57 (m, 1H), 3.55 (s, 3H), 3.49-3.40 (m, 2H), 3.39 (s, 3H), 3.40 - 3.32 (m, 1H), 2.13 (s, 3H); ^{13}C NMR δ 168.8, 94.2, 87.2, 80.3, 75.5, 70.1, 61.0, 60.4, 59.3, 30.1, 20.9; Anal. Calcd. for $C_{11}H_{19}O_6I$: C, 35.31; H, 5.12. Found: C, 35.40; H, 5.13.

General Procedure for Deuterium Incorporation Studies. A solution of halohydrins (1.0 mmol) in CH_3OD (4 mL) was cooled to 5° C and Cs_2CO_3 (1.0 mmol) was added. The reaction mixture was stirred at 5° C for 4 hrs and then was warmed to room temperature and stirred until consumption of starting materials was indicated by thin layer chromatography (SiO_2, Et_2O/hexanes, 1:1). The mixture was quenched with H_2O, then extracted with CH_2Cl_2 (3x25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* . The crude mixtures were purified by column chromatography (SiO_2, Et_2O/hexanes, 1:1) and analyzed by ^1H and ^2H NMR. Acetylation of the isolated diastereomers with d_6-Ac_2O in pyridine gave the fully deuterated C-2 acetates which were used to quantify the extent of ^2H-incorporation in the C-2 position of the sugar.

Cyclization of Bromohydrins (4a-d). Bromohydrins (**4a-d**) (0.28g, 1.0 mmol) and Cs_2CO_3 (0.32 g, 1.0 mmol) in CH_3OD (9 mL) gave aldehyde **5** (0.05 g, 0.23 mmol, 23.8 %), partially deuterated **methyl 3,4,6-tri-O-methyl-β-D-glucopyranoside (8b)**[14] (0.07 g, 0.29 mmol, 29.7 %), and partially deuterated **methyl 3,4,6-tri-O-methyl-α-D-mannopyranoside (8a)**[15] (0.01 g, 0.06 mmol, 5.9 %). Acetylation (d_6-Ac_2O, pyridine) of **8b** gave **methyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucopyranoside (9b)**: ^2H NMR δ 4.82 (br s); 20 % ^2H-incorporation. Acetylation of **8a** gave **methyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-mannopyranoside (9a)**: ^2H-NMR δ 5.24 (br s); 71 % ^2H-incorporation.

Cyclization of Chlorohydrins (6a-d). Chlorohydrins (**6a-d**) (0.7 g, 2.8 mmol) and Cs_2CO_3 (0.9 g, 2.8 mmol) in CH_3OD (9 mL) gave aldehyde **5** (trace), **8b** (0.28 g, 1.2 mmol, 42.9 %), and **8a** (0.04 g, 0.17 mmol, 6.1 %). Acetylation under the described conditions gave **9b** (79 % ^2H-incorporation) and **9a** (88 % ^2H-incorporation).

Cyclization of the Iodohydrins (7a-d). Iodohydrins (**7a-d**) (0.8 g, 2.5 mmol) and Cs_2CO_3 (0.8 g, 2.5 mmol) in CH_3OD (11 mL) gave aldehyde **5** (0.08g, 0.32 mmol, 13.1 %), **8b** (0.16 g, 0.69 mmol, 28 %) and **8a** (0.05 g, 0.23 mmol, 9.2 %). Acetylation (d_6-Ac_2O, pyridine) gave **9b** (14 % ^2H-incorporation) and **9a** (59 % ^2H-incorporation).

Cyclization of the Bromohydrins (1a-d) with LiHMDS and Trapping with Sodium Phenylthiolate. A solution of the bromohydrins **4a-d** (210 mg, 0.73 mmol) in anhydrous THF (8 mL) was cooled to 5° C. LiHMDS (0.73 mmol, 1.0 M in THF) was added over 5 minutes. The reaction progress was monitored by thin layer chromatography until the bromohydrins had been consumed. The sodium phenylthiolate (0.289 g, 2.1 mmol) was added and the solution was slowly warmed to room temperature (3 hrs.). The reaction mixture was stirred overnight (15 hrs), diluted with water (25 mL), and extracted with CH_2Cl_2 (3x50 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (0.14 g, 62%, 10 : 1 ratio). The products were purified by SiO_2 chromatography (50 % Et_2O in hexanes) to give **phenyl 3,4,6-tri-O-methyl-1-thio-α-D-mannopyranoside 4a** (0.067g 40%), and **phenyl 3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside 3a** (0.092 g 5.5%).

2-Bromo-2-deoxy-3,4,6-tri-O-methyl-D-glucopyranose (1a, 1b). To a solution of trimethyl glucal (0.57 g, 3 mmol) in CCl_4 (5 mL) was added a 1M solution of bromine in CCl_4 (approx. 8.5 mL) over a period of 1 hr until the bromine color persisted. Argon was bubbled into the solution to remove the excess bromine and then the solvent was evaporated *in vacuo* to give a mixture of dibromides (1.02 g). The crude dibromide (0.54 g) mixture was dissolved in 10% aq. THF (11 mL) and the solution was cooled to 5 °C. Silver carbonate (0.42 g) was added and the solution was warmed to room temp. After an additional 16 hrs, the suspension was filtered through celite. The celite was rinsed with Et_2O and the combined organic solvents were washed with H_2O (20 mL), dried and evaporated to give bromohydrins (0.315 g). The celite was rinsed with additional solvent, CH_2Cl_2 (2x20 mL), which was evaporated to give bromohydrins (0.098g); total recovery (0.414 g, 93%). Recrystallization (Et_2O hexane) gave **2-bromo-2-deoxy-3,4,6-tri-O-methyl-α-D-glucopyranose (1a)** (0.066g, 15%).

Cyclization of 2-Bromo-2-Deoxy-3,4,6-tri-O-methyl-α-D-glucopyranose (1a) with NaH and Trapping Sodium Phenylthiolate. NaH in mineral oil (60 %, 14 mg, 0.36 mmol) was washed 3x with hexanes under Ar. The oil-free NaH was suspended in dry THF (7 mL) and the resulting suspension was cooled to 5° C. The solid bromohydrin **1a** (102 mg, 0.36 mmol) was added in portions to the stirred NaH suspension. The reaction progress was followed by thin-layer chromatography (SiO_2; 1:1 hexanes:Et_2O) until the starting material had been consumed (approx. 6 hrs). The nucleophile (140 mg, 1.07 mmol) was added, and the reaction mixture was gradually warmed to room temperature (3 hrs). The reaction mixture was stirred overnight (15 hrs), diluted with water (25 mL), and extracted with CH_2Cl_2 (3x50 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give **phenyl 3,4,6-tri-O-methyl-1-thio-α-D-mannopyranoside 4a** (0.044 g, 38%) as the only product.

2-Deoxy-2-Iodo-3,4,6-tri-O-methyl-D-mannopyranose (7c,7d). A solution of 3,4,6-tri-O-methyl-D-glucal (1.09 g, 5.8 mmol) in 10% aqueous propionitrile (30 mL) was cooled to -68 °C, and N-iodosuccinimide (1.43 g, 6.4 mmol) was added. The reaction mixture was stirred at -68 °C for 6 hrs, then gradually warmed to room temperature and stirred overnight (14 hrs). The reaction mixture was worked up as in previously described hydroxy halogenations to afford a diastereomeric mixture of iodohydrins **7a-d** (1.8 g, 92%). ^1H NMR of the anomeric protons indicated a manno : gluco ratio of 18 :1.

Cyclization of the Manno Iodohydrins (7c,7d) with KH. A mineral oil suspension of KH (35%, 1 equiv.) was washed 3x with hexanes under Ar. The washed KH was suspended in a solution of 18-crown-6 (1 equiv.) in anhydrous $PhCH_3$ (7 mL), and the suspension was cooled to -72 °C. The manno iodohydrin mixture **7c,7d** (1 equiv.) was dissolved in anhydrous $PhCH_3$ (3 mL) and was added in portions to the KH suspension. The mixture was stirred at -72 °C for 4 hrs, and then was warmed to 5 °C over 30 min. The nucleophile (3 equiv) was added, and the mixture was slowly warmed to room temperature and was stirred overnight (18 hrs). The reaction mixture was diluted with water (25 mL), and extracted with CH_2Cl_2 (3x25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The products were purified by SiO_2 chromatography (33-50% Et_2O in hexanes).

Trapping of the α-Epoxide with Sodium Phenylthiolate. Iodohydrins **7c,7d** (0.23 g, 0.7 mmol), KH (0.09g, 0.7 mmol), 18-Crown-6 (0.18 g, 0.7 mmol), and sodium phenyl thiolate (0.27 g, 2.1 mmol) afforded **phenyl 3,4,6-tri-O-methyl-1-thio-α-D-mannopyranoside 4a** (0.005 g, 0.02 mmol, 2.3%), and **phenyl 3,4,6-tri-O-methyl-1-thio-β-D-glucopyranoside 3a** (0.08 g, 0.25 mmol, 36.8%).

Trapping of the α-Epoxide with Sodium Azide. Iodohydrins **7c,7d** (0.29 g, 0.9 mmol), KH (0.1 g, 0.9 mmol), 18-crown-6 (0.23 g, 0.9 mmol) and sodium azide (0.17 g, 2.6 mmol) afforded exclusively **3,4,6-tri-O-methyl-β-D-glucopyranosyl azide 3b** (0.07 g, 0.3 mmol, 33%).

Cyclization of Manno Iodohydrins (7c,7d) with Cesium Carbonate and *in situ* Trapping with Methanol. A solution of iodohydrins **7c,7d** (0.28 g, 0.8 mmol) in anhydrous methanol (6 mL) was cooled to 5 °C and cesium carbonate (0.28 g, 0.8 mmol) was added. The solution was maintained at 5° C for 4 hrs and then was gradually warmed to room temperature (3 hrs) and stirred overnight (15 hrs). The reaction mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (3x25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. SiO_2 chromatography (50% Et_2O in hexanes) afforded **methyl 3,4,6-tri-O-methyl-α-D-mannopyranoside 4d** (0.01 g, 0.06 mmol, 6.7%), **methyl 3,4,6-tri-O-methyl-β-D-glucopyranoside 3d** (0.07 g, 0.3 mmol, 36.1%) and aldehyde **5** (0.03 g, 0.2 mmol, 19 %).

ACKNOWLEDGMENTS

We thank the NSF REU program (CHE9200156) for a fellowship for LMT, the University of Missouri-St. Louis for a dissertation fellowship for CHM. In addition, we thank the University of Missouri Research Board for their financial support of this work, and the National Science Foundation for a grant to purchase the XL300 NMR spectrometer (CHE8506671).

REFERENCES

1. Marzabadi, C.H.; Spilling, C.D. *J. Org. Chem.*, **1993**, *58*, 3761.
2. a) Halcomb, R.L.; Danishefsky, S.J. *J. Am. Chem. Soc.*, **1989**, *111*, 6661; b) Chow, K.; Danishefsky, S. J. *J. Org. Chem.*, **1990**, *55*, 4211; c) Gordon, D.M.; Danishefsky, S.J. *Carbohydr. Res.*, **1990**, *206*, 361; d) Dushin, R.G.; Danishefsky, S.J. *J. Am. Chem. Soc.*, **1992**, *114*, 3471.
3. These trends are similar to previously reported results from haloglycosidation reactions with small alcohols. For examples of haloglycosidation see; Fischer, E.; Bergmann, M.; Schotte, H. *Chem. Ber.*, **1920**, *53*, 509; Tatsuta, K.; Fujimoto, K.; Kinoshita, M. *Carbohydr. Res.*, **1977**, *54*, 85; Gnichtel, H; Rebentisch, D; Tompkins, T.C.; Gross, P.H. *J. Org. Chem.*, **1982**, *47*, 2691; Bischofberger, K.; Eitelman, S.J.; Jordan, A. *Carbohydrate Res.*, **1979**, *74*, 145; Lundt, I.; Thiem, J.; Prahst, A. *J. Org. Chem.*, **1984**, *49*, 3063; Horton, D; Priebe, W.; Varela, O. *J. Org. Chem.*, **1986**, *51*, 3479; Kottenhahn, M.; Kessler, H. *Liebigs Ann. Chem.*, **1991**, 727.
4. Dihalogenation of glucal derivatives has also been well studied. Bromination in non-polar solvents was reported to favor the gluco product. For examples see; Igarashi, K.; Honma, T.; Imagawa, T. *J. Org.*

Chem., **1970**, *35*, 610; Lemieux, R.U.; Fraser-Reid, B. *Can. J. Chem.*, **1964**, *42*, 532; Lemieux, R.U.; Fraser-Reid, B. *Can. J. Chem.*, **1965**, *43*, 1460.

5. Roush, W.R.; Briner, K.; Sebesta, D.P. *Syn. Lett.*, **1993**, 264.
6. Intermediate epoxides have been proposed for the reaction of 2-mesylates, and 1,2,6-tribromides in methanol solution. Jones, J.K.N.; Nicholson, W.H. *J. Chem. Soc.*, **1955**, 3050; Smith, D.C.C. *J. Chem. Soc.*, **1957**, 2690; Bock, K.; Lundt, I.; Pedersen, C.; Pedersen, H. *Acta Chem. Scand.*, **1988**, *B42*, 640.
7. Barton, D.H.R.; Lewis, D.A.; McGhie, J.F. *J. Chem. Soc.*, **1957**, 2907.
8. Pigman, W. and Anet, E.F.L.T. Mutarotations and Actions of Acids and Bases. In *The Carbohydrates: Chemistry and Biochemistry*, second edition, Pigman, W. and Horton, D. Eds. Academic Press, London, Vol. 1A, 1972, 165-194; Rendleman, Jr., J.A. Ionization of Carbohydrates. In *"Carbohydrates in Solution", A.C.S. Adv. Chem. Series*, Isbell, H.S., Ed., Vol 117, 1973, 51-69; Isbell, H. Enolization and Oxidation Reactions of reducing Sugars. In *"Carbohydrates in Solution", A.C.S. Adv. Chem. Series*, Isbell, H.S., Ed., Vol 117, 1973, 70-87.
9. Sebesta, D.P.; Roush, W.R. *J. Org. Chem.*, **1992**, *57*, 4799.
10. a) Roseman, S.; Comb, D.G. *J. Am. Chem. Chem.*, **1958**, *80*, 3166; b) Kuhn, R; Brossmer, R. *Liebigs Ann. Chem.*, **1958**, *616*, 221; c) Carlo, M.J.; Cosmatos, H.; Zimmerman, Jr., K. *Liebigs Ann. Chem.*, *1961*, **650**, 187; d) Szilagyi, L.; Herczegh, P.; Bujtas, G. *Z. Naturforsch*, **1977**, *32B*, 296.
11. Pfeffer, P.E.; Rothman, E.S.; Moore, G.G. *J. Org. Chem.*, **1976**, *41*, 2925.
12. Schmidt, R.R. *Ang. Chem. Int. Ed. Engl.*, **1986**, *25*, 212 and references cited therein.
13. Hirst, E.L.; Woolvin, C.S. *J. Chem. Soc.*, **1931**, 1131; Flaherty, B.; Overend, W. G.; Williams, N. R. *J. Chem. Soc. (C)*, **1966**, 398-403.
14. Ekborg, G.; Lindberg, B.; Lonngren, J. *Acta Chem. Scand.*, **1972**, *26*, 3287.
15. Handa, V.K.; Barlow, J.J.; Matta, K.L. *Carbohydr. Res.*, **1979**, *76*, C-1.

(*Received in USA* 7 *December* 1993; *accepted* 7 *April* 1994)