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Chemistry of glucal halohydrins (II): An unusual protecting group effect in the competitive formation of formyl furanosides and methyl glycosides

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Abstract

A remarkable protecting group influence was observed in the base-induced reaction of protected halohydrins derived from D-glycals. Tri-*O*-methyl and tri-*O*-benzyl halohydrins react with cesium carbonate in methanol at room temperature to give methyl glycosides as the major product and unsaturated formyl furanosides as the minor product. Whereas, the tri-*O*-*tert*-butyldimethylsilyl (*t*-$BuMe_2Si$)-protected halohydrins reacted with cesium carbonate in methanol at room temperature to give a mixture of epimeric formyl furanosides, and at reflux to give an unsaturated formyl furanoside, as the only products. The tri-*O*-methyl and tri-*O*-benzyl halohydrins react slowly at elevated temperature to give predominantly furans. In comparison, the tri-*O*-*t*-$BuMe_2Si$ halohydrins reacted completely after five minutes to give a mixture of epimeric formyl furanosides. The tri-*O*-*t*-$BuMe_2Si$ iodohydrins were oxidized to the corresponding iodolactones, which also underwent a based-induced ring contraction in methanol to give the furanose 1-methylcarboxylate esters. © 1997 Elsevier Science Ltd.

Keywords: Halohydrins; Glycosides; *C*-Formyl furanosides; Iodolactone; Ring contraction

1. Introduction

C-Formyl furanosides and pyranosides are useful intermediates in the synthesis of other biologically active *C*-glycosyl compounds, termed '*C*-glycosides' [1]. Consequently, several methods for the preparation of these formyl glycosides have been developed. Both formyl pyranosides and furanosides have been prepared by the introduction of a formyl anion synthon at the anomeric center [2], and formyl furanoside sugars (2,5-anhydrohexoses) are uniquely available by the ring contraction of hexopyranose sugars [3–9]. Methods for ring contraction include, deamination of 2-amino-2-deoxyaldoses [1e], [4], acid-catalyzed dehydrations [5], action of oxidizing metals on glucals

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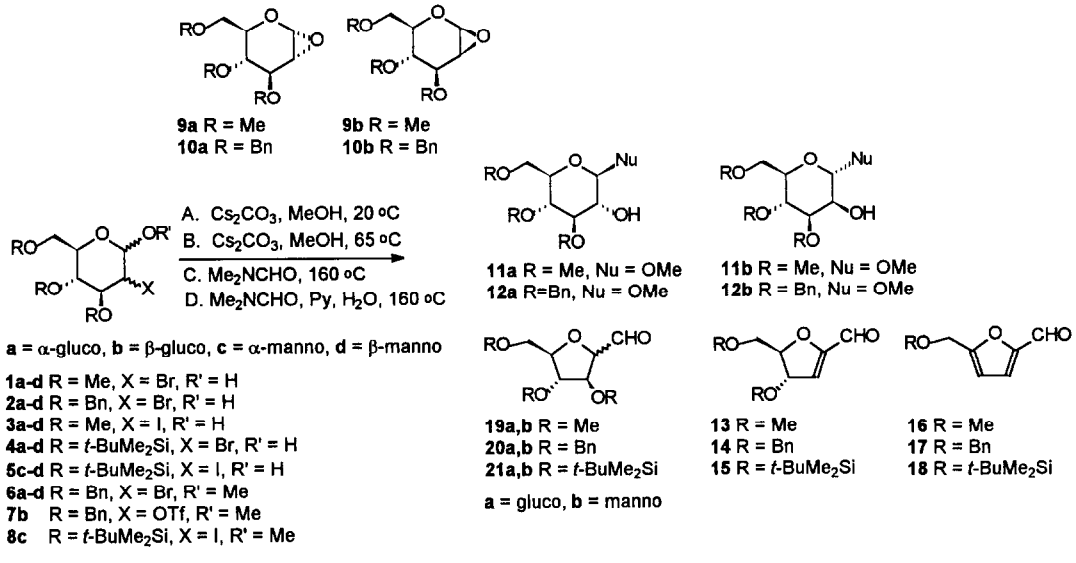
[6], reaction of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-D-glucose with Br_2/Ag^+ [7], and intramolecular halide [8] and sulfonate ester displacements [9].

During a recent investigation into the based-induced formation of glucal epoxides from halohydrins, we observed the formation of a significant quantity of unsaturated formyl furanosides along with the expected methyl glucosides [10]. The straightforward nature of this reaction and potential synthetic applications of the formyl furanoside products prompted us to investigate the factors that contributed to their formation.

2. Results

We previously reported that reaction of the tri-*O*-methyl bromohydrins **1a–d** (manno:gluco, 3.5:1) with KH/18-crown-6 in toluene or NaH in THF yielded glucal epoxides **9a** and **9b**, which upon reaction with nucleophiles (Nu = MeOH, N_3^-, PhS^-, etc.) gave substituted glycosides **11a** and **11b** as the only isolable products (Scheme 1) [10]. In contrast, reaction of the bromohydrins **1** with one equivalent of Cs_2CO_3 in anhydrous methanol at room temperature gave a mixture of the expected methyl glycosides **11a** and **11b** (4:1 ratio, 37–55% yield) and an additional product (15–24%) identified as the aldehyde **13** (Table 1). Similarly, the tri-*O*-benzyl bromohydrins **2a–d** reacted with Cs_2CO_3 to give glycosides **12a** and **12b** (55–62%) and aldehyde **14** (11–28%) [10]. We later determined that the related tri-*O*-methyl iodohyrins **3a–d** would also give a significant proportion of aldehyde **13** (up to 24%) when treated with Cs_2CO_3 in methanol-d_1. Other experimental variations with halohydrins **1–3** led to some small changes in the ratio of glycosides to aldehyde in the product mixture [11].

The aldehydes **13** and **14** were unstable and easily lost methanol or benzyl alcohol on standing to give the furans **16** and **17**. Replacing an alkyl ether with a silyl ether can often lead to enhanced stability toward elimination [12]. We therefore decided to prepare the corresponding *t*-$BuMe_2Si$-protected aldehydes as more stable and potentially more useful fomyl furanose synthons. Tris *t*-$BuMe_2Si$- glucal [13] was reacted with NIS in propionitrile to give **5a–d**, predominantly as the α-manno iodohydrin **5c** (manno:gluco > 30:1) [14]. Surprisingly, when the *t*-$BuMe_2Si$-protected iodohydrin **5c** was treated in methanol with Cs_2CO_3 at room temperature, a mixture of the epimeric saturated aldehydes **21a,b** was obtained as the major product (Table 1). When the reaction was performed in refluxing methanol, the unsaturated aldehyde **15** was formed in near quantitative yield. Similarly, the *t*-$BuMe_2Si$-protected bromohydrin **4c** reacted with Cs_2CO_3 in methanol giving a mixture of saturated aldehydes **21a,b** at room temperature and only the α,β-unsaturated aldehyde **15** at reflux. In contrast, reaction of the *t*-$BuMe_2Si$-methoxyiodide **8c**, which lacks the free hydroxyl at the anomeric center, produced only starting materials after one hour with Cs_2CO_3 in refluxing methanol.



Scheme 1.

Table 1
Reaction of 2-deoxy-2-halo sugars with cesium carbonate in methanol [a]

Cmpd No.	Substrate R, X, R′	Ratio manno:gluco	Conditions	Time (h)	Satd aldehydes	Unsatd aldehyde	Methyl glycoside
3	Me, I, H	3.5:1	B	0.5		15	55
3	Me, I, H	> 18:1	A	16		19	43
1	Me, Br, H	1.8:1	A	16		6	51
1	Me, Br, H	1.8:1	A [b]	18		24	37
2	Bn, Br, H	approx. 3:1	A	20		11	55
2	Bn, Br, H	approx 3:1	B	0.5		28	62
6	Bn, Br, Me	approx 2:1	B	3		recovered s.m.	
5	*t*-BuMe$_2$Si, I, H	> 30:1	A	24	95 (6:1)	5	
5	*t*-BuMe$_2$Si, I, H	> 30:1	B	1	5	95	
4	*t*-BuMe$_2$Si, Br, H	α-manno	A	24	100 (6:1)		
8	*t*-BuMe$_2$Si, I, Me	α-manno	B	1		recovered s.m.	

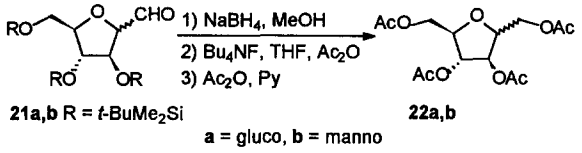
[a] Conditions: A = MeOH, Cs_2CO_3 (1 equiv), 5 °C and B = MeOH, Cs_2CO_3 (1 equiv), 65 °C (reflux).
[b] In methanol-d_1.

Baer et al. [9a] and Charette et al. [9b,9c] had reported that 2-sulfonates undergo a concerted ring contraction at elevated temperature to give formyl furanosides, and we decided to compare the reactions of the sugar halohydrins under similar conditions. A series of 2-halo-2-deoxy sugars were reacted in Me_2NCHO–pyridine at 160 °C (Table 2), and the individual components in the crude reaction mixtures were assigned and quantified by ^1H NMR spectroscopy. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-β-D-glucopyranose (**7b**) was prepared and reacted for comparison [9b]. The tri-*O*-methyl- and tri-*O*-benzyl-protected bromohydrins **1** and **2** reacted slowly in refluxing Me_2NCHO to give furan aldehydes (**16** 100%, and **17** 40%, respectively) as the major products. Addition of water (82 equiv) and pyridine (10 equiv) to the Me_2NCHO solution of bromohydrins **1a–d** slowed the reaction, and a small quantity of unsaturated aldehyde (**13**, 7%) was observed in addition to furan aldehyde (**16**, 23%). The tri-*O*-methyl iodohydrins **3a–d** were more reactive than the corresponding bromohydrins, giving a mixture of saturated aldehyde (**19a,b**, 5%), α,β-unsaturated aldehyde (**13**, 14%), furan aldehyde (**16**, 49%) and starting material after 15 min, and complete conversion (**13** 25%, and **16** 75%) after 30 min.

Table 2
Reaction of 2-deoxy-2-halo sugars at elevated temperature in MeN_2CHO solution [a]

Cmpd No.	Substrate R, X, R′	Ratio manno:gluco	Conditions	Time (min)	Satd aldehyde	Unsatd aldehyde	Furan	SM
1	Me, Br, H	3.5:1	C	45			100	
1	Me, Br, H	3.5:1	D	80		7	23	70
3	Me, I, H	> 18:1	D	15	5	14	49	32
3	Me, I, H	> 18:1	D	30		25	75	
2	Bn, Br, H	aprox. 3:1	C	40			40	60
6	Bn, Br, Me	2:1	D	300				98
4	*t*-BuMe$_2$Si, Br, H	α-manno	D	5	100			
5	*t*-BuMe$_2$Si, I, H	> 30:1	D	5	100			
7	Bn, OTf, Me	β-gluco	D	5	100			
8	*t*-BuMe$_2$Si, I, Me	α-manno	D	30				100

[a] Conditions: C = Me_2NCHO, Py (10 equiv), 160 °C and D = Me_2NCHO Py (10 equiv) H_2O (82 equiv) 160 °C.

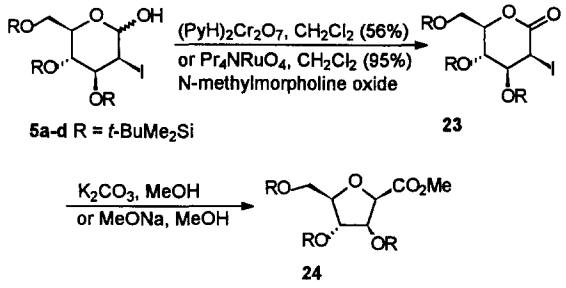


Scheme 2.

The tri-*O*-benzyl methoxybromides (**6a–d**) gave only trace amounts of saturated (**20a,b**) and α,β-unsaturated (**14**) aldehydes after 80 min at reflux, whereas, in comparison, methyl 3,4,6-tri-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-β-D-glucopyranoside (**7b**), quantitatively gave aldehydes **20a,b** after 5 min [9c]. A change in protecting group again gave quite different results. The *t*-$BuMe_2Si$-protected bromohydrin **4c** or iodohydrins **5c** reacted in refluxing Me_2NCHO–pyridine–water to give saturated aldehydes (**21a,b**; 7:1) in quantitative yields after only 5 min. However, the *t*-$BuMe_2Si$-protected methoxyiodide **8c**, which lacks the free hydroxyl at the anomeric center, again failed to react. See Scheme 2.

The saturated aldehyde mixture **21a,b** slowly decomposed when applied to a column of either silica gel or neutral alumina (BA I), making chromatographic separation difficult. The crude aldehyde mixture was reduced with $NaBH_4$ to the corresponding 2,5-anhydroalditols (85%) for purification and characterization. Column chromatography on the mixture (SiO_2; 3:1 hexanes–Et_2O) afforded two fully silylated components (48%), as well as substantial amounts of desilylated material (25%). All fractions from chromatography were treated with a mixture of Bu_4NF–Ac_2O in THF [15] to give a mixture of tri- and tetra-acetylated sugars. The mixture was exhaustively acetylated by additional treatment with Ac_2O in pyridine to give tetra-acetylated derivatives **22a,b**. Assignments of the relative stereochemistry at C-2 for the two diastereoisomers were made by comparison of their ^1H NMR chemical shifts and coupling constants with those of known standards [16]. Overall, 1,3,4,6-tetra-*O*-acetyl-2,5-anhydro-D-glucitol (**22a**) was obtained in 63% and 1,3,4,6-tetra-*O*-acetyl-2,5-anhydro-D-mannitol (**22b**) was present in 11%, reflecting the contents of the original aldehyde mixture. See Scheme 3.

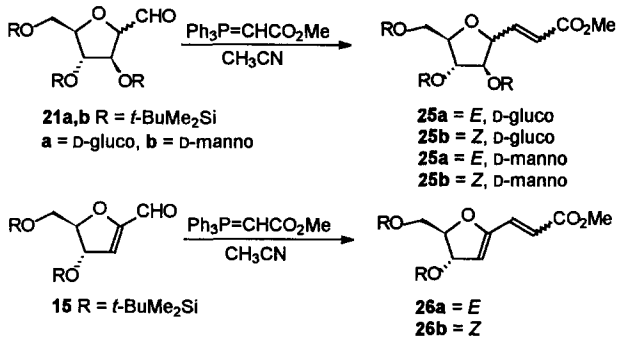
Fleet and co-workers have shown that sugar lactone 2-triflates undergo base-induced ring contraction in methanol to produce furanose 1-methylcarboxylate esters [17]. These esters are extremely useful intermediates in the synthesis of *C*-spiroglycosides such as hydantocidin [18]. For further comparison of 2-halides



Scheme 3.

and 2-triflates from the gluco/manno halohydrin series, we prepared the corresponding *t*-$BuMe_2Si$-iodolactone. The *t*-$BuMe_2Si$-iodohydrin **5c** was oxidized with either pyridium dichromate in CH_2Cl_2 or Pr_4NRuO_4–*N*-methylmorpholine oxide in CH_2Cl_2 to give the iodolactone **23** in good yield [19,20]. The iodolactone reacted smoothly with either sodium methoxide or potassium carbonate in methanol solution at room temperature to give the methyl ester **24** in high yield as a single isomer. Elimination of the β-silyloxy group was not observed even in refluxing methanol. See Scheme 4.

The Wittig reaction has found numerous applications in the carbohydrate chemistry for chain-extension and chain-branching [21], and consequently was appropriate to demonstrate the synthetic utility of the aldehydes **15** and **21a,b**. Reaction of the mixture of 2,5-anhydrosugars **21a,b**, with methyl(triphenylphosphorylidene) acetate [22], provided a mixture of four olefinic products **25a–d** (3:1 E:Z) in 79% yield. Repeated column chromatography on the mixture (neutral alumina; 1:9 Et_2O–hexanes) afforded the major diastereomer (**25a**). The ^1H NMR spectrum showed two olefinic resonances at 6.90 (dd) and 6.09 (dd) ppm assigned to the β olefinic proton and the α olefinic proton, respectively. The H_α–H_β coupling constant of 15 Hz indicated the expected a trans-



Scheme 4.

arrangement of olefinic protons. Reaction of α,β-unsaturated aldehyde **15**, with methyl(triphenylphosphorylidene) acetate, gave two exocyclic double-bond isomers (**26a,b**). The major diastereomer **26a** was isolated by column chromatography (74%). The ^{1}H NMR spectrum displayed three olefinic resonances. The H_α–H_β coupling constant of 15 Hz again indicated the trans-arrangement of olefinic protons.

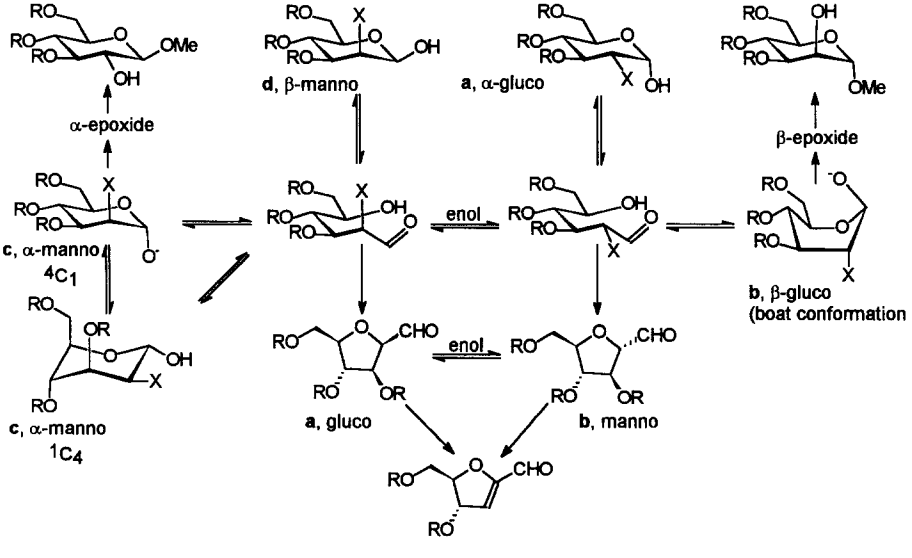
3. Discussion

Some general observations can be made for the reactions of the halohydrins. Epoxide formation and hence glycoside formation is favored by nonpolar, nonprotic solvents and methyl or benzyl protecting groups [10]. Whereas, ring contraction is favored by the use of polar solvents, an axial C-2 halide, and the *tert*-butyldimethylsilyl protecting group. The most plausible mechanism for the formation of the aldehydes (Scheme 5) involves an S_N2 reaction of the 5-OH group (or the corresponding anion) with the C-2 halide in the ring-open aldehyde form of the sugar. We had previously demonstrated the intermediacy of the open-chain sugar by deuterium incorporation at C-2 (14–71%) in reaction of tri-*O*-methyl bromohydrins **1a–d** and iodohydrins **3a–d** in deuterated methanol [10].

The highly branched, equatorial *t*-$BuMe_2Si$ ethers are known to experience gauche interactions in the pyranose $^4C_1$ conformation, and, as a consequence, also populate the $^1C_4$ conformation [23]. The X-ray crystal structure of **5c** (Fig. 1) shows the conformation in the solid state as $^4C_1$ with both the C-1 hydroxyl group and the C-2 iodide in axial positions.

In contrast, variable-temperature ^{1}H NMR spectra of **5c** in methanol and $CDCl_3$ solutions indicate that a significant amount of the molecules adopt the $^1C_4$ conformation (approx 36% at room temp), and that at room temperature the two species are in equilibrium [24]. The ^{1}H NMR spectrum of **5c** in CD_3OD solution (Fig. 2) at 313 K shows a doublet at δ 5.24 (d, J_{H1-H2} 5.1 Hz) for the anomeric proton. A spectrum recorded at 213 K shows signals at δ 5.39 ($^4C_1$, H-1, s, $J_{H1-H2} < 1$ Hz) and 5.0 ($^1C_4$, H-1, d, J_{H1-H2} 8.8 Hz) for the anomeric proton, which coalesce at 273 K. A similar observation is made for ^{1}H NMR spectra recorded in $CDCl_3$. At 299 K, the signal for the anomeric proton appears as a doublet of doublets ($J_{H1-OH} = J_{H1-H2} = 5.5$ Hz) at δ 5.32 ppm, whereas the ^{1}H NMR spectrum recorded at 218 K shows signals at δ 5.47 ($^4C_1$, H-1, d, J_{H1-OH} 3.9, $J_{H1-H2} < 1$ Hz) and 5.1 ($^1C_4$, H-1, dd, $J_{H1-OH} = J_{H1-H2} = 8.3$ Hz) that broaden upon warming and coalesce at 258 K.

The presence of a $^1C_4$ conformation reduces the concentration of the $^4C_1$ conformation, where the 1-OH and 2-iodide are in the diaxial arrangement required for epoxide formation. The steric interactions between the *t*-$BuMe_2Si$ groups could also provide the driving force for ring opening, increasing the



Scheme 5.

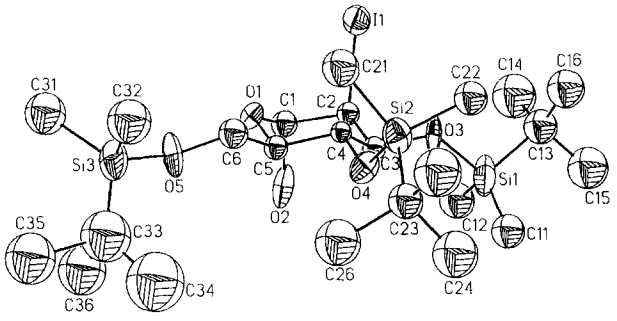


Fig. 1. A projection view of the iodohydrin **5c** with non-hydrogen atoms represented by 50% probability ellipsoids, and showing the atom labeling.

concentration of open-chain sugar. In addition, the transition state leading to the epoxide could be higher energy for the *t*-$BuMe_2Si$ compounds due to strain induced during the flattening of the ring. Since the epoxide formation and ring contraction are in direct competition, the overall effect is to slow epoxidation, and thus favor the ring contraction.

In both the thermal- and base-catalyzed ring-contraction reactions of the *t*-$BuMe_2Si$ halohydrins, a mixture of epimeric aldehydes is formed. In an S_N2 ring closure, the ratio of aldehydes should mirror the gluco/manno ratio in the precursor halohydrin. However, when *t*-$BuMe_2Si$-protected iodohydrins (**5a–d**, manno:gluco > 30:1) are heated to 160 °C, or treated with Cs_2CO_3 in methanol at room temperature, a mixture of 2,5-anhydrogluco aldehyde **21a** and 2,5-anhydromanno aldehyde **21b** are formed in a 7:1 ratio. This is probably the result of epimerization of either the halohydrins **5a–d** or the aldehydes **21a,b**. Once formed, the formyl furanosides **21** can undergo β-elimination to produce the conjugated system **15** and eventually, by acid-catalyzed or thermal elimination, the furan **18**.

In summary, the choice of protecting group for glucal halohydrins has a profound effect on the base-induced reaction pathway. The methyl and benzyl ethers favor epoxidation, whereas the *t*-$BuMe_2Si$ ether favors a ring contraction.

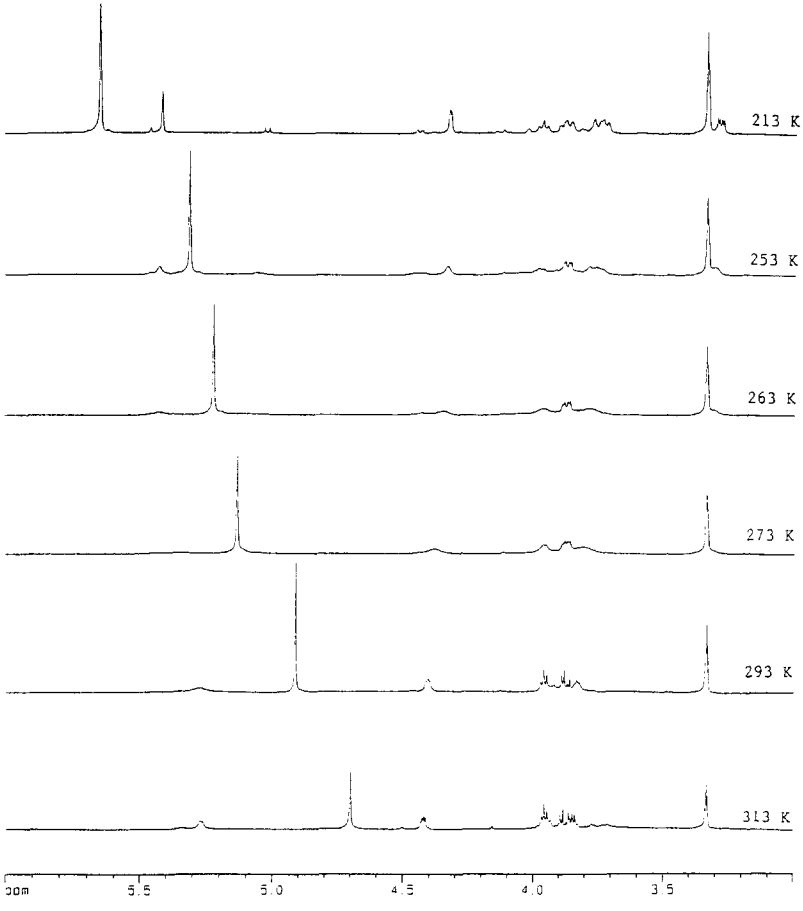


Fig. 2. Variable-temperature ^1H NMR spectra of **5c** in CD_3OD solution.

4. Experimental

^1H and ^{13}C spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz, respectively. The ^1H chemical shifts are reported in ppm downfield from internal Me_4Si, and the ^{13}C chemical shifts are reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. High-resolution FAB mass spectra were acquired on a Finnigan MAT 90 mass spectrometer using a nitrobenzyl alcohol–LiCl (aq) matrix. Microanalyses were performed by Atlantic Microlab, Inc. Optical rotations were recorded on an Autopol III polarimeter (Rudolph Research) under standard conditions. Column chromatography was performed on SiO_2 (E. Merck, 230–400 mesh) or on neutral alumina (BA I, 80–200 mesh, Fischer Scientific).

THF and Et_2O were distilled from sodium–benzophenone ketyl, while CH_2Cl_2, CH_3CN, and $PhCH_3$ were distilled from CaH_2, and methanol was distilled from Mg. All reagents were used as supplied by Aldrich Chemical Co. Tris-*O*-(*tert*-butyldimethylsilyl)-D-glucal [13] was prepared from tri-*O*-acetyl-D-glucal by methanolysis, followed by silylation (*t*-$BuMe_2SiCl$, imidazole, Me_2NCHO). The tri-*O*-methyl bromohydrins **1**, and iodohydrins **3**, and the tri-*O*-benzyl bromohydrins **2** were prepared by previously published procedures [10].

Hydroxybromination of tris-O-(tert-*butyldimethylsilyl*)-D-*glucal.*—A solution of tris-*O*-(*tert*-butyldimethylsilyl)-D-glucal [13] (0.63 g, 1.3 mmol) and $NaHCO_3$ (0.12 g, 1.4 mmol) in 10% aq THF (15 mL) was cooled to 5 °C, and *N*-bromosuccinimide (0.25 g, 1.4 mmol) was added. The reaction mixture was stirred at 5 °C for an additional 4 h, then was slowly warmed to room temperature (1 h) and stirred for 18 h. The reaction mixture was diluted with Et_2O (60 mL) and washed with distilled water (60 mL). The aqueous layer was extracted with additional portions of Et_2O (2 × 60 mL). The combined Et_2O extracts were washed with saturated $Na_2S_2O_3$ (60 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a mixture of bromohydrins (**4**) (0.74 g, 99%). ^1H NMR (anomeric protons) δ 5.35 (d, *J* 7.5 Hz), 5.25 (d, *J* 4.8 Hz) 5.06 (d, *J* 3.9 Hz), 4.76 (d, *J* 1.2 Hz); ^{13}C NMR (anomeric carbons) δ 95.6, 93.7, 93.5, 92.2. Column chromatography (SiO_2, 95:5 Et_2O–hexanes) gave 2-bromo-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-D-mannopyranose (**4c**) as a white solid: mp 104–110 °C; IR (NaCl): 3428, 2929, 2886 cm^{-1}; ^1H NMR: δ 5.25 (dd, 1 H, *J* 4.8 Hz), 4.20–4.17 (m, 1 H), 4.00–3.68 (m, 4 H), 0.95 (s, 9 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 0.16 (s, 3 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.075 (s, 3 H), 0.068 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR: δ 93.3, 77.5, 72.9, 70.1, 62.8, 56.1, 26.4, 26.0, 25.8, 18.6, 18.5, 18.1, −3.4, −3.6, −4.4, −4.5, −5.1, −6.5. Anal. Calcd for $C_{24}H_{53}BrO_5Si_3$: C, 49.21; H, 9.12. Found: C, 49.23; H, 9.09.

Hydroxyiodination of tris-O-(tert-*butyldimethylsilyl*)-D-*glucal.*—A solution of tris-*O*-(*tert*-butyldimethylsilyl)-D-glucal (0.94 g, 1.9 mmol) in 10% aq propionitrile (40 mL) was cooled to −65 °C, and *N*-iodosuccinimide (0.48 g, 2.1 mmol) was added. The reaction was maintained at −65 °C for 6 h, then was slowly warmed to room temperature (1 h) and stirred overnight (16 h). The reaction mixture was diluted with Et_2O (60 mL) and washed with distilled water (60 mL). The aqueous layer was extracted with additional portions of Et_2O (2 × 60 mL). The combined Et_2O extracts were washed with saturated $Na_2S_2O_3$ (60 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give the iodohydrins (**5**) (1.1 g, 93%, predominantly the α-manno diastereoisomer > 30:1), which were generally used without further purification. Column chromatography (SiO_2, 9:1 hexanes–Et_2O) or recrystallization from MeOH–H_2O afforded a single diastereoisomer 3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-iodo-α-D-mannopyranose (**5c**) (25% and 48%, respectively): mp 122–123 °C; $[\alpha]_D$ +25.4° (*c* 1.00, $CHCl_3$); IR (NaCl): 3442, 2931, 2858 cm^{-1}; ^1H NMR: δ 5.35 (dd, 1 H, *J* 5.4 Hz), 4.39 (dd, 1 H, *J* 4.8, 2.7 Hz), 3.93–3.72 (m, 3 H), 3.65 (br s, 1 H), 2.95 (d, 1 H, *J* 5.1 Hz), 0.97 (s, 9 H), 0.90 (s, 18 H), 0.19 (s, 3 H), 0.14 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR: δ 93.7, 78.4, 74.0, 70.3, 62.2, 37.3, 26.4, 26.1, 26.0, 18.5, 18.4, 18.1, −3.2, −4.3, −4.5, −4.9, −5.1, −6.5. Acetylation of the crude iodohydrin mixture (**5**) with Ac_2O and pyridine in CH_2Cl_2 at 5 °C gave a mixture of acetates (83%, predominantly the α-manno diastereoisomer). IR (NaCl): 2928, 2857, 1760 cm^{-1}; ^1H NMR (anomeric proton): δ 6.24 (d, *J* 4.8 Hz) (acetate methyl) 2.10 (s). Anal. Calcd for $C_{26}H_{55}IO_6Si_3$: C, 46.27; H, 8.22. Found: C, 46.35; H, 8.19.

Methyoxybromination of 3,4,6-tri-O-*benzyl*-D-*glucal.*—A solution of tri-*O*-benzyl-D-glucal (0.51 g, 1.2 mmol) in 1:9 MeOH–THF (12 mL) was cooled to 5 °C, and *N*-bromoacetamide (0.19 g, 1.3 mmol) was added as a single portion. The reaction mixture was maintained at 5 °C for 3 h, then was gradually warmed to room temperature (2 h) and stirred

overnight (18 h). The mixture was diluted with water (25 mL) and extracted with Et_2O (3 × 25 mL). The combined Et_2O extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a diastereoisomeric mixture of methyl 3,4,6-tri-*O*-benzyl-2-bromo-2-deoxy-D-glucopyranosides [25] and methyl 3,4,6-tri-*O*-benzyl-2-bromo-2-deoxy-D-mannopyranosides [25] (0.69 g, 100%) as an oil; IR (NaCl, neat): 3030, 2865 cm^{-1}; ^1H NMR (OMe resonances): δ 3.67, 3.50 (s), 3.36 (s), 3.28 (s); ^{13}C NMR (anomeric carbons): 103.4, 101.0, 99.6, 99.2. Anal. Calcd for $C_{28}H_{31}BrO_5 \cdot 2H_2O$: C, 59.68; H, 6.26. Found: C, 59.36; H, 6.20.

*Methyl 3,4,6-tri-*O*-benzyl-2-O-(trifluoromethanesulfonyl)-β-D-glucopyranoside* (**7b**) *[9b].*—To a solution of methyl glycoside (**12b**) (0.16 g, 0.3 mmol) and pyridine (0.1 mL, 1.4 mmol) in CH_2Cl_2 (4 mL) at −20 °C was added triflic anhydride (0.1 mL, 0.7 mmol) slowly (15 min) with stirring. The reaction mixture was slowly warmed to 0 °C (1 h), and stirred for an additional 2 h. Saturated $NaHCO_3$ (2 mL) was added, the reaction mixture was diluted with water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined Et_2O extracts were washed with brine (1 × 25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was resuspended in 12:88 EtOAc–hexanes and rapidly filtered through SiO_2 to afford, after concentration, **7b** (0.14g, 0.2 mmol, 69%) as an oil; ^1H NMR: δ 7.36–7.25 (m, 13 H), 7.15–7.12 (m, 2 H), 4.88–4.75 (m, 3 H), 4.64–4.50 (m, 4 H), 4.41 (d, 1 H, *J* 7.1 Hz), 3.77–3.71 (m, 4 H), 3.56 (s, 3 H), 3.51–3.48 (m, 1 H); ^{13}C NMR: δ 137.7, 137.3, 137.0, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 116.2, 100.6, 85.0, 81.7, 78.2, 75.8, 75.2, 75.1, 73.6, 68.1, 57.3.

Methyl 3,4,6-tris-O-(tert-butyldimethylsilyl)-2-deoxy-2-iodo-α-D-mannopyranoside (**8c**) *[23a].*—Tris-*O*-(*tert*-butyldimethylsilyl)-D-glucal (0.58 g, 1.2 mmol) was dissolved in 10% methanolic propionitrile (15 mL), the solution was cooled to −70° C and *N*-iodosuccinimide (0.29 g, 1.3 mmol) was added in a single portion. The reaction mixture stirred at −70 °C for 6 h, then was slowly warmed to room temperature (4 h) and was stirred overnight (16 h). The reaction mixture was diluted with water (25 mL) and extracted with Et_2O (3 × 25 mL). The combined Et_2O extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a mixture of two diastereoisomers (**8**) (0.62 g, 92%). Column chromatography (SiO_2, 9:10 Et_2O–hexanes) afforded **8c** (0.15 g, 22%) as a solid: $[\alpha]_D$ +19.70° (*c* 0.66, $ChCl_3$); IR (NaCl): 2928, 2857 cm^{-1}; ^1H NMR: δ 4.94 (d, 1 H, *J* 3 Hz); 4.30 (t, 1 H, *J* 3.3 Hz), 3.85–3.69 (m, 4 H), 3.67–3.46 (m, 1 H), 3.35 (s, 3 H), 0.95 (s, 9 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR: δ 123.3, 101.6, 77.4, 71.1, 62.5, 55.1, 26.5, 26.4, 26.3, 26.2, 26.1, 25.8, 18.5, 18.4, 18.1, −3.1, −4.1, −4.3, −4.8, −5.1; Anal. Calcd for $C_{25}H_{55}IO_5$: C, 46.49; H, 8.43. Found: C, 46.55; H, 8.40.

General procedure for base-catalyzed ring contraction reactions.—The halohydrin or methoxyhalide (0.5 mmol) and cesium carbonate (0.5 mmol) was dissolved in anhydrous methanol (8 mL) and stirred at 5 °C, or heated at reflux until TLC indicated that the starting material had been consumed. The cooled reaction was diluted with water (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixtures were analyzed by ^1H NMR spectroscopy. The individual reaction products were purified by column chromatography (SiO_2; 1:9–1:3 Et_2O–hexanes).

Reaction of trimethyl bromohydrins with cesium carbonate in methanol.—To a solution of bromohydrins **1a–d** (230 mg, 0.8 mmol, manno:gluco, 3.5:1) in anhydrous methanol (6 mL) at 5 °C was added cesium carbonate (263 mg, 0.8 mmol). The solution was maintained at 5 °C for 4 h, and then it was gradually warmed to room temp. (3 h) and stirred overnight (15 h). The reaction mixture was worked up as described above. Chromatography gave methyl 3,4,6-tri-*O*-methyl-α-D-mannopyranoside (**11b**) [10] (41%), methyl 3,4,6-tri-*O*-methyl-α-D-gluopyranoside (**11a**) [10] (10%), and 2,5-anhydro-3-deoxy-4,6-di-*O*-methyl-*aldehydo*-D-*erythro*-hex-2-enitol (**13**) (6%). an oil; IR (NaCl): 3102, 2934, 2828, 1702 cm^{-1}; ^1H NMR: δ 9.23 (s, 1 H), 6.10 (d, 1 H, *J* 2.7 Hz), 4.71 (dd, 1 H, *J* 2.7, 4.7 Hz), 4.65 (m, 1 H), 3.59 (dd, 1 H, *J* 4.8, 10.5 Hz), 3.49 (dd, 1 H, *J* 4.8, 10.5 Hz), 3.39 (s, 3 H), 3.37 (s, 3 H); ^{13}C NMR: δ 182.3, 157.7, 115.2, 85.7, 83.8, 71.8, 59.4, 55.8; MS (DP/EI) *m/z* (rel. intensity): 172 (M^+, 4), 127 (31), 111 (28), 53 (24), 45 (100).

Reaction of tribenzyl bromohydrins with cesium carbonate in methanol.—A mixture of tribenzyl bromohydrins **2a–d** (413 mg, 0.8 mmol) was reacted with cesium carbonate (262 mg, 0.8 mmol) in methanol (6 mL) as above to give methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**12a**) [10,26] (40 mg, 0.09 mmol, 11%), methyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**12b**) [10,27] (163 mg, 0.3 mmol, 44%) and 2,5-anhydro-3-deoxy-4,6-*O*-dibenzyl-*aldehydo*-

D-*erythro*-hex-2-enitol (**14**) (40 mg, 0.09 mmol, 11%): IR (NaCl, neat): 3029, 2856, 1696, 1618 cm^{-1}; ^1H NMR: δ 9.50 (s, 1 H), 7.37–7.25 (m, 10 H), 6.02 (d, 1 H, *J* 2 Hz), 4.90 (dd, 1 H, *J* 3.0, 3.9 Hz), 4.79–4.73 (m, 1 H), 4.69 (br s, 1 H), 4.58–4.53 (m, 2 H). 3.64 (dd, 1 H, *J* 4.7, 10.3 Hz), 3.51 (dd, 1 H, *J* 4.7, 10.3 Hz); ^{13}C NMR: δ 182.3, 157.6, 137.5, 137.45, 128.5, 128.4, 128.3, 127.95, 127.9, 127.8, 127.7, 126.9, 116.1, 86.3, 82.3, 73.6, 70.9, 69.2; MS (DP/EI) *m/z* (rel. intensity): 324 (M^+, 100), 295 (31), 233 (97), 92 (67).

*Reaction of 3,4,6-tris-*O-(tert-*butyldimethylsilyl)-2-deoxy-2-iodo-α-*D-*mannopyranoside* (**5c**) *with cesium carbonate in refluxing methanol.*—Iodohydrin **5** (0.18 g, 0.3 mmol) was reacted with cesium carbonate (0.09 g, 0.3 mmol) in methanol (5 mL) at reflux to give a mixture of aldehydes **21a**, **21b**, **15** (0.10 g, 99%). Column chromatography (SiO_2, 9:1 hexanes–Et_2O) afforded 2,5-anhydro-3-deoxy-4,6-bis-*O*-(*tert*-butyldimethylsilyl)-*aldehydo*-D-*erythro*-hex-2-enitol (**15**) (75%) as an oil: $[\alpha]_D$ +7.63° (*c* 0.59, $CHCl_3$); IR (NaCl, neat): 2956, 2930, 2858, 1706 cm^{-1}; ^1H NMR: δ 9.55 (s, 1 H), 5.98 (d, 1 H, *J* 2.7 Hz), 5.20 (dd, 1 H, *J* 3 Hz), 4.52–4.48 (m, 1 H), 3.85 (d, 1 H, *J* 11.1, 4.2 Hz), 3.69 (dd, 1 H, *J* 11.1, 6.0 Hz), 0.95 (s, 9 H), 0.92 (s, 9 H), 0.17 (s, 6 H), 0.11 (s, 3 H), 0.85 (3s, 12 H); ^{13}C NMR: δ 182.5, 156.9, 118.9, 89.9, 75.6, 62.3, 25.9, 25.8, 18.4, −4.21, −4.35, −5.26.

*Reaction of 3,4,6-tris-*O-(tert-*butyldimethylsilyl)-2-deoxy-2-iodo-α-*D-*mannopyranoside* (**5c**) *with cesium carbonate in methanol at 5 °C.*—Iodohydrin **5** (0.16 g, 0.25 mmol) was reacted with cesium carbonate (0.08 g, 0.25 mmol) in methanol (5 mL) at 5 °C to give a mixture of 2,5-anhydro-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-*aldehydo*-D-glucose (**21a**) and 2,5-anhydro-3,4-6-tris-*O*-(*tert*-butyldimethylsilyl)-*aldehydo*-D-mannose (**21b**) (0.115 g, 88%). IR (NaCl): 2929, 2859, 1737 cm^{-1}; ^1H NMR: δ 9.64 (d, *J* 2.1 Hz) (major), 9.58 (d, *J* 1.2 Hz) (minor), 4.37 (m, 1 H), 4.28 (m, 1 H), 4.16 (m, 1 H), 4.02 (m, 1 H), 3.75 (m, 2 H); ^{13}C NMR (major only): δ 202.6, 89.0, 86.4, 81.2, 79.0, 63.4, 26.0, 25.8, 25.7, 18.4, 18.2, −4.40, −4.43, −4.53, −5.13, −5.19. HRMS (FAB): Calcd: 511.3283; Found: 511.3270 (Δ mmu 1.3).

General procedure for the thermal ring contraction reaction.—A solution of halohydrin, methoxy halide, or 2-*O*-triflate (0.5 mmol) in Me_2NCHO (8 mL), pyridine (5 mmol) and deionized water (50 mmol) was placed in an oil bath, which had been pre-heated to 160 °C. After the allowed time period, the mixture was cooled to room temp, and then was diluted with water (25 mL) and was extracted with EtOAc (3 × 25 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude reaction mixtures were analyzed by ^1H NMR spectroscopy.

*Thermal ring contraction reaction of 3,4,6-tris-*O-(tert - *butyldimethylsilyl) - 2 - deoxy - 2 - iodo - α -* D - *mannopyranoside* (**5c**).—Iodohydrin **5c** (0.26 g, 0.4 mmol), pyridine (0.3 mL, 4.2 mmol), and water (0.6 mL, 34 mmol) in Me_2NCHO (8 mL) gave a mixture of 2,5-anhydro-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-*aldehydo*-D-glucose (**21a**) and 2,5-anhydro-3,4-6-tris-*O*-(*tert*-butyldimethylsilyl)-*aldehydo*-D-mannose (**21b**) (0.18 g, 85%): Attempts to isolate the individual aldehydes from the mixture by column chromatography using either SiO_2 or neutral alumina resulted in decomposition. The mixture (**21a,b**) was dissolved in MeOH (5 mL), and sodium borohydride (0.04 g, 1.0 mmol) was added in a single portion. After 1 h at room temp, the reaction mixture was diluted with water and was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Column chromatography (SiO_2; 4:1 hexanes–Et_2O) gave a mixture of 2,5-anhydro-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-D-glucitol and 2,5-anhydro-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-D-mannitol (0.17 g, 98%): IR (NaCl, neat): 3461, 2930, 2858 cm^{-1}; ^1H NMR: δ 4.15–4.11 (m), 4.02–3.99 (m), 3.86–3.61 (m), 1.82 (br s), 0.89, 0.88, 0.87 (3s), 0.11, 0.09, 0.06 (3s); ^{13}C NMR: δ 86.6, 81.1, 79.5, 78.9, 63.6, 62.2, 26.1, 25.9, 25.8, −4.31, −4.41, −4.96, −5.23; HRMS (FAB) Calcd: 513.3439; Found: 513.3487 (Δ mmu 4.8); Anal. Calcd for $C_{24}H_{54}O_5Si_3$: C, 56.86; H, 10.74. Found: C, 56.82; H, 10.77. The alcohol mixture (**22a**, **22b**) (0.23 g, 0.5 mmol) was dissolved in THF (7 mL) and Ac_2O (1 mL, 11 mmol), and Bu_4NF (4.6 mL, 4.6 mmol) were added. The reaction was stirred overnight (18 h), then extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was suspended in pyridine (0.24 mL, 3.0 mmol) and additional Ac_2O (0.24 mL, 2.5 mmol) was added. The mixture was stirred overnight (18 h) at room temp, then diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with satd $CuSO_4$ (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the crude tetracetates (0.12 g). Column chromatography (SiO_2; 1:3 Et_2O–hexanes) gave an inseparable mixture (3:1) of 1,3,4,6-tetra-*O*-

acetyl-2,5-anhydro-D-glucitol (**22a**) [16] and 1,3,4,6-tetra-*O*-acetyl-2,5-anhydro-D-mannitol (**22b**) (3:1; 0.05 g; 30%): IR (neat): 2929, 1747 cm^{-1}; ^1H NMR: δ 5.32 (dd, *J* 3.9, 1.5 Hz) (H-3; **22a**), 5.16 (d, *J* 1.8 Hz) (H-3; **22b**).

*Oxidation of 3,4,6-tris-*O-(tert-*butyldimethylsilyl)-2-deoxy - 2 - iodo - α - D - mannopyranoside* (**5c**) *with pyridinium dichromate.*—Iodohydrin **5c** (0.15 g, 0.24 mmol) was dissolved in freshly distilled CH_2Cl_2 (7 mL) and cooled to 5 °C in an ice-water bath. Pyridinium dichromate (0.098 g, 0.26 mmol, 1.1 equiv) was added, and the reaction was stirred for 24 h at room temp. The reaction mixture was diluted with additional CH_2Cl_2 (15 mL) and washed with 1 M HCl (5 mL) and satd $NaHCO_3$ (15 mL). The organic layer was dried (Na_2SO_4), filtered through Celite, and concentrated *in vacuo*. Chromatography (SiO_2, gradient hexane to 10:1 hexanes–Et_2O) gave the lactone **23** as a white crystalline solid (0.084 g, 0.13 mmol, 56%); mp 89–90 °C (MeOH); IR (KBr): 2927, 2854, 1739 cm^{-1}; ^1H NMR ($CDCl_3$): 5.30 (dd, 1 H, *J* 3, 1 Hz), 4.26 (m, 1 H), 4.13 (dd, 1 H, *J* 3.2 Hz), 4.02, (dd, 1 H, *J* 3.6, 2.6 Hz), 3.86 (d, 1 H, *J* 2.2 Hz), 3.84 (d, 1 H, *J* 1 Hz), 0.94 (s, 9 H), 0.91 (s, 18 H), 0.25 (s, 3 H), 0.16 (s, 3 H), 0.14 (s, 6 H), 0.9 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$): 165.1, 86.0, 81.5, 77.6, 68.3, 62.7, 26.1, 26.0, 25.8, 18.5, 18.3, 17.9, −3.5, −4.3, −4.5, −4.54, −5.1, −5.2. Anal. Calcd for $C_{24}H_{51}IO_5Si_3$: C, 45.70; H, 8.15. Found: C, 45.93; H, 8.22.

*Oxidation of 3,4,6-tris-*O-(tert-*butyldimethylsilyl)-2-deoxy-2-iodo-α-*D-*mannopyranoside* (**5c**) *using tetra-n-propylammonium tetra-oxoruthenate.*—To a solution of the iodohydrin **5c** (0.20 g, 0.32 mmol) in CH_2Cl_2 (10 mL) at room temp was added dried, powdered 4 Å molecular sieves (100 mg), and 4-methylmorpholine *N*-oxide (56 mg, 0.47 mmol, 1.5 equiv). After 10 min at room temp, Pr_4NRuO_4 (11 mg, 0.031 mmol, 0.1 equiv) was added, and the reaction mixture was stirred for an additional 2.5 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and was washed with 5% sodium sulfite (10 mL) and brine (10 mL). Filtration through Celite and concentration *in vacuo* gave the pure lactone **23** (0.19 g, 0.3 mmol, 95%).

Reaction of iodolactone **23** *with sodium methoxide in methanol.*—To a solution of iodolactone **23** (50 mg, 0.079 mmol) in distilled methanol (1.5 mL) was added sodium methoxide in methanol (0.12 mmol, 1.5 equiv). The reaction was stirred for 1 h, then diluted with Et_2O (5 mL), washed water (5 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give the ester **24** (35 mg, 0.065 mmol, 83%) as an oil; IR (NaCl, neat): 2931, 2857, 1776, 1738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.71 (d, 1 H, *J* 3.4 Hz), 4.21 (brd d, 1 H, *J* 3.4), 4.18 (brd s, 1H), 3.94 (dd, 1 H, *J* 10.1, 5.4 Hz), 3.84 (dd, 1 H, *J* 9.7, 5.4 Hz), 3.75 (s, 3 H), 3.71 (dd, 1 H, *J* 9.8, 9.8 H z), 0.90 (s, 18 H), 0.86 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$): 169.6, 88.4, 81.8, 80.1, 76.4, 63.2, 51.7, 26.0, 25.8, 25.6, 18.4, 17.9, 17.8, −4.4, −4.6, −5.2, −5.3, −5.4. Anal. Calcd for $C_{25}H_{54}O_6Si_3$: C, 56.13; H, 10.17. Found: C, 56.40; H, 10.23.

Reaction of iodolactone **23** *with potassium carbonate.*—To a solution of iodolactone **23** (300 mg, 0.475 mmol) in distilled methanol (20 mL) was added potassium carbonate (197 mg, 1.43 mmol, 3 equiv). The reaction was stirred for 1.3 h at room temp and was then diluted with Et_2O (15 mL), washed with distilled water (15 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give the ester **24** (24 mg, 0.38 mmol, 80%).

*Methyl 4,7-anhydro-5,6,8-tris-*O-(tert-*butyldimethylsilyl) - 2, 3 - dideoxy* - D - arabino - *oct - 2(*E*) - enoate* (**25**).—Aldehydes **21a** and **21b** (0.03 g, 0.06 mmol) were dissolved in anhydrous CH_3CN (4 mL), and methyl (triphenylphosphoranylidene) acetate (0.02 g, 0.06 mmol) was added as a single portion to the reaction mixture. The mixture was stirred for 20 min, and was then concentrated *in vacuo*. Column chromatography (neutral alumina (BA I; 80–200 mesh); 9:1 hexanes–Et_2O) gave a mixture of olefins **25a–d** (0.03 g, 79%): 4 diastereoisomers, 3:1 trans:cis. Repeated chromatography gave the major diastereoisomer **25a** as an oil: $[\alpha]_D$ +7.94° (*c* 0.34, $CHCl_3$); IR (NaCl, neat): 2930, 2858, 1731 cm^{-1}; ^1H NMR: δ 6.90 (dd, 1 H, *J* 15, 5.7 Hz), 6.09 (dd, 1 H, *J* 15.6, 1.8 Hz), 4.64 (m, 1 H), 4.12 (s, 1 H), 3.93–3.78 (m, 2 H), 3.73–3.61 (m, 2 H), 3.72 (s, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.84 (s, 9 H), 0.09 (s, 6 H), 0.06 (s, 6 H), 0.012 (s, 3 H), 0.009 (s, 3 H); ^{13}C NMR: δ 160.8, 144.6, 122.3, 87.8, 81.1, 80.5, 79.6, 63.7, 51.5, 26.1, 26.0, 25.95, 25.92, 25.86, 25.8, 25.72, 25.7, 18.5, −4.37, −4.49, −4.52, −4.89, −5.12, −5.19; Anal. Calcd for $C_{27}H_{56}O_6Si_3$: C, 57.81; H, 10.06. Found: C, 57.71, H, 10.03.

*Methyl 4,7-anhydro-6,8-bis-*O-(tert-*butyldimethylsilyl)-2,3,4,5-tetradeoxy-*D-erythro-*octa-2,4-dienoate* (**26**).—To a solution of aldehyde **15** (0.09 g, 0.2 mmol) in CH_3CN (5 mL), methyl (triphenylphophorylidene) acetate (0.08 g, 0.2 mmol) was added in a single portion. The mixture was stirred at room temp, and the course of the reaction was followed by

TLC (SiO_2, 9:1 hexanes–Et_2O) until consumption of aldehyde was indicated (1 h, 20 min). The reaction mixture was concentrated *in vacuo*. Flash column chromatography (SiO_2, 95:5 hexanes–Et_2O) gave methyl 4,7-anhydro-6,8-bis-(*tert*-butyldimethylsilyl)-D-*erythro*-octa-2(*E*),4(*Z*)-dienoate (**26a**) (0.07 g, 74%): IR (NaCl, neat): 2929,2858, 1728, 1650, 1600 cm^{-1}; ^1H NMR: δ 7.10 (d, 1 H, *J* 15.6 Hz), 6.22 (d, 1 H, *J* 15.6 Hz), 5.32 (d, 1 H, *J* 2.7 Hz), 4.97 (t, 1 H, *J* 3.0 Hz), 4.39–4.35 (m, 1 H), 3.76 (s, 3 H), 3.82–3.72 (m, 1 H), 0.90, 0.89, 0.88 (3s, 18 H), 0.09, 0.08, 0.07, 0.04 (4s, 12 H); ^{13}C NMR: δ 166.8, 155.5, 132.5, 121.0, 110.2, 89.5, 76.7, 62.9, 51.7, 26.5, 25.3, 26.2, 26.1, 26.0, 25.9, 25.8, 25.7, 25.6, 18.4, −4.13, −4.26, −5.20, −5.22; MS (DP/CI) *m/z* (rel. intensity): 429 [(M + H^+), 7], 239 (43), 165 (100), 89 (31).

*X-ray structure determination for 2-deoxy-2-iodo-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-α-*D*-mannopyranose* (**5c**).—Recrystallization of **5c** from methanol at 0 °C gave colorless needle-shaped crystals suitable for X-ray crystallographic studies. A crystal of dimensions 0.30 × 0.10 × 0.06 mm was mounted on a glass fiber in random orientation. Preliminary examination and data collection were performed using a Siemens SMART Charge Coupled Device (CCD) Detector system single-crystal X-ray diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 A) equipped with a sealed tube X-ray source (50 KV X 40 mA) at 25 °C. Preliminary unit cell constants were determined with a set of 45 narrow frames (0.3° in ω) scans. A total of 1325 frames of intensity data were collected with a frame width of 0.3° in ω and counting time of 10 s/frame at a crystal to detector distance of 3.891 cm. The double pass method of scanning was used to exclude any noise. Data was collected at room temperature for a total time of 13 h. The collected frames were integrated using an orientation matrix determined from the narrow frame scans. SMART software package (Siemen's Analytical X-Ray, Madison, WI, 1994) was used for data collection as well as frame integration. Analysis of the integrated data did not show any decay. Final cell constants were determined by a global refinement of *xyz* centroids of 1426 reflections ($\theta < 14.0°$). The integration process yielded 6137 reflections of which 3179 ($2\theta < 40°$) were independent reflections. Crystal data and intensity data collection parameters are listed in Table 3.

Structure solution and refinement were carried out using the SHELXTL-PLUS (5.03) software package (G.M. Sheldrick, Siemens Analytical X-Ray Division, Madison, WI, 1995). The structure was solved by Direct Methods and refined successfully in the space group C_2. Full matrix least-squares refinement was carried out by minimizing $\Sigma w(F_o^2 - F_c^2)^2$. I, Si and O atoms were refined anisotropically, whereas C atoms were refined isotopically to convergence. The hydrogen atoms were treated using appropriate riding model (AFIX m3). The final residual values were $R(F) = 13.5\%$ for 2072 observed reflections [$I > 2\sigma(I)$] and $wR(F^2) = 34.8\%$; $s = 1.59$ for all data. The absolute structure was confirmed by Flack's method ($x = 0.16$). Structure refinement parameters are listed in Table 3. The atomic coordinates for the non-hydrogen atoms and the geometrical parameters have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

Table 3
Crystal data and structure refinement

Empirical formula	$C_{24}H_{53}IO_5Si_3$
Formula weight	632.83
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C_2
Unit cell dimensions	a = 29.2795(4) Å, alpha = 90°
	b = 7.4239(3) Å, beta = 122.321(5)°
	c = 18.8529(7) Å, gamma = 90°
Volume, Z	3463.1(2) Å^3, 4
Density (calculated)	1.214 Mg/m^3
Absorption coefficient	1.055 mm^{-1}
$F(000)$	1328
Crystal size	0.30 × 0.10 × 0.06 mm
θ range for data collection	1.28 to 20.00°
Limiting indices	$-21 \le h \le 32$, $-8 \le k \le 8$, $-21 \le l \le 19$
Reflections collected	6137
Independent reflections	3179 (R_{int} = 0.1791)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3082/1/178
Goodness-of-fit on F^2	1.589
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.1352, $wR2$ = 0.2851
R indices (all data)	$R1$ = 0.2017, $wR2$ = 0.3486
Absolute structure parameter	0.16(11)
Largest diff. peak and hole	1.190 and −0.541 eÅ^{-3}

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References

[1] (a) G. Trummlitz and J.G. Moffatt, *J. Org. Chem.*, 38 (1973) 1841–1845; (b) C.R. Bertozzi, P.D. Hoeprich, Jr., and M.D. Bednarski, *J. Org Chem.*, 57 (1992) 6092–6094; (c) C.R. Bertozzi, D.G. Cook, W.R. Kobertz, F. Gonzales-Scarano, and M.D. Bednarski, *J. Am Chem. Soc.*, 114 (1992) 10639; (d) H. Dietrich and R.R. Schmidt, *Carbohydr. Res.*, 250 (1993) 161; (e) S. Hanessian, P.C. Tyler, G. Demailly, and Y. Chapleur, *J. Am. Chem. Soc.*, 103 (1981) 6243–6246; (f) J.G. Buchanan, *Prog. Chem. Nat. Prod.*, 44 (1983) 243.

[2] (a) A. Dondoni and M.-C. Scherrmann, *J. Org. Chem.*, 59 (1994) 6404–6412; (b) H. Albrecht, D.B. Repke, and J.G. Moffatt, *J. Org. Chem.*, 38 (1973) 1836–1840; (c) S.A. Babirad, Y. Wang, and Y. Kishi, *J. Org. Chem.*, 52 (1987) 1370–1372; (d) Y. Wang, S.A. Babirad, and Y. Kishi, *J. Org. Chem.*, 57 (1992) 468–481; (e) T. Haneda, P.G. Goekjian, S.H. Kim, and Y. Kishi, *J. Org. Chem.*, 57 (1992) 490–498; (f) W.R. Kobertz, C.R. Bertozzi, and M.D. Bednarski, *Tetrahedron Lett.*, 33 (1992) 737–740; (g) C.R. Bertozzi, and M.D. Bednarski, *Tetrahedron Lett.*, 33 (1992) 3109–3112.

[3] H. Redlich, *Angew. Chem. Int. Ed. Engl.*, 33 (1994) 1345–1347.

[4] (a) G. Ledderhose, *Z. Physiol. Chem.*, 4 (1880) 139; (b) B.C. Bera, A.B. Foster, and M. Stacey, *J. Chem. Soc.*, (1956) 4531–4535; (c) D. Horton and K.D. Philips, *Carbohydr. Res.*, 30 (1973) 367–374; (d) A.B. Foster, *Chem. Ind.*, (1955) 627; (e) J. Defaye, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 181–228; (f) J. Defaye, *Bull. Soc. Chim. Fr.*, 1964, 999–1002; (g) P.A. Levene, *J. Biol. Chem.*, 39 (1919) 69–76; (h) *ibid.*, 59 (1924) 135–139.

[5] For some examples see: (a) J.M. Sugihara and D.L. Schmidt, *J. Org. Chem.*, 26 (1961) 4612–4615; (b) P. Brigl and H. Grüner, *Chem. Ber.*, 66 (1933) 1945–1949; (c) R.C. Hockett, M. Zief, and R.M. Goepp, *J. Am. Chem. Soc.*, 68 (1946) 935–937; (d) R.C. Hockett, M. Conley, M. Yusem, and R.I. Mason, *J. Am. Chem. Soc.*, 68 (1946) 922–926; (e) S. Soltzberg, R.M. Goepp, and S. Freudenberg, *J. Am. Chem. Soc.*, 68 (1946) 919–921.

[6] (a) A. Kirschning, *Liebigs Ann. Chem.* (1995) 2053–2056; (b) K.R. Wood and P.W. Kent, *J. Chem. Soc. (C)* (1967) 2422–2425; (c) A. Kaye, S. Neidle, and C.B. Reese, *Tetrahedron Lett.* (1988) 29, 1841–1844.

[7] (a) R.U. Lemieux and B. Fraser-Reid, *Can. J. Chem.*, 42 (1964) 539–546; (b) R.U. Lemieux and B. Fraser-Reid, *Can. J. Chem.*, 42 (1964) 547–549.

[8] G. Arpad, *Magy. Kem. Foly.*, 68 (1962) 211–212.

[9] (a) H.H. Baer, F.H. Mateo, and L. Siemsen, *Carbohydr. Res.*, 187 (1989) 67–92; (b) A.B. Charette and B. Côté, *J. Org. Chem.*, 58 (1993) 933–936; (c) A.B. Charette, J. Marcoux, and B. Côté, *Tetrahedron Lett.*, 49 (1991) 7215–7218; (d) G.W.J. Fleet and L.C. Seymour, *Tetrahedron Lett.*, 28 (1987) 3015–3018; (e) F.M. El Sayed Ahamed, S. David, and J.-M. Vatele, *Carbohydr. Res.*, 155 (1986) 19–31; (f) A. Grouiller, H. Bazin, and C. Gagnieu, *Tetrahedron Lett.*, 23 (1982) 2559–2562. For reviews, see: D.H. Bal and F.W. Parrish, *Adv. Carbohydr. Chem. Biochem.*, 24 (1969) 139–197; L. Hough and A.C. Richardson, in W. Pigman and D. Horton (Eds.), *The Carbohydrates*, 2nd ed., Vol. 1A, Academic Press, New York, 1972, pp 140–146; J.G. Buchanan, in G. O Aspinall (Ed.), *Carbohydrates*, MTP International Review of Science, Vol. 7, 1973, pp 37–70.

[10] (a) C.H. Marzabadi and C.D. Spilling, *J. Org. Chem.*, 58 (1993) 3761–3766; (b) C.H. Marzabadi, C.D. Spilling, and L.M. Tyler, *Tetrahedron*, 50 (1994) 6783–6796.

[11] C.H. Marzabadi, *Reactions of Glucal Halohydrins*, Ph.D. dissertation, University of Missouri-St. Louis, 1994.

[12] (a) T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, 1981; (b) K.K. Ogilvie, S.L. Beaucage, D.W. Entwistle, E.A. Thompson, M.A. Quillam, and J.B. Westmore, *J. Carbohydr. Nucleosides. Nucleotides.*, 3 (1976) 197–227; (c) K.K. Ogilvie, *Can. J. Chem.*, 51 (1973) 3799–3807.

[13] R.L. Halcomb and S.J. Danishefsky, *J. Am. Chem. Soc.*, 111 (1989) 6661–6666.

[14] W.R. Roush, K. Briner, and D.P. Sebesta, *Synlett*, (1993) 264–266.

[15] S.L. Beaucage and K.K. Ogilvie, *Tetrahedron Lett.*, (1977) 1691–1694.

[16] T.A.W. Koerner, R.J. Voll, and E.S. Younathan, *Carbohydr. Res.*, 59 (1977) 403–416.

[17] a) J.C. Estevez, A.J. Fairbanks, K.Y. Hsia, P. Ward, and G.W.J. Fleet, *Tetrahedron Lett.*, 35 (1994) 3361–3364; (b) J.R. Wheatley, A.R. Beacham, P.M. De Q. Lilley, D.J. Watkin, and G.W.J. Fleet, *Tetrahedron: Asymmetry*, 5 (1994) 2523–2534.

[18] (a) S.J. Mantell, P.S. Ford, D.J. Watkin, G.W.J. Fleet, and D. Brown, *Tetrahedron Lett.*, 33 (1992) 4503–4506; (b) J.C. Estevez, M.D. Smith, A.L. Lane, S. Crook, D.J. Watkin, G.S. Besra, P.J. Brennan, R.J. Nash, and G.W.J. Fleet, *Tetrahedron: Asymmetry*, 7

(1996) 387–390; (c) J.C. Estevez, M.D. Smith, M.R. Warmold, G.S. Besra, P.J. Brennan, R.J. Nash, and G.W.J. Fleet, *Tetrahedron: Asymmetry*, 7 (1996) 391–394.

[19] R. Lopez and A. Fernandez-Mayoralas, *J. Org. Chem.*, 59 (1994) 737–745.

[20] (a) W.P. Griffith, S.V. Ley, G.P. Whitcombe, and A.D. White, *J. Chem. Soc., Chem. Commun.*, (1987) 1625–1627; (b) R. Benhaddou, S. Czernecki, W. Farid, G. Ville, J. Xie, and A. Zegar, *Carbohydr. Res.*, 260 (1994) 243–250.

[21] For a review see: Y.A. Zhdanov, Y.E. Alexeev, and V.G. Alexeev, *Adv. Carbohydr. Chem. Biochem.*, 27 (1972) 227–299.

[22] K.M. Sun and B. Fraser-Reid, *Synthesis*, (1982) 28.

[23] (a) S. Moutel and J. Prandi, *Tetrahedron Lett.*, 35 (1994) 8163–8166; (b) T. Hosoya, Y. Ohashi, T. Matsumoto, and K. Suzuki, *Tetrahedron Lett.*, 37 (1996) 663–666; (c) M.A. Tius and J. Busch-Petersen, *Tetrahedron Lett.*, 35 (1994) 5181–5184.

[24] (a) N.S. Bhacca and D. Horton, *J. Am. Chem. Soc.*, 89 (1967) 5993–5994; (b) P.L. Durette and D. Horton, *J. Chem. Soc., Chem. Commun.*, (1969) 516–518.

[25] B. Classon, P.J. Garegg, and B. Samuelsson, *Can. J. Chem.*, 59 (1981) 339–343.

[26] (a) V.K. Handa, J.J. Barlow, and K.L. Matta, *Carbohydr. Res.*, 76 (1979) C-1; (b) F.R. Seymour, *Carbohydr. Res.*, 34 (1974) 65–70.

[27] G. Ekborg, B. Lindberg, and J. Lönngren, *Acta Chem. Scand.*, 26 (1972) 3287–3292.