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Rearrangement of Carbohydrate Epoxides to Acetals Using a Hemiacetal Neighbouring Group

Steffen Jacobsen and Frank Sløk

Department of Organic Chemistry, The Technical University of Denmark, DK-2800 Lyngby, Denmark

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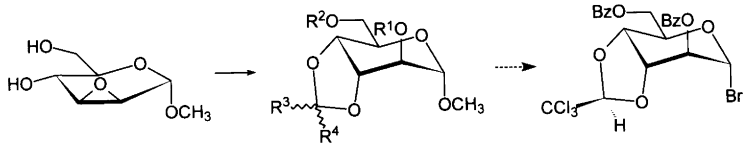
When glycosides containing an epoxide functionality are treated with a non-enolisable aldehyde and sodium hydride, the free hydroxy groups are converted into hemiacetal salts, which subsequently open the epoxide ring to give sugar acetals. The reaction was carried out on manno-, gulo- and galacto-pyranosides, manno-, gulo-, altro- and galacto-1,6-anhydropyranoses and lyxo- and arabino-pyranosides. It was found that the *trans*-diaxial epoxide opening took place between vicinal *trans*-substituted hydroxy epoxides and formaldehyde, 2,2-dimethylpropanal, benzaldehyde and chloral, if no 1,3-diaxial substituents were present. Ketones did not react. Methyl trifluoroacetate did react to form an orthoester derivative, but other non-enolisable esters, benzyl 2,2-dimethylpropanoate, methyl benzoate and trichloroacetate were unreactive.

In general the preparation of carbohydrates protected with acetal groups takes place under acidic conditions. The single exception to this general rule is Garegg's base-promoted condensation of alkylidene halides with unprotected carbohydrate hydroxy groups.[1] The present paper describes a method for the preparation of carbohydrate acetals under alkaline conditions, utilising the neighbouring-group participation from a hemiacetal salt in the opening of epoxides. McCombie and Metz[2] have shown that 2,3-epoxy alcohols react with paraformaldehyde and potassium or caesium carbonate at room temperature in acetonitrile to give 1,3-dioxolanes. Other non-enolisable aldehydes (chloral, *p*-nitrobenzaldehyde) did not give useful amounts of substituted dioxolanes under these mild conditions. Myers and Widdowson[3] have reported incomplete conversion when attempting to use this reaction on slightly more complex substrates.

A number of experiments were carried out using the easily available methyl 2,3-anhydro-α-D-mannopyranoside[4] (**1**) as a model compound (Scheme 1). When **1** was treated with paraformaldehyde and anhydrous potassium carbonate a crude product was obtained,[2] which consisted of two parts of recovered starting material and one part of a product showing two singlets, at δ 4.92 and 5.15, in the ^{1}H NMR spectrum, indicating that a formaldehyde acetal (**2a**) had been formed. When the base was changed to caesium carbonate, this product was formed exclusively, and if sodium hydride was used, the time for complete conversion into the methylene compound could be reduced from 20 to 1 h at room temperature. Although the product prepared in this manner could be obtained in 70–80% yield as the benzoate, varying amounts of by-products with an NMR spectrum very similar to that of the main product, but with additional absorptions in the



1 **2h**

2a: $R^1 = R^2 = R^3 = R^4 = H$
2b: $R^1 = R^2 = Bz$, $R^3 = R^4 = H$
2c: $R^1 = Bz$, $R^2 = CH_2OBz$, $R^3 = R^4 = H$
2d: $R^1 = R^2 = Bz$, $R^3 = C_6H_5$, $R^4 = H$
2e: $R^1 = R^2 = Bz$, $R^3 = CCl_3$, $R^4 = H$
2f: $R^1 = R^2 = Bz$, $R^3 = CF_3$, $R^4 = OCH_3$
2g: $R^1 = R^2 = Bz$, $R^3 = CH_3$, $R^4 = H$
2i: $R^1 = R^2 = H$, $R^3 = CCl_3$, $R^4 = H$

Scheme 1.

range δ 5.6–5.7, were observed. The extra absorptions indicate that the by-products are derived from formaldehyde hemiacetals of the primary product. Variations in the amount of by-product formed under similar reaction conditions are probably due to the heterogeneous nature of the reaction. Use of 1,3,5-trioxane or formaldehyde hydrogensulfite in place of the paraformaldehyde gave only a very low conversion. A change of solvent to pyridine caused the reaction mixture to become homogeneous, and the longer reaction time required (15–20 h) allowed the reaction to be run to completion without any of the by-products resulting from conversion of the primary product into hemiacetals (e.g. **2c**). The structure of the product, methyl 3,4-*O*-methylene-α-D-altropyranoside (**2a**), was deduced from the ^{1}H NMR spectra by comparison of **2a** with its benzoate (**2b**), giving the location of the acetal as 3,4, and from hydrolysis to 1,6-anhydro-β-D-altropyranose establishing the carbohydrate configuration as *altro*.

When the reaction conditions developed here were used, the acetalisation reaction could be extended to other non-enolisable aldehydes. Reaction with benzaldehyde gave 66% of methyl 2,6-di-*O*-benzoyl-3,4-*O*-benzylidene-α-D-altropyranoside[5] (**2d**) accompanied by a small amount of methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-idopyranoside. The latter product could result from base-catalysed rearrangement of the anhydromannoside **1** to methyl 3,4-anhnydro-α-D-altroside[4] and subsequent acetalisation from a 6-*O*-hemiacetal. The potential product resulting from epoxide opening by a 2-*O*-hemiacetal of the anhydro-altroside was not observed. Preliminary experiments indicate that 2,2-dimethylpropanal reacts in a similar manner. Reaction with chloral under the same conditions is very slow, but runs to completion within 2 h when carried out in THF, giving 70% methyl 2,6-di-*O*-benzoyl-3,4-*O*-(2,2,2-trichloroethylidene)-α-D-altropyranoside (**2e**).

Extension of the acetalisation procedure to ketones was not possible. Hexachloroacetone did not react, and acetone gave only self-condensation products. Likewise, reaction with the non-enolisable esters, benzyl 2,2-dimethylpropanoate and methyl benzoate did not take place, but methyl trifluoroacetate reacted to give 70–80% of the epimeric orthoesters, methyl 2,6-di-*O*-benzoyl-3,4-(1-methoxy-2,2,2-trifluoroethylidene)-α-D-altropyranoside (**2f**), while ethyl trichloroacetate did not react.

The products obtained in high yield in the conversions of the manno-epoxide to various acetals, had a common property, namely a pronounced resistance to hydrolysis. The methylene-altroside **2a** was identified as the 1,6-anhydride and not as the methyl glycoside, because acid hydrolysis of the acetal and the glycoside proceeded at a comparable rate. Even after complete hydrolysis of the methyl glycoside, which required reflux for 30 min with trifluoroacetic acid–water, some methylene altrose remained, since after benzoylation 47% of 2-*O*-benzoyl-3,4-*O*-methylene-β-D-altropyranose was isolated in addition to 38% of the altrosan tribenzoate. The benzoylated trichloroacetaldehyde acetal **2e** showed no sign of hydrolysis after reflux with 50% aqueous acetic acid for 1 h, while reflux with trifluoroacetic acid containing 10% water for 1 h completely hydrolysed the methyl glycoside leaving a complex mixture containing at least four different chloral acetals. The orthoester, methyl 3,4-*O*-(1-methoxy-2,2,2-trifluoroethylidene)-α-D-altropyranoside, was resistant to hydrolysis with refluxing 50% aqueous acetic acid for 1 h, and the benzoate **2f** was not hydrolysed with 90% trifluoroacetic acid–water at room temperature after 6 days. This unusual resistance to hydrolysis makes most of these products a dead end from a synthetic point of view, except for the chloral acetal, which underwent reduction with tributylstannane to give the 3,4-ethylidene compound, a compound with normal

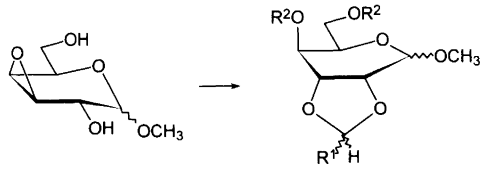
Table 1. Reaction between epoxy sugars and aldehydes to give cyclic acetals.

	Formaldehyde			Chloral		
Epoxide	*t*/h	Recv. (%)	Product (%)	*t*/h	Recv. (%)	Product (%)
Methyl 2,3-anhydro-α-D-mannopyranoside (**1**)	17[a]	0	76 (**2b**)	2	0	82 (**2e**)
	1[b]	0	71 (**2b**)			
Methyl 3,4-anhydro-α-D-galactopyranoside (α-**9**)				20	77	17 (α-**10b**)
Methyl 3,4-anhydro-β-D-galactopyranoside (β-**9**)	1	0	82 (β-**10a**)	19	0	82 (β-**10b**)
Methyl 2,3-anhydro-α-D-gulopyranoside (**7**)	1	25[c]	40 (**8a**)	20		56 (**8b**)
1,6 : 2,3-Dianhydro-β-D-gulopyranose	1	100[d]	0[d]	17	100[d]	0[d]
1,6 : 3,4-Dianhydro-β-D-altropyranose	15	84	0	15	>90[d]	<10[d]
1,6 : 3,4-Dianhydro-β-D-galactopyranose	21	17[e]		15	100[d]	0[d]
1,6 : 2,3-Dianhydro-β-D-mannopyranose				15	100[d]	0[d]
Methyl 2,3-anhydro-α-D-lyxopyranoside (**3a**)	2	9	82 (**4a**)	17	31	36 (**4c**)
Methyl 3,4-anhydro-α-D-arabinopyranoside (**5a**)	2	12	64 (**6a**)	17	19	74 (**6b**)
5,6-Anhydro-1,2-isopropylidene-α-D-glucofuranose	18	0[d]	0[d]			

[a] Pyridine. [b] Acetonitrile. [c] Rearrangement of **7** to methyl 3,4-anhydro-α-D-galactopyranoside took place (6%). [d] As judged from an NMR spectrum of the crude product. [e] Rearrangement of the starting material to 1,6 : 2,3-dianhydro-β-D-gulopyranose took place (69%).

acetal reactivity. The low reactivity of the chloral acetal includes resistance to oxidation with *N*-bromosuccinimide and survival of conversion of the methyl glycoside into the glycosyl bromide **2h** with hydrogen bromide in acetic acid, altogether making it a potential protecting group.

Application of the knowledge gained from the experiments with the anhydro-mannoside **1** to other anhydro-monosaccharides gave the results summarized in Table 1. In several cases a large amount of epoxide was recovered, but this result does not indicate that a higher yield could be obtained by increasing the reaction time or temperature. The acetalisation reaction is apparently in competition with the destruction or rearrangement of the epoxide and the products are unstable under the reaction conditions.



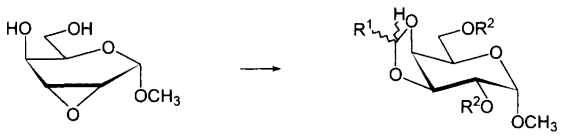
9

10a: $R^1 = H$, $R^2 = OBz$
10b: $R^1 = CCl_3$, $R^2 = H$

Scheme 2.

When the anhydro-galactosides α-**9**[6] and β-**9**[7] were treated with sodium hydride and chloral, the epoxide opening could take place from either the 2- or 6-position. However, no attack from the 6-position was observed, not even in the case of α-**9** where the attack from the 2-position is slow and most of the epoxide is recovered unchanged (Scheme 2). Similarly 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose[8] does not give any 3,5-dioxane-derivative when reacted. Both these results indicate that neighbouring group participation in the form of a six-membered ring is less favourable than the corresponding reaction involving a five-membered ring. The reaction between benzaldehyde and methyl 3,4-anhydro-α-D-altropyranoside mentioned earlier, indicates that the formation of *cis*-fused 1,3-dioxanes may be more favourable than formation of the *trans*-fused acetals which would result from the galactosides α-**9** and β-**9**.

Comparison of the anhydro-galactosides α-**9** and β-**9** reveals that the α-methoxy-group exerts a strong 1,3-diaxial interaction which hinders attack from the 2-position. The same kind of interaction is found in



7

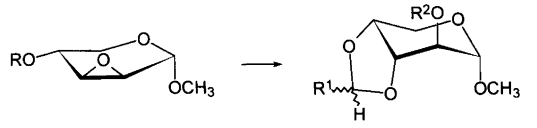
8a: $R^1, R^2 = H$
8b: $R^1 = CCl_3$, $R^2 = Bz$

Scheme 3.

1,6 : 2,3-dianhydro-β-D-gulopyranose[9] and 1,6 : 3,4-dianhydro-β-D-altropyranose and the result of attempted acetalisation was that the starting material was recovered.

Treatment of methyl 2,3-anhydro-α-D-gulopyranoside[10] **7** with sodium hydride and formaldehyde or chloral gave low yields of acetals and in the case of formaldehyde 25% of recovered starting material accompanied by 6% of rearranged epoxide, methyl 3,4-anhydro-α-D-galactopyranoside (α-**9**). The lower reactivity of **7**, compared with the previous examples, is probably due to the fact that the products, **8a** and **8b**, are a result of *trans*-diequatorial opening of the epoxide, a reaction path usually considered unfavourable compared with the *trans*-diaxial (Fürst–Plattner) opening (Scheme 3). The failure of 1,6 : 3,4-dianhydro-β-D-galactopyranose[11] and 1,6 : 2,3-dianhydro-β-D-mannopyranose[12] to react under these conditions may be ascribed to the same unfavourable mode of attack.

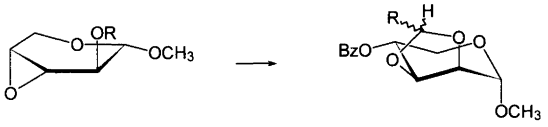
The pentosides, methyl 2,3-anhydro-α-D-lyxopyranoside[13] **3a** and methyl 3,4-anhydro-α-D-arabinopyranoside[13] **5a**, both adopt conformations[14,15] which allow a *trans*-diaxial attack without a change in conformation, and both react with formaldehyde and chloral to give acetals, **4** and **6**, in good yield (Schemes 4 and 5).



3a: R = H
3b: R = Bz

4a: $R^1, R^2 = H$
4b: $R^1 = H$, $R^2 = Bz$
4c: $R^1 = CCl_3$, $R^2 = Bz$

Scheme 4.



5a: R = H
5b: R = Bz

6a: R = H
6b: R = CCl_3

Scheme 5.

When the results obtained here are compared with previous results[9] on the opening of epoxides with neighbouring trichloroacetimidoyl groups, it is seen that the present reaction is slower and the detrimental effect of 1,3-diaxial interactions more pronounced. This difference may be ascribed to the larger steric requirements of the tetrahedral hemiacetal carbon atom next to the attacking oxygen atom as compared with the planar carbon atom next to the imidoyl nitrogen atom.

Experimental

Thin layer chromatography (TLC) was performed on silica gel PF_{254} (Merck). For preparative work, 1 mm

layers were used on 20 × 40 cm plates. Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. NMR spectra were recorded on Bruker HXE 90, WH 90, AC 200, AC 250 or AM 500 instruments. Flash chromatography was carried out as described by Still, Kahn and Mitra.[16]

*Methyl 2,6-di-*O*-benzoyl-3,4-*O*-methylene-*α*-*D*-altropyranoside* (**2b**). *In pyridine solution.* Methyl 2,3-anhydro-α-D-mannopyranoside[4] (**1**, 528 mg), imidazole (10 mg) and paraformaldehyde (300 mg) were suspended in pyridine (10 ml), 150 mg of a 50% suspension of NaH in mineral oil were added and the mixture was stirred at 25°C for 17 h during which period most of the paraformaldehyde dissolved and the mixture turned yellow. MeOH (10 ml) was added, the clear solution was evaporated to dryness, redissolved in MeOH and gaseous CO_2 was passed through for 5 min. The solution was evaporated to dryness, redissolved in $CHCl_3$, treated with charcoal and the solvents removed. Benzoylation with BzCl (1.0 ml) in pyridine (10 ml) gave 1184 mg of crude **2b**, which was crystallized from AcOEt–hexane to give 857 mg (69%) of **2b**, m.p. 112–113°C. Recrystallization from AcOEt–hexane gave m.p. 112–113°C, $[\alpha]_D^{25} + 62°$ (*c* 1.6, $CHCl_3$), anal. $C_{22}H_{22}O_8$: C, H, ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.80 (H1), 5.48 (H2), 4.25–4.29 (H3,H4), 4.15 (H5), 4.64 (H6), 4.55 (H6′), 4.98 and 5.26 (OCH_2O), 3.43 (OMe); $J_{12} = 2.6$ Hz, $J_{23} = 4.0$, $J_{56} = 2.5$, $J_{56'} = 6.6$, $J_{66'} = 12.0$. ^{13}C NMR (22.63 MHz, $CDCl_3$): δ 98.9 (C1), 74.9, 70.4, 69.9, 66.3 (C2–C5), 64.3 (C6), 55.4 (OMe), 95.2 (OCH_2O). Preparative TLC of the mother liquors in Et_2O–pentane (1 : 1) gave an additional 81 mg of **2b**, m.p. 110–112°C.

In acetonitrile solution. The reaction was carried out as described above, except that the imidazole was omitted, acetonitrile replaced pyridine as the solvent, and the reaction time was reduced to 1 h, to yield 876 mg (71%) of **2b**, m.p. 112–113°C. Preparative TLC gave an additional 97 mg of **2b**, m.p. 112°C followed by 81 mg of an impure fraction containing 85% of a compound, tentatively identified as methyl 2-*O*-benzoyl-6-*O*-benzoyloxymethyl-3,4-*O*-methylene-α-D-altropyranoside (**2c**) from the NMR spectra. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.73 (H1), 5.43 (H2), 4.21 (H3), 4.25 (H4), 3.96 (H5), 4.07 (H6), 3.98 (H6′), 5.19 and 4.92 (3,4-methylene), 5.64 and 5.63 (6-methylene); $J_{12} = 2.9$ Hz, $J_{23} = 4.6$, $J_{34} = 6.4$. ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 99.0 (C1), 74.9, 70.1, 70.0, 69.9 (C2–C5), 67.1 (C6), 55.5 (OMe), 95.1 and 89.9 (OCH_2O). Rechromatography in AcOEt–hexane did not improve the purity of this fraction.

*Methyl 3,4-*O*-methylene-*α*-*D*-altropyranoside* (**2a**). The benzoate **2b** (2.04 g) was debenzoylated with MeONa in MeOH overnight, neutralized with IR-120 (H^+) and crystallized from Et_2O–AcOEt to give 715 mg (71%) of **2b**, m.p. 65–67°C, $[\alpha]_D^{25} + 116°$ (*c* 1.3, $CHCl_3$), anal. $C_8H_{14}O_6$: C, H, ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.58 (H1), 3.88 (H2), 4.09 (H3), 4.21 (H4), 3.78 (H5), 3.90 (H6), 3.76 (H6′), 4.92 and 5.15 (OCH_2O), 3.46 (OMe); $J_{12} = 5.0$ Hz, $J_{23} = 7.1$, $J_{34} = 7.3$, $J_{45} = 8.8$, $J_{56} = 2.5$, $J_{56'} = 5.0$, $J_{66'} = 11.5$.

Hydrolysis of **2a**. Reflux of **2a** (282 mg) with CF_3COOH–H_2O (10 ml 9 : 1) for 30 min and evaporation with H_2O (2×) gave a mixture of two products. One of the components was identified by ^{13}C NMR spectroscopy as 1,6-anhydro-β-D-altropyranose,[17] the second component showed ^{13}C NMR (22.63 MHz, D_2O): δ 101.6, 96.0, 77.7, 76.8, 74.1, 72.0, 67.1. Benzoylation with BzCl (0.60 ml) in pyridine (10 ml) overnight, followed by preparative TLC in AcOEt–hexane (1 : 2) gave 249 mg (38%) of 1,6-anhydro-β-D-altropyranose tribenzoate[18] followed by 180 mg (47%) of 1,6-anhydro-2-*O*-benzoyl-3,4-*O*-methylene-β-D-altropyranose, as a syrup, $[\alpha]_D^{20} - 223°$ (*c* 1.7, $CHCl_3$), anal. $C_{14}H_{14}O_6$: C, H. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.63 (H1), 4.96 (H2), 4.54 (H3), 4.06 (H4), 4.92 (H5), 3.90 (H6,H6′), 5.25 and 5.08 (OCH_2O); $J_{12} = 2.5$ Hz, $J_{23} = 5.8$, $J_{34} = 6.3$, $J_{45} = 1.5$.

*Methyl 2,6-di-*O*-benzoyl-3,4-*O*-benzylidene-*α*-*D*-altropyranoside* (**2d**). The reaction was carried out in pyridine as described above for the methylene compound, with substitution of benzaldehyde (1.05 g) for the paraformaldehyde, to yield a crude product which was crystallized from Et_2O to give 707 mg (48%) of **2d** as an epimeric mixture with the *endo*-H isomer predominating.[5] Preparative TLC (AcOEt–hexane) of the mother liquors gave an additional 258 mg (18%) of **2d** followed by 101 mg (7%) of methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-idopyranoside, m.p. 130–150°C, which, on recrystallization, gave m.p. 158–159°C (mixed m.p. 158–160°C) and ^{1}H NMR identical with an authentic sample obtained on benzoylation of methyl 4,6-*O*-benzylidene-α-D-idopyranoside,[19] m.p. 158–159°C, $[\alpha]_D^{20} - 1.9°$ (*c* 1.1, $CHCl_3$), anal. $C_{28}H_{26}O_8$: C, H. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.04 (H1), 5.17 (H2), 5.41 (H3), 4.17 (H4), 4.07 (H5), 4.41 (H6), 4.18 (H6′), 5.,65 (benzylidene), 3.53 (OMe); J_{12}, J_{23}, J_{34}, J_{45}, J_{56}, $J_{56'} < 2$ Hz, $J_{66'} = 12.2$. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 99.0 (C1), 71.5, 69.7, 68.2, 66.3 (C2–C5), 59.4 (C6), 101.1 (benzylidene), 55.7 (OMe).

*Methyl 2,6-di-*O*-benzoyl-3,4-*O*-(2,2,2-trichloroethylidene)-*α*-*D*-altropyranoside* (**2e**). Methyl 2,3-anhydro-α-D-mannopyranoside[4] (**1**, 528 mg) and imidazole (30 mg) were dissolved in THF, 50% NaH in mineral oil (300 mg) was added and the suspension was stirred for 5 min at room temperature. Chloral (1.00 ml) was added and a slight rise in temperature and gas evolution were observed. The reaction mixture was stirred at 25°C for 2 h and worked up as described above for the methylene compound, to yield 1148 mg (72%) of an epimeric mixture of **2e** on crystallization from Et_2O–pentane, m.p. 85–95°C. Recrystallization from EtOH gave 998 mg of the *endo*-H epimer of **2e**, m.p. 103–105°C, $[\alpha]_D^{25} + 46.5°$ (*c* 3.7, $CHCl_3$) anal. $C_{23}H_{21}Cl_3O_8$: C, H, Cl, ^{1}H NMR

(500 MHz, $CDCl_3$): δ 4.81 (H1), 5.49 (H2), 4.81 (H3), 4.74 (H4), 4.21 (H5), 4.70 (H6), 4.60 (H6'), 5.60 (ethylidene), 3.41 (OMe); $J_{12} = 2.6$ Hz, $J_{23} = 4.5$, $J_{34} = 6.4$, $J_{45} = 9.3$, $J_{56} = 3.3$, $J_{56'} = 6.5$, $J_{66'} = 11.9$. Preparative TLC (AcOEt–hexane, 1 : 1) of the mother liquors from the first crystallization gave an additional 153 mg (10%) of *endo*-H **2e**, m.p. 100–103°C, followed by 42 mg (3%) of impure *exo*-H **2e**, m.p. 127–130°C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.80 (H1), 5.62 (H2), 4.58 (H3), 4.53 (H4), 4.49 (H5), 4.64 (H6), 4.59 (H6'), 5.37 (ethylidene), 3.41 (OMe); $J_{12} = 3.1$ Hz, $J_{23} = 4.7$, $J_{34} = 6.2$, $J_{45} = 9.0$, $J_{56} = 3.1$, $J_{56'} = 5.6$, $J_{66'} = 12.0$.

*Methyl 2,6-di-*O*-benzoyl-3,4-*O*-ethylidene-*α*-*D*-altropyranoside* (**2g**). To a solution of **2e** (532 mg) and azoisobutyronitrile (AIBN, 10 mg) in refluxing benzene (50 ml) under N_2 was added tri-*n*-butyltin hydride (1.31 g) in 10 ml of benzene over 25 min. The reaction mixture was refluxed for 6 h, and an additional 10 mg of AIBN were added after 2 and 4 h. After evaporation of the solvent, the residue was dissolved in acetonitrile (10 ml), and the tin compounds were removed by extraction with pentane (3 × 25 ml). Preparative TLC (AcOEt–hexane 1 : 3) of the essentially pure crude product gave 337 mg (79%) of **2g** as a syrup, which could not be purified to analytical purity even after repeated chromatography, anal. $C_{23}H_{24}O_8$: found C 63.68, H 5.75, calc. C 64.48, H 5.65. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.78 (H1), 5.50 (H2), 4.42 (H3), 4.35 (H4), 4.18 (H5), 4.67 (H6), 4.53 (H6'), 5.51 (ethylidene), 1.37 (Me), 3.42 (OMe); $J_{12} = 3.4$ Hz, $J_{23} = 5.5$, $J_{34} = 6.2$, $J_{45} = 9.5$, $J_{56} = 2.5$, $J_{56'} = 6.8$, $J_{66'} = 12.0$. Debenzoylation with MeONa in MeOH and flash chromatography (AcOEt) gave the hygroscopic methyl 3,4-*O*-ethylidene-α-D-altropyranoside, ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.57 (H1), 3.92 (H2), 4.26 (H3), 4.30 (H4), 3.78 (H5), 3.89 (H6), 3.73 (H6'), 5.32 (ethylidene), 1.36 (Me), 3.46 (OMe); $J_{12} = 5.1$ Hz, $J_{23} = 7.2$, $J_{34} = 7.0$, $J_{45} = 9.0$, $J_{56} = 2.8$, $J_{56'} = 5.5$, $J_{66'} = 11.5$, $J_{acetal} = 4.9$. Rebenzoylation and rechromatography gave a pure sample of **2g**, anal. C, H, $[\alpha]_D^{25} + 49.3°$ (*c* 1.4, $CHCl_3$).

*3,4-*O*-(2,2,2-Trichloroethylidene)-α-D-altropyranosyl bromide* (**2h**). The methyl glycoside *endo*-H **2e** (504 mg) was dissolved in 10 ml of 30% HBr in AcOH at room temp. (15 min) and stirred for a further 1 h, after which the reaction mixture was diluted with $CHCl_3$ (EtOH-free) and poured into a mixture of ice, water and $CHCl_3$. The organic phase was washed with ice-cold, aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated to give 533 mg of a syrup consisting mainly of **2h**, which was too unstable to be purified chromatographically. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.37 (H1), 5.85 (H2), 4.84 (H3), 4.88 (H4), 4.40 (H5), 4.74 (H6), 4.63 (H6'); $J_{12} = 2.5$ Hz, $J_{23} = 3.5$, $J_{34} = 5.8$, $J_{45} = 9.0$, $J_{56} = 3.3$, $J_{56'} = 5.5$, $J_{66'} = 12.2$, ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 81.7 (C1), 75.8, 72.6, 71.8, 69.8 (C2, C3, C4, C5), 63.1 (C6), 107.3 (ethylidene), 98.8 (CCl_3). Instead the crude bromide was treated with MeONa (from 96 mg of Na) in 10 ml of MeOH overnight, the reaction mixture neutralized with mixed-bed ion-exchange resin and evaporated to dryness. Flash chromatography combined with preparative TLC of some mixed fractions (AcOEt) gave 195 mg (71%) of methyl 3,4-*O*-(2,2,2-trichloroethylidene)-α-D-altropyranoside (**2i**) as a syrup, identical with the product obtained by debenzoylation of **2e** [^{1}H NMR (500 MHz, CD_3COCD_3): δ 4.54 (H1), 3.84 (H2), 4.56 (H3), 4.65 (H4), 3.77 (H5), 3.81 (H6), 3.70 (H6'), 5.56 (ethylidene), 3.37 (OMe); $J_{12} = 4.0$ Hz, $J_{23} = 5.8$, $J_{34} = 6.9$, $J_{45} = 8.2$, $J_{56} = 3.0$, $J_{56'} = 5.5$, $J_{66'} = 11.7$, ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 98.9 (C1), 76.5, 73.3, 69.1, 65.8 and 64.1 (C2, C3, C4, C5, C6), 107.3 (ethylidene), 55.6 (OMe).

*Methyl 2,6-di-*O*-benzoyl-3,4-*O*-(1-methoxy-2,2,2-trifluoroethylidene)-α-D-altropyranoside* (**2f**). The reaction was carried out as described above for the methylene compound **2b** using methyl trifluoroacetate (1.28 g) and a reaction time of 2 h, but with THF as the solvent. Preparative TLC in AcOEt–hexane (1 : 3) gave two epimeric orthoesters **2f** as syrups. The faster moving compound (602 mg, 39%), $[\alpha]_D^{20} + 34.5°$ (*c* 1.1, $CHCl_3$), anal. $C_{24}H_{23}F_3O_9$: C, H, showed ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.79 (H1), 5.60 (H2), 4.66 (H3), 4.59 (H4), 4.35 (H5), 4.67 (H6), 4.54 (H6'), 3.61 and 3.41 (OMe); $J_{12} = 4.7$ Hz, $J_{23} = 7.0$, $J_{34} = 8.0$, $J_{45} = 9.5$, $J_{56} = 3.0$, $J_{56'} = 7.0$, $J_{66'} = 12.0$. The slower moving compound (560 mg, 36%) contained 5% of another compound, which was not completely removed on rechromatography, $[\alpha]_D^{20} + 37.0°$ (*c* 1.2, $CHCl_3$), anal. $C_{24}H_{23}F_3O_9$: calc. C 56.25, H 4.52, found C 55.76, H 4.46, and showed ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.79 (H1), 5.56 (H2), 4.80 (H3), 4.71 (H4), 4.29 (H5), 4.64 (H6), 4.57 (H6'), 3.45 and 3.41 (OMe); $J_{12} = 4.0$ Hz, $J_{23} = 5.8$, $J_{34} = 7.4$, $J_{45} = 9.2$, $J_{56} = 3.3$, $J_{56'} = 6.2$, $J_{66'} = 12.0$.

*Methyl 3,4-*O*-methylene-α-D-arabinopyranoside* (**4a**). The reaction was carried out in acetonitrile as described above for **2b**. The crude product was crystallized from Et_2O to give 374 mg (72%) of **4a**, m.p. 117–118°C. Recrystallization from AcOEt–hexane gave m.p. 119–120°C, $[\alpha]_D^{20} - 30.2°$ (*c* 1.2, $CHCl_3$), anal. $C_7H_{12}O_5$: C, H, ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.14 (H1), 3.58 (H2), 4.14 (H3), 4.04 (H4), 4.23 (H5), 3.78 (H5'), 5.21 and 5.03 (OCH_2O), 3.52 (OMe); $J_{12} = 7.2$ Hz, $J_{23} = 7.6$, $J_{34} = 5.2$, $J_{45} = 2.8$, $J_{45'} = 3.8$, $J_{55'} = 13.0$. Benzoylation of the mother liquors with BzCl (0.3 ml) in pyridine (5 ml) followed by preparative TLC (AcOEt–hexane 1 : 2) gave 9% of recovered starting material (as the benzoate **3b**) and 80 mg (10%) of methyl 2-*O*-benzoyl-3,4-*O*-methylene-α-D-arabinopyranoside (**4b**), m.p. 95–115°C. Recrystallization from AcOEt–hexane gave m.p. 117–119°C, $[\alpha]_D^{20} - 4.6°$ (*c* 0.6, $CHCl_3$), anal. $C_{14}H_{16}O_6$: C, H, ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.54 (H1), 5.29 (H2), 4.31 (H3), 4.25 (H4), 4.10 (H5), 3.83 (H5'), 5.28 and 5.02 (OCH_2O), 3.46 (OMe); $J_{12} = 5.5$ Hz, $J_{23} = 5.5$, $J_{34} = 6.0$, $J_{45} = 5.0$, $J_{45'} = 4.2$, $J_{55'} = 12.5$.

Methyl 2-O-benzoyl-3,4-O-(2,2,2-trichloroethylidene)-α-D-arabinopyranoside (**4c**). The epoxide **3a** (438 mg, 3 mmol), chloral (0.60 ml, 6 mmol) and imidazole (10 mg) were treated with NaH (300 mg 50%, 6 mmol) in THF for 17 h as described above for **2e**. Preparative TLC (AcOEt–hexane 1 : 2) gave 235 mg (31%) of recovered starting material (as the benzoate **3b**) followed by **4c** (308 mg, 26%, >90% *endo*-H), m.p. 138–146°C. Recrystallization from AcOEt–hexane gave the pure *endo*-H **4c**, m.p. 150–151°C, $[\alpha]_D^{20} - 15.9°$ (*c* 1.1, $CHCl_3$), anal. $C_{15}H_{15}Cl_3O_6$: C, H, Cl, ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.56 (H1), 5.31 (H2), 4.75–4.80 (H3,H4), 4.17 (H5), 3.87 (H5′), 5.52 (ethylidene), 3.46 (OMe); $J_{12} = 5.2$ Hz, $J_{23} = 5.4$, $J_{45} = 4$, $J_{45'} = 4$, $J_{55'} = 13$.

Methyl 4-O-benzoyl-2,3-O-methylene-α-D-lyxopyranoside (**6a**). The epoxide **5a** (438 mg, 3 mmol) was treated with paraformaldehyde and NaH in acetonitrile as described above for **2b**. Benzoylation of the crude product, ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.70 (H1), 4.00 (H2), 4.16 (H3), 3.85 (H4), 3.80 (H5), 3.70 (H5′), 3.46 (OMe), 5.19 and 4.94 (OCH_2O); $J_{12} = 5.5$ Hz, $J_{23} = 6.0$, $J_{34} = 3.8$, $J_{45} = 3.0$, $J_{45'} = 4.5$, $J_{55'} = 12.0$, gave 778 mg of a product, which on preparative TLC (AcOEt–hexane 1 : 2) gave 537 mg (64%) of **6a** as a semisolid followed by 93 mg (12%) of recovered starting material as the benzoate **5b**. Recrystallization of **6a** from Et_2O–pentane gave 416 mg of pure **6a**, m.p. 68–70°C, $[\alpha]_D^{25} + 1.1°$ (*c* 1.5, $CHCl_3$), anal. $C_{14}H_{16}O_6$: C, H. ^{1}H NMR (90 MHz, $CDCl_3$): δ 4.73 (H1), 4.00 (H2), 4.36 (H3), 5.18 (H4), 3.87 (H5), 3.71 (H5′), 3.44 (OMe), 5.22 and 5.00 (OCH_2O); $J_{12} = 3.0$ Hz, $J_{23} = 5.5$, $J_{34} = 5.5$, $J_{45} = 5.1$, $J_{45'} = 7.0$, $J_{55'} = 11.7$.

Methyl 4-O-benzoyl-2,3-O-(2,2,2-trichloroethylidene)-α-D-lyxopyranoside (**6b**). The epoxide **5a** (438 mg, 3 mmol), chloral (0.9 ml, 9 mmol) and imidazole (10 mg) were treated with NaH (450 mg, 9.4 mmol) in THF for 17 h as described above for **2e**. Crystallization from AcOEt–hexane gave 783 mg (66%) of *endo*-H **6b**, m.p. 154–155°C. Recrystallization from Et_2O–AcOEt gave m.p. 156–157°C, $[\alpha]_D^{20} - 23.6°$ (*c* 1.3, $CHCl_3$), anal. $C_{15}H_{15}Cl_3O_6$: C, H, Cl, ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.88 (H1), 4.57 (H2), 4.85 (H3), 5.25 (H4), 3.90 (H5), 3.72 (H5′), 3.46 (OMe), 5.55 (ethylidene); $J_{12} = 2.2$ Hz, $J_{23} = 5.5$, $J_{34} = 6.5$, $J_{45} = 5.0$, $J_{45'} = 8.7$, $J_{55'} = 11.5$. Preparative TLC (AcOEt–hexane, 1 : 2) of the mother liquors gave an additional 68 mg of **6b**, followed closely by 34 mg *exo*-H **6b**, ^{1}H NMR (90 MHz, $CDCl_3$): δ 4.96 (H1), 4.32 (H2), 4.64 (H3), 5.53 (H4), 3.92 (H5), 3.82 (H5′), 3.49 (OMe), 5.37 (ethylidene); $J_{12} = 3.2$ Hz, $J_{23} = 6.3$, $J_{34} = 5.0$, $J_{45} = 4.8$, $J_{45'} = 6.7$, $J_{55'} = 12.0$ and 19% of recovered starting material (as the benzoate **5b**).

Methyl 3,4-O-methylene-α-D-galactopyranoside (**8a**). The epoxide **7** (512 mg, 2.91 mmol) and paraformaldehyde (262 mg, 8.73 mmol) was treated with NaH (146 mg, 3.04 mmol) in acetonitrile as described above for **2b**. Crystallization from AcOEt–Et_2O gave 121 mg (20%) of **8a**, m.p. 109–112°C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.81 (H1), 3.74 (H2), 4.25 (H3), 4.04 (H4), 4.08 (H5), 3.97 (H6), 3.86 (H6′), 3.47 (OMe), 5.19 and 4.99 (OCH_2O); $J_{12} = 4.0$ Hz, $J_{23} = 7.0$, $J_{34} = 6.0$, $J_{45} = 2.3$, $J_{56} = 6.6$, $J_{56'} = 4.5$, $J_{66'} = 12.0$. Flash chromatography of the mother liquors first in AcOEt–EtOH (5 : 1) and then in AcOEt gave 161 mg of a fraction, m.p. 80–90°C, which was a mixture of **8a** and methyl 3,4-anhydro-α-D-galactopyranoside (3 : 1) followed by 127 mg (25%) of recovered **7**. The two fractions of **8a** were combined and recrystallized twice from AcOEt–Et_2O to give a product with m.p. 113–116°C, $[\alpha]_D^{20} + 179°$ (*c* 1.2, $CHCl_3$), anal. $C_8H_{14}O_6$: C, H.

Methyl 2,6-di-O-benzoyl-3,4-(2,2,2-trichloroethylidene)-α-D-galactopyranoside (**8b**). The epoxide **7** (302 mg, 1.72 mmol), chloral (0.55 ml, 5.7 mmol) and imidazole (10 mg) was treated with NaH (165 mg, 3.5 mmol) in THF for 20 h as described above for **2e**. Flash chromatography (AcOEt) gave 371 mg of a product, which on benzoylation and preparative TLC (AcOEt–hexane, 1 : 2) gave 506 mg (56%) of **8b** as a syrup, $[\alpha]_D^{20} + 108°$ (*c* 1.1, $CHCl_3$), anal. $C_{23}H_{21}Cl_3O_8$: C, H, Cl, ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 (H1), 5.18 (H2), 4.96 (H3), 4.81 (H4), 4.36 (H5), 4.681 (H6), 4.680 (H6′), 5.54 (ethylidene), 3.40 (OMe); $J_{12} = 3.5$ Hz, $J_{23} = 8.0$, $J_{34} = 5.5$, $J_{45} = 2.3$, $J_{56} = 6.8$, $J_{56'} = 6.0$, $J_{66'} = 11.5$.

Methyl 2,3-(2,2,2-trichloroethylidene)-α-D-gulopyranoside (α-**10b**). The epoxide α-**9** (528 mg, 3 mmol), chloral (0.98 mg, 10 mmol) and imidazole (15 mg) were treated with NaH (300 mg, 6 mmol) in THF for 20 h as described above for **2e**. Crystallization of the crude product from AcOEt–hexane gave 365 mg (69%) of recovered α-**9**. Flash chromatography of the mother liquors (AcOEt) gave 164 mg (17%) of α-**10b**, m.p. 93–99°C, followed by an additional 42 mg (8%) of **9**. Recrystallization of the crude α-**10b** from AcOEt–hexane gave 109 mg, m.p. 100–101°C, $[\alpha]_D^{20} + 46°$ (*c* 1.1, $CHCl_3$), anal. $C_9H_{13}Cl_3O_6$: C, H, Cl. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.96 (H1), 4.69 (H2), 4.57 (H3), 4.29 (H4), 3.97–4.04 (H5, H6, H6′), 3.44 (OMe), 5.56 (ethylidene); $J_{12} = 5.2$ Hz, $J_{23} = 5.6$, $J_{34} = 2.8$.

Methyl 4,6-di-O-benzoyl-2,3-O-methylene-β-D-gulopyranoside (β-**10a**). The reaction was carried out in acetonitrile as described for **2b** to give 1021 mg (82%) of β-**10a** as a syrup, $[\alpha]_D^{20} - 114°$ (*c* 1.1, $CHCl_3$), anal. $C_{22}H_{22}O_8$: C, H. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.48 (H1), 4.11 (H2), 4.20 (H3), 5.63 (H4), 4.34 (H5), 4.65 (H6), 4.45 (H6′), 3.61 (OMe), 5.27 and 5.00 (OCH_2O); $J_{12} = 6.7$ Hz, $J_{23} = 5.5$, $J_{34} = 2.5$, $J_{45} = 1.9$, $J_{56} = 7.1$, $J_{56'} = 5.7$, $J_{66'} = 11.3$.

Methyl 2,3-(2,2,2-trichloroethylidene)-β-D-gulopyranoside (β-**10b**). The epoxide β-**9** (528 mg, 3 mmol), chloral (0.98 ml, 10 mmol) and imidazole (15 mg) were treated

with NaH (300 mg, 6 mmol) in THF for 19 h as described above for **2e**. Crystallization of the crude product from Et_2O–pentane gave 1067 mg (67%) of β-**10b**, m.p. 100–113°C. Preparative TLC of the mother liquors (AcOEt–hexane 1 : 4) gave an additional 237 mg (15%) of β-**10b**, which after two recrystallizations from Et_2O–pentane gave m.p. 115–117°C, $[\alpha]_D^{25} - 70°$ (*c* 1.1, $CHCl_3$), anal. $C_{23}H_{21}Cl_3O_8$: C, H, Cl. ^1H NMR (250 MHz, $CDCl_3$): δ 4.55 (H1), 4.51 (H2), 4.82 (H3), 5.68 (H4), 4.35 (H5), 4.65 (H_6), 4.43 ($H_{6'}$), 3.62 (OMe), 5.54 (ethylidene); $J_{12} = 6.5$ Hz, $J_{23} = 5.3$, $J_{34} = 2.3$, $J_{45} = 2.0$, $J_{56} = 7.0$, $J_{56'} = 6.0$, $J_{66'} = 11.2$.

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References

1. Garegg, P. J., Maron, L. and Swahn, C.-G., *Acta Chem. Scand. 26* (1972) 518; Garegg, P. J. and Swahn, C.-G. *Acta Chem. Scand. 26* (1972) 3895.
2. McCombie, S. W. and Metz, W. A. *Tetrahedron Lett. 28* (1987) 383.
3. Myers, A. G. and Widdowson, K. L. *Tetrahedron Lett. 29* (1988) 6389.
4. Buchanan, J. G. and Schwarz, J. C. P. *J. Chem. Soc.* (1962) 4770.
5. Jacobsen, S. and Mols, O. *Acta Chem. Scand., Ser. B 35* (1981) 169.
6. Buchanan, J. G. *J. Chem. Soc.* (1958) 2511.
7. Dahlgard, M., Chastain, B. H. and Han, R.-J. L. *J. Org. Chem. 27* (1962) 929.
8. Ohle, H. and von Vargha, L. *Ber. Dtsch. Chem. Ges. 62* (1929) 2435.
9. Jacobsen, S. *Acta Chem. Scand., Ser. B 42* (1988) 605.
10. Buchanan, J. G. and Fletcher, H. *J. Chem. Soc.* (1965) 6316.
11. Höök, J. E. and Lindberg, B. *Acta Chem. Scand. 20* (1966) 2362.
12. Doležová, J., Trnka, T. and Černý, M. *Collect. Czech. Chem. Commun. 47* (1982) 2415.
13. Buchanan, J. G. and Fletcher, R. *J. Chem. Soc. C* (1966) 1926.
14. Krajewski, J. W., Gluzińsky, P., Urbańczyk–Lipowska, Z., Banaszck, A., Párkányi, L. and Kálmán, A. *Carbohydr. Res. 144* (1985) 13.
15. Buchanan, J. G., Fletcher, R., Parry, K. and Thomas, W. A. *J. Chem. Soc. B* (1969) 377.
16. Still, W. C., Kahn, M. and Mitra, A. *J. Org. Chem. 43* (1978) 2923.
17. Ritchie, R. G. S., Cyr, N. and Perlin, A. S. *Can. J. Chem. 54* (1976) 2301.
18. Hori, H., Nakajima, T., Nishida, Y., Ohrui, H. and Meguro, H. *J. Carbohydr. Chem. 5* (1986) 585.
19. Sorkin, E. and Reichstein, T. *Helv. Chim. Acta 28* (1945) 1.

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