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Enantiomerically Pure, Highly Functionalized Tetrahydrofurans from Simple Carbohydrate Precursors

Inge Lundt*, Holger Frank

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

Abstract: 6-Bromo-6-deoxy-1,4-aldonolactones and 6-bromo-6-deoxy-alditols with D-*galacto*-, D-*altro*-, D-*manno*- and D-*ido*-configuration were selectively converted into hydroxylated tetrahydrofuran derivatives by simple heating in water. The 6-bromo-6-deoxy-D-altritol (**10**) and 6-bromo-6-deoxy-D-iditol (**25**) reacted even at room temperature. Likewise, the 6-bromo-2,6-dideoxy-aldonolactones with D-*arabino*- (**29**) and D-*lyxo*-configuration (**31**) gave the corresponding 2-deoxy-3,6-anhydrides, when heated in water. The rate of formation of the furan ring by intramolecular nucleophilic substitution was determined by the conformation of the bromopolyols in water.

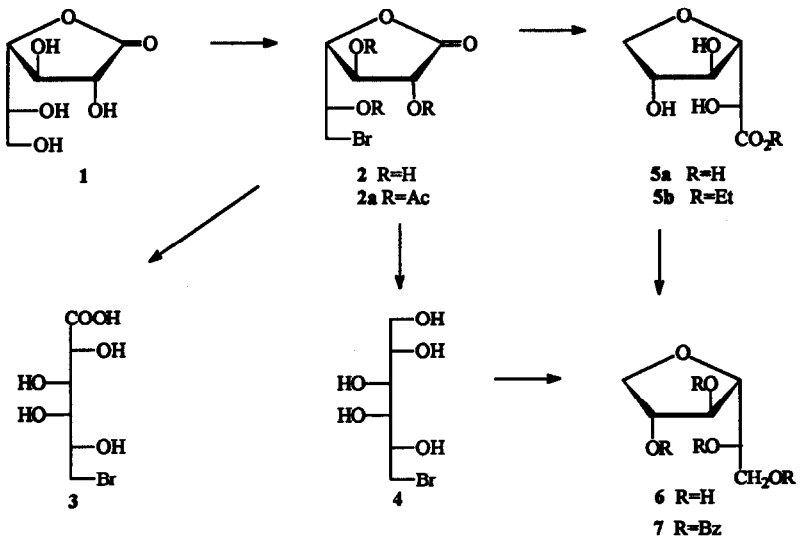
Tetrahydrofuran (THF) structures are found in many natural products in a wide range of stereochemical complexity. Due to their biological importance, the synthesis of chiral heterocycles of this type has received increasing attention. A variety of different approaches have been developed,[1] some of them using the "chiral pool",[2] to synthesize tetrahydrofurans with substituents both at C-2 and C-5. These structures are the most abundent in nature as found in nucleosides or polyether antibiotics.[3] But also non-natural tetrahydrofurans might be of interest from a biological point of view. The platelet activating factor (PAF)[4] is a naturally occuring, simple phosphoglyceride with strong biological activity.[5] Tetrahydrofurans with a diol side-chain, in which the PAF structure is partially fixed as a part of the heterocyclic skeleton, have been shown to be very potent agonists of PAF.[6]

Because of the well established synthetic availability, THF derivatives are not only attractive as target molecules for natural product synthesis, but might also be used in other contexts. Phosphite derivatives of chiral tetrahydrofurans are used as ligands for catalysts in asymmetric reactions, *e.g.* asymmetric hydrogenation and hydroformylation;[7] for similar purposes phosphine derivatives have been prepared.[8]

Carbohydrates as precursors in tetrahydrofuran synthesis have been used extensively. Ring closure by attack of an OH- or OR-group on an activated double bond, normally the most applied method to prepare the furan moiety, has been used in only few cases within the carbohydrates.[9] The general method to create

hydroxylated furans from carbohydrates is by nucleophilic attack of a OH-group on a suitably introduced leaving group. Hydroxy groups have been transformed into leaving groups simply by protonation with acid[10] or by treatment with HF and formic or acetic acid[11] to give acyloxonium ions. Triflates[2a,12], mesylates[2b,8] or tosylates[13] are commonly used as leaving groups, but often protecting group chemistry is required for their preparation. Bromodeoxyaldonolactones are easily available by treatment of the corresponding lactone or acid salt with hydrogen bromide in acetic acid.[14] In these compounds the bromine is prone to nucleophilic substitution and they have recently been used for the synthesis of polyhydroxylated pyrrolidines which are potential glycosidase inhibitors.[15]

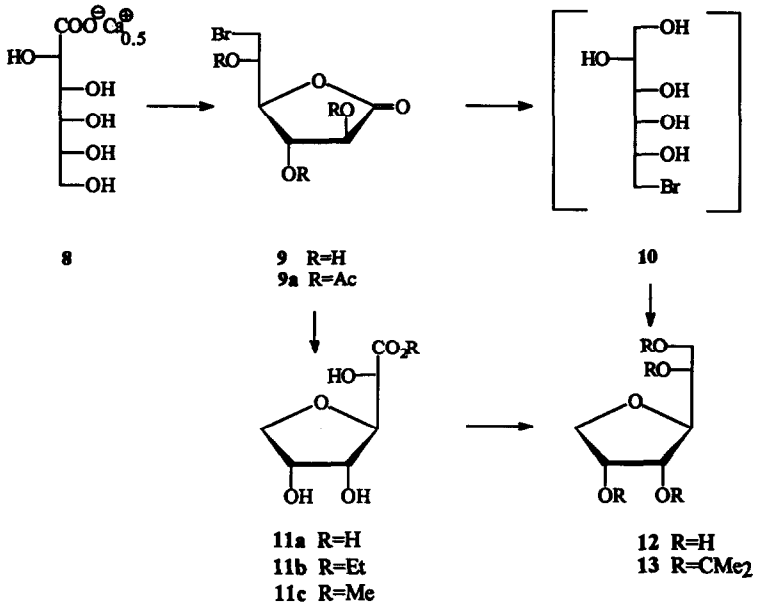
We have now investigated the reaction of bromodeoxyaldonolactones and bromodeoxyalditols aiming to synthesize enantiomerically pure tetrahydrofurans as potential building blocks for biologically relevant compounds. The intramolecular substitution of the bromine to create the tetrahydrofuran ring takes place by simple heating in water. Most of the HBr formed can be removed easily by co-destillation with water. When syrupy products are obtained, complete removal of HBr by treatment with a weakly basic ion exchange resin is necessary. When 2,6-dibromo-2,6-dideoxy-hexonolactones[14] were heated in water, mixtures were obtained, mainly elimination products. In contrast, 6-bromo-6-deoxy-aldonolactones, 6-bromo-2,6-dideoxy-aldonolactones and 6-bromo-6-deoxy-alditols yielded the tetrahydrofurans as the only products by a 3,6-anhydro formation. Lactones and alditols with D-*galacto*-, D-*altro*-, D-*manno*- and D-*ido*-configuration have been investigated and in only a single case a small amount of a 6-membered ring was also formed.



Scheme I

When 6-bromo-6-deoxy-D-galactono-1,4-lactone (**2**)[14a] or 6-bromo-6-deoxy-D-galactonic acid (**3**) was heated in water to reflux (Scheme I), the acid **5a** was obtained in a quantitative yield as seen from the ^{13}C-NMR spectrum. After esterification with EtOH/HCl, **5b** was isolated in 88 % yield. Reduction with $NaBH_4$ gave pure 3,6-anhydro-D-galactitol (1,4-anhydro-L-galactitol) (**6**), a compound which is not otherwise available enantiomerically pure from galactitol by simple treatment with acid.[10] Likewise, when 6-bromo-6-

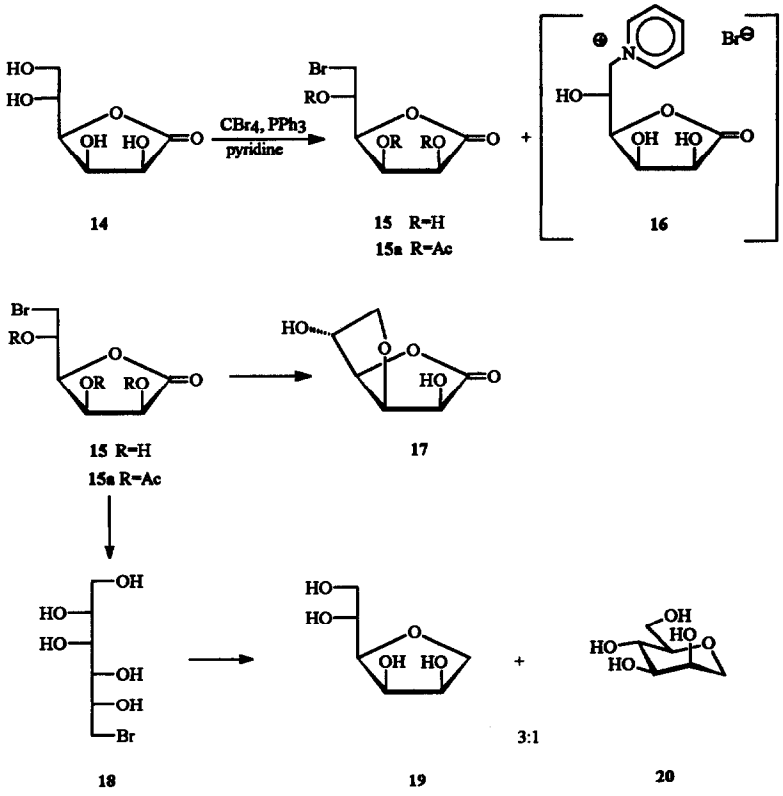
deoxy-D-galactitol (1-bromo-1-deoxy-L-galactitol) (4), prepared by reduction of the bromolactone 2 or, in a better yield, by reduction of the acetylated lactone 2a, was heated in water, the 3,6-anhydride 6 was also formed. In some experiments a small amount (< 10 %) of galactitol was observed too. This hydrolysis may be dependent on the concentration, since it was only found when the reaction was carried out on a larger scale. The galactitol could be removed quantitatively simply by crystallization from ethanol. Although 3,6-anhydro-D-galactitol (6) appeared completely pure by ^{13}C-NMR[16] and optical rotation,[17] it could not be crystallized, but was characterized as the crystalline 1,2,4,5-tetrabenzoate 7, the enantiomer of the known derivative of 1,4-anhydro-D-galactitol.[17]



Scheme II

6-Bromo-6-deoxy-D-altrono-1,4-lactone (9) prepared[14d] from calcium D-altronate (8)[18] gave, when heated in water (Scheme II), quantitatively the 3,6-anhydro-D-altronic acid (11a). Esterification gave 11b and 11c, both being syrups. Reduction of 11b gave syrupy 3,6-anhydro-D-altritol (1,4-anhydro-D-tallitol) (12), which was characterized as the crystalline 1,2;4,5-diisopropylidine derivative 13.[19] When the bromolactone 9 was reduced with $NaBH_4$ in water or methanol, none of the expected 6-bromo-6-deoxy-D-altritol (10) could be isolated or observed by ^{13}C-NMR, measured immediately after neutralization with acid ion exchange resin. In both solvents mixtures of two products were formed, namely the anhydro-acid 11a and the corresponding polyol 12, when the reduction was performed in water, and the ester 11c and 12 when run in methanol. Obviously, in this case the 3,6-anhydro formation is particularly favored even at room temperature. Reduction of the acetylated bromolactone 9a[14d] with $NaBH_4$ in ethanol, followed by careful acidic deacetylation with HCl in MeOH did lead to crude 6-bromo-6-deoxy-D-altritol (10), as seen from the ^{13}C-NMR spectrum. The compound was, however, not stable since it reacted completely to 3,6-anhydro-D-altritol (12) within one day at room temperature.

6-Bromo-6-deoxy-D-mannono-1,4-lactone (**15**) was prepared by treatment of D-mannono-1,4-lactone (**14**) with CBr_4/PPh_3 in pyridine[20] at r.t. Besides **15**, a by-product was also obtained (10-20 %). This was probably the 6-deoxy-6-(N-pyridinium)-derivative **16** (Scheme III), assigned through ^{13}C- and ^1H-NMR spectra, in which signals from a pyridinium moiety were observed. Furthermore, the absorptions for H-6 and H-6' in the ^1H-NMR, normally being below 4 ppm, were shifted downfield. The compound has not been further characterized.

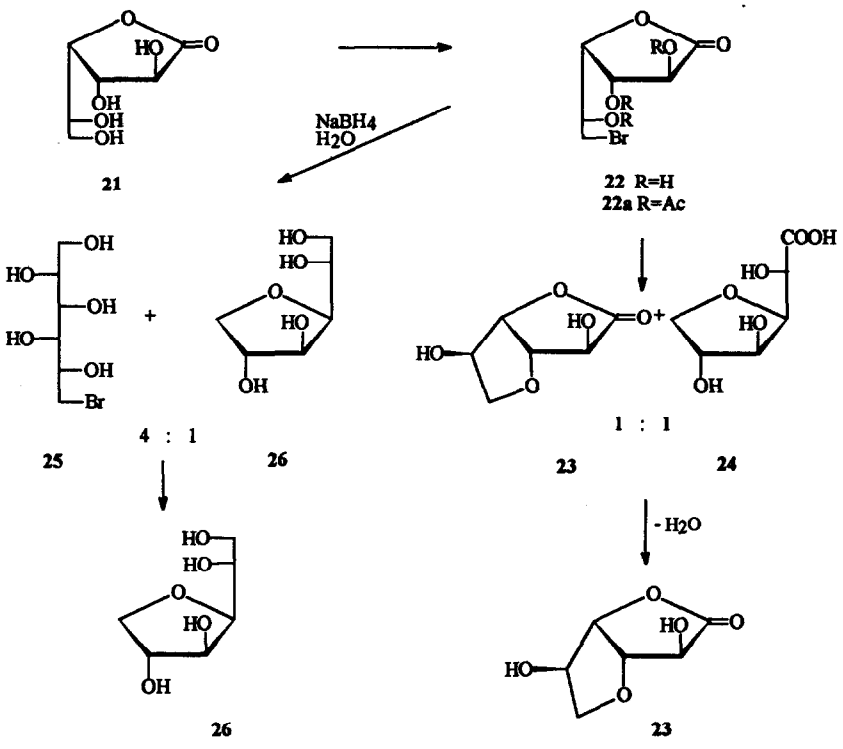


Scheme III

Heating of the bromolactone **15** in water for 4 h yielded exclusively the 3,6-anhydro-lactone **17**, which did only crystallize after filtration over an basic ion exchange resin. Reduction of bromolactone **15** gave 6-bromo-6-deoxy-D-mannitol (1-bromo-1-deoxy-D-mannitol) (**18**). Again the yield was much better when the acetylated bromolactone **15a** was reduced with $NaBH_4$ in ethanol, followed by hydrolysis of the remaining acetate groups. Heating of **18** in water led, as the only observed exception, to a 3:1 mixture of 3,6-(1,4)-anhydro-D-mannitol (**19**) and 2,6-(1,5)-anhydro-D-mannitol (**20**). The 1,4-anhydro-mannitol **19**, identical with the described product,[21] could be separated easily by crystallization from ethanol, leaving a mother liquor which contained almost only compound **20** (≈80 %). Thus, for the preparation of a pure 5-membered ether, the reaction of the lactone **15** instead of the polyol **18** should be choosen. The lactone **17** can be reduced with $NaBH_4$[15b] to give the polyol **19**. Formation of a 5-membered ring is normally favored compared to formation

of a 6-membered ring. In this case the energy difference between the two transition states seems to be very small, because all substituents at the 5-membered ring are *cis*-oriented, and the occurring sterical interactions may have a significant destabilizing effect in the transition state leading to **19**.

Treatment of D-idono-1,4-lactone (**21**)[22] with HBr/AcOH yielded the 6-bromolactone **22** as a slightly impure syrup. Chromatography to purify the product failed, because the impurities could not be separated, and a remarkable loss of substance did occur on the silica gel column, apparently due to opening of the lactone ring. When crude 6-bromo-6-deoxy-D-idono-1,4-lactone (**22**) was heated in water, a mixture of 3,6-anhydro-D-idono-1,4-lactone (**23**) and 3,6-anhydro-D-idonic acid (**24**) was obtained (Scheme IV). Co-destillation with



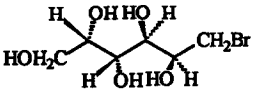
Scheme IV

toluene to remove water gave **23** as an almost pure syrup, as seen from a ^{13}C-NMR spectrum. The tendency to form an 3,6-anhydride is very big, similar to the compounds with D-*altro*-configuration discussed above; *e.g.* a sample of syrupy bromolactone **22** contained after two weeks at room temperature ca. 50% 3,6-anhydro-lactone **23**. Similarly, it was not possible to isolate the 6-bromo-6-deoxy-D-iditol (**25**) in a pure state when the reduction of **22** with $NaBH_4$ was performed in water. Careful work up gave a 4:1 mixture of **25** and the already formed 3,6-anhydro-D-iditol (1,4-anhydro-D-iditol). Subsequent heating in water gave in a fast reaction pure 1,4-anhydro-D-iditol (**26**). Alternative procedures using ethanol or methanol as a solvent, as well as reduction of the acetylated bromolactone **22a**, also gave products containing the anhydride.

The difference in the rates, with which the isomeric 6-bromo-6-deoxy-alditols form anhydrides, can be explained by the different conformations they adopt in solution. While the bromoalditols with D-*galacto*- (**4**)

and D- *manno*-configuration (**18**), according to their ^{1}H-NMR data, have the same extended, planar zig-zag conformation as the unsubstituted alditols[23] and the 2,6-dibromo-alditols,[24] the compounds with D-*altro*- (**10**) and D-*ido*-configuration (**25**) exist in other conformations trying to avoid O-O 1,3-parallel interactions. Because of their instability we were not able to measure the proton-proton coupling constants of the 6-bromo-altritol **10** and the 6-bromo-iditol **25**, but assuming that the conformation of these derivatives might be similar to the ones adopted by the unsubstituted and the 2,6-dibromosubstituted alditols as outlined above, the reactivity can be discussed using data for the latter compounds.

The crystal structure of D-altritol (**27**)[25] (Scheme V) shows a sickle conformation with a parallel 1,3-interaction between O-3 and C-6, and the proton-proton coupling constants of D-altritol[23] and 2,6-dibromo-2,6-dideoxy-D-altritol[24] indicate a structure in solution close to this crystal structure. Assuming a similar conformation of **10**, the 3,6-anhydro formation is very likely, because of the small distance between O-3 and the bromosubstituted C-6 (Scheme V). Thus, the reaction is very fast and takes readily place at room temperature. The crystal structure of D-iditol (**28**)[26] shows a bent conformation, adopted by a 120° rotation



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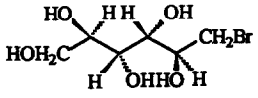

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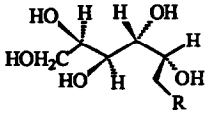
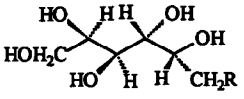
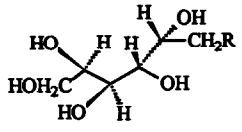


A (X-ray)

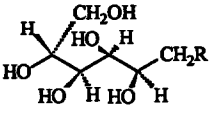
27 : R = OH
10 : R = Br



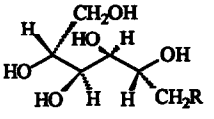
B (solution)



A (X-ray)



B (solution)



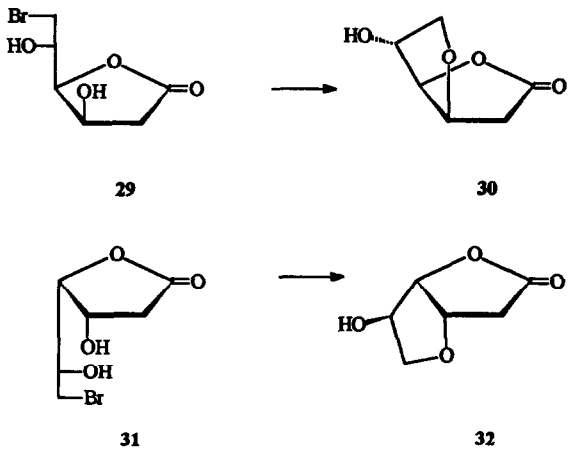
C (solution)

28 : R = OH
25 : R = Br

Scheme V

about C-3/C-4 (**A**) from the disfavored zig-zag conformation. In aqueous solution iditol, besides *ca.* 49% of **A**, contains a large proportion of conformations with twisted chain at C-2/C-3 [= C-4/C-5 because of C_2-symmetry] (**B**, 24 %) and with double twisted chain both at C-2/C-3 and C-4/C-5 (**C**, 26 %).[23] In the latter two conformations, the OH-3 and C6-Br are again oriented to give facile formation of an 3,6-anhydride, also due to the convertability between the three conformations.

Finally, the reactions of the 6-bromo-2,6-dideoxy-hexono-1,4-lactones with D-*arabino*- (**29**)[14b] and D-*xylo*-configuration (**31**)[14c] were investigated (Scheme VI). When heated in water they gave the 3,6-anhydro-lactones **30** and **32**, respectively, as the only products. Because of the *cis*-relationship between the 3-OH group and the side chain at C-4, the lactone ring was not opened, as was also observed in the products **17** and **23** derived from mannonolactone **14** and idonolactone **22**, respectively.



Scheme VI

In summary, simple heating of 6-bromo-6-deoxy-lactones and -alditols in water provides enantiomerically pure complex tetrahydrofurans in high yields in a very convenient way. The procedure is general and can be used for all carbohydrate lactones and requires no protecting group chemistry, because both the bromination and the formation of the 5-membered rings are selective. Only in a single case a 6-membered ring is formed as a by-product. The products, especially the acids and lactones, are very useful starting materials for further synthetic uses, yielding highly functionalized tetrahydrofuran derivatives.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were determined on a Perkin Elmer 241 polarimeter. NMR spectra were recorded on Bruker AC-250 and AM-500 (only when indicated) instruments. Chemical shifts were measured in ppm and coupling constants (*J*) in Hz. Dioxane (δ = 67.4) was used as internal standard for ^{13}C NMR spectra in D_2O and HDO (δ = 4.60) for ^1H-NMR spectra. For spectra in $CDCl_3$ the solvent signals were used as internal standard (δ = 76.9 for ^{13}C and 7.26 for ^1H). Evaporations were carried out at 40 °C *in vacuo*. For column chromatography silica gel 60, particle size 0.040-0.063 mm, from *Merck* was used. All solvents were destilled. Microanalyses were performed by *Leo Microanalytical Laboratory*. HBr/AcOH was a 32 % solution of hydrogen bromide in acetic acid.

6-Bromo-6-deoxy-D-galactono-1,4-lactone (**2**). D-galactono-1,4-lactone (**1**) (10.03 g, 56.3 mmol) was stirred with HBr/AcOH (75 ml) until a homogeneous solution was obtained (2 h)[14a] After that time MeOH (150 ml) was added slowly through a reflux condenser and the solution kept overnight. Concentration gave a

residue which was co-concentrated with H_2O (3 x 70 ml). The residue was dissolved in H_2O (50 ml) and extracted with EtOAc (5 x 30 ml), dried (Na_2SO_4), filtered over active carbon and concentrated to give **2** (5.50 g, 22.8 mmol, 40 %) as a syrup. The product was used directly for further reactions. ^{13}C NMR (D_2O): δ 33.4 (C-6), 68.8, 73.4, 74.0 (C-2, C-3, C-5), 80.6 (C-4), 175.8 (C-1).

6-Bromo-6-deoxy-D-galactonic acid (**3**). The lactone **2** (5.50 g, 22.8 mmol) was dissolved in a mixture of EtOAc (15 ml) and H_2O (2 ml) and stirred for 3 d. The precipitate was filtered off, washed with EtOAc and dried *in vacuo* to give **3** (2.24 g, 8.6 mmol; 38 %), mp. 130-131 °C, $[\alpha]_D^{20}$ -5.2° (*c* 1, H_2O). *Anal.* Found: C, 28.07; H, 4.35; Br, 30.84. Calc. for $C_6H_{11}O_6Br$: C, 27.82; H, 4.28; Br, 30.85. ^{13}C NMR (D_2O): δ 35.1 (C-6), 70.4, 70.6, 71.2, 72.1 (C-2, C-3, C-4, C-5), 177.6 (C-1). The mother liquor consisted of the lactone **2**.

6-Bromo-6-deoxy-D-galactitol (**4**). The acetylated lactone **2a**[14a] (6.11 g, 17.4 mmol) was dissolved in EtOH (135 ml) and ion exchange resin (IR-120, H^+, 35 ml) was added. The mixture was cooled with ice and $NaBH_4$ (4.25 g, 111.1 mmol) was added in such a rate that the pH was kept below 6, and stirring was continued for 30 min more, followed by additional ion exchange resin (IR-120, H^+, 40 ml) lowering the pH to ≈ 2-3. After 30 min the resin was filtered off and the solution was concentrated. The residue was co-destilled with MeOH (3 x 30 ml) to give a semi-crystalline residue. This was dissolved in MeOH (50 ml) containing AcCl (3 ml) and kept overnight at +5 °C. The precipitate formed was filtered off and dried to give **4** (2.33 g, 9.5 mmol; 55 %). Concentration of the mother liquor gave a further amount of **4** (190 mg), bringing the total yield to 59 %, mp. 145-146 °C, $[\alpha]_D^{20}$ +1.1° (*c* 0.95, H_2O). The product was too insoluble in all solvents to be recrystallized. ^{13}C NMR (D_2O): δ 35.2 (C-6), 64.1 (C-1), 70.4, 70.6, 70.9, 71.0 (C-2, C-3, C-4, C-5). ^1H NMR (D_2O, 500 MHz): δ 3.58 (dd, $J_{6,6'}$ 10.4, H-6), 3.61 (dd, H-6'), 3.70 (dd, $J_{3,4}$ 9.3, H-3), 3.71 (m, H-1, H-1'), 3.82 (dd, H-4), 3.99 (ddd, $J_{2,3}$ 1.4, $J_{2,1'}$ 6.0, $J_{2,1}$ 6.8, H-2), 4.12 (ddd, $J_{5,4}$ 1.5, $J_{5,6'}$ 5.9, $J_{5,6}$ 7.8, H-5).

A sample was acetylated for microanalysis : **4** (500 mg, 2.04 mmol) was dissolved in Ac_2O (20 ml) and a few drops $HClO_4$ were added. After standing overnight, the solution was poured on ice and stirred for 1 h to give 847 mg (1.86 mmol, 91 %) of crystalline pentaacetate. Recrystallization twice from ethanol gave 1,2,3,4,5-penta-*O*-acetyl-6-bromo-6-deoxy-D-galactitol as colorless plates, mp. 137-138 °C, $[\alpha]_D^{20}$ -10.1 ° (*c* 1.0, $CHCl_3$). *Anal.* Found: C, 42.88; H, 5.43; Br, 16.10. Calc. for $C_{16}H_{23}O_{10}Br$: C, 42.21; H, 5.09; Br, 17.55. (Even after drying the product contained significant amounts of EtOH). m/z (CI, NH_3) 472, 100% and 474, 91% ($M + NH_4^+$). ^{13}C NMR ($CDCl_3$): δ 20.4, 20.5 (OAc), 28.9 (C-6), 62.1 (C-1), 67.3, 67.5, 67.6, 69.3 (C-2, C-3, C-4, C-5), 169.6, 169.8, 170.1, 170.2 (OAc). ^1H NMR ($CDCl_3$): δ 1.93, 2.00, 2.03 (each s, OAc), 2.04 (s, 2 x OAc), 3.19 (dd, $J_{6,5}$ 7.6, $J_{6,6'}$ 10.8, H-6), 3.27 (dd, $J_{6',5}$ 5.8, H-6'), 3.72 (dd, $J_{1,2}$ 7.6, $J_{1,1'}$ 11.4, H-1), 4.20 (dd, $J_{1',2}$ 4.4, H-1'), 5.15-5.27 (m, H-2, H-3, H-5), 5.35 (dd, $J_{4,5}$ 1.6, $J_{4,3}$ 10.0, H-4).

Ethyl 3,6-anhydro-D-galactonate (**5b**). The 6-bromo-lactone **2** (2.68 g, 11.1 mmol) was dissolved in H_2O (30 ml) and heated under reflux for 2 h, followed by concentration to give crude 3,6-anhydro-galactonic acid **5a** [^{13}C-NMR (D_2O): δ 73.8 (C-6), 70.7, 77.3, 78.2 (C-2, C-4, C-5), 86.0 (C-3), 176.0 (C-1)]. This was dissolved in EtOH (50 ml) and AcCl (1 ml) was added. The mixture was refluxed for 2 h, followed by concentration to give crude **5b** (2.40 g). The syrup was dissolved in EtOH (20 ml), filtered over ion exchange resin (IR-45, OH^-, 20 ml) and concentrated to give **5b** (2.01 g, 9.75 mmol; 88%) as a syrup. Column chromatography (toluene - EtOH 3:1) gave an analytical sample, $[\alpha]_D^{20}$ +33.5° (*c* 1.0, H_2O). *Anal.* Found: C, 45.94; H, 7.04. Calc. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. ^{13}C NMR (D_2O): δ 14.3, 63.4 (OEt), 73.9 (C-6), 70.9, 77.2, 78.1 (C-2, C-4, C-5), 86.0 (C-3), 173.9 (C-1).

3,6-Anhydro-D-galactitol (*1,4-anhydro-L-galactitol*) (**6**). *a) from 6-bromo-6-deoxy-D-galactitol* (**4**). A suspension of **4** (2.0 g, 8.16 mmol) in H_2O (20 ml) was heated under reflux for 3 h. After cooling to r.t. the solution was treated with ion exchange resin (IR-45, OH^-, 50 ml) and filtered. Concentration of the filtrate gave a colorless syrup (1.36 g), which consisted of a ≈ 10 : 1 mixture of **6** and galactitol according to the ^{13}C NMR data. The syrup was dissolved in EtOH (50 ml) and within 1 d galactitol (130 mg, 0.71 mmol; 9 %) had crystallized completely, mp. 183-186 °C (Lit.[23]: 188.5 °C). ^{13}C NMR data were in accordance with those described.[27] The mother liquor was concentrated to give **6** as a syrup (1.10 g, 6.70 mmol; 82 %), $[\alpha]_D^{20}$ +34.5° (*c* 1.9, EtOH) (Lit.[17]: $[\alpha]_D^{20}$ -35.2°, (*c* 1.6, EtOH, for 1,4-anhydro-D-galactitol). ^{13}C NMR data were identical with those described for the enantiomeric 1,4-anhydro-D-galactitol.[16]

b) from ethyl 3,6-anhydro-D-galactonate (**5b**). To a solution of **5b** (2.01 g, 9.75 mmol) in EtOH (70 ml) $NaBH_4$ (3.35 g, 88.1 mmol) was added in small portions at 0 °C. Then EtOH (50 ml) was added and the solution allowed to warm up to r.t. within 1 h. Acidification with ion exchange resin (IR-120, H^+) to pH ≈ 4 and stirring for 30 min, followed by filtration and concentration gave a residue, which was co-destilled with MeOH (3 x 30 ml) to give syrupy **6** (1.22 g, 7.43 mmol; 76 %). ^{13}C NMR data were identical with the ones described above.

3,6-Anhydro-tetra-O-benzoyl-D-galactitol (1,4-anhydro-tetra-O-benzoyl-L-galactitol) (**7**). To a solution of **6** (1.22 g, 7.43 mmol) in dry CH_2Cl_2 (100 ml) and dry pyridine (6.0 ml, 74.3 mmol), benzoyl chloride (3.9 ml, 33.4 mmol) was added and the solution was stirred at r.t. overnight. Then H_2O (50 ml) was added and the mixture was stirred for 1 h. The organic layer was separated and washed with 2N HCl (4 x 25 ml) and saturated aq. $NaHCO_3$ (4 x 25 ml). The organic phase was dried (Na_2SO_4) and filtered over active carbon. Concentration of the filtrate gave an oily yellow residue, which was dissolved in Et_2O (10 ml). After addition of pentane the product crystallized slowly at +5 °C, to give yellow crystals (3.10 g, 5.18 mmol; 70 %). Recrystallization from Et_2O gave an analytical sample, mp. 99-100 °C, $[\alpha]_D^{20}$ -42.9° (*c* 1.24, $CHCl_3$), (Lit.[17] mp. 99-101 °C, $[\alpha]_D^{20}$ +41.7° (*c* 1.03, $CHCl_3$) for the enantiomeric 1,4-anhydro compound). ^{13}C NMR ($CDCl_3$): δ 63.6 (C-1), 70.8, 72.5, 78.6, 79.0 (C-2, C-4, C-5, C-6), 82.8 (C-3), 128-134 ppm (aromatic carbons), 165-166 ppm (C=O). ^1H NMR ($CDCl_3$): δ 4.29 (dd, $J_{6,6'}$ 10.8, H-6), 4.38 (dd, H-6'), 4.46 (dd, $J_{3,4}$ 3.6, H-3), 4.74 (dd, $J_{1,1'}$ 12.0, H-1), 4.86 (dd, H-1'), 5.65 (ddd, $J_{5,4}$ 1.6, $J_{5,6}$ 2.2, $J_{5,6'}$ 4.6, H-5), 5.77 (dd, H-4), 6.07 (ddd, $J_{2,3}$ 5.0, $J_{2,1'}$ 4.0, $J_{2,1}$ 6.8, H-2).

6-Bromo-6-deoxy-D-altrono-1,4-lactone (**9**)[14d] *and corresponding acetate* **9a**[14d] were prepared in the usual way[14] to give crystalline products. ^{13}C NMR: **9** (H_2O): δ 33.7 (C-6), 70.9, 74.0, 74.9 (C-2, C-3, C-5), 81.1 (C-4), 176.8 (C-1). **9a** ($CDCl_3$): δ 20.3, 20.5 (OAc), 28.9 (C-6), 70.5, 72.4, 72.6, (C-2, C-3, C-5), 78.1 (C-4), 168.0 (C-1), 169.3, 169.5 (OAc).

Ethyl 3,6-anhydro-D-altronate (**11b**). 6-Bromo-6-deoxy-D-altrono-1,4-lactone (**9**) (521 mg, 2.16 mmol) was dissolved in H_2O (40 ml) and heated under reflux for 1 h. After cooling to r.t. the solution was concentrated to give the crude acid **11a** [^{13}C NMR (D_2O): δ 70.2, 71.7, 72.3 (C-2, C-4, C-5), 73.9 (C-6), 82.6 (C-3), 176.2 (C-1)]. This was dissolved in EtOH (30 ml), AcCl (0.75 ml) was added and the solution heated to reflux for 2 h. After cooling to r.t. it was filtered over ion exchange resin (IR-45, OH^-, 5 ml). The filtrate was concentrated to give **11b** (379 mg, 1.83 mmol; 85 %) as a syrup. An analytical sample was obtained by column chromatography (toluene - EtOH 3:1), $[\alpha]_D^{20}$ -53.6° (*c* 1.0, H_2O). *Anal.* Found: C, 46.02; H, 6.98. Calc. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. ^{13}C NMR (D_2O): δ 14.3, 63.4 (OEt), 70.6, 71.7, 72.3 (C-2, C-4, C-5), 73.9 (C-6), 82.8 (C-3), 174.5 (C-1).

Methyl 3,6-anhydro-D-altronate (**11c**). Treatment of the bromolactone **9** (5.0 g, 20.74 mmol) as described above to give **11a** and heating in MeOH (30 ml) and AcCl (0.5 ml) gave after work up **11c** (3.82 g, 19.88 mmol; 95 %) as a syrup, $[\alpha]_D^{20}$ -50.5° (*c* 1.0, H_2O). ^{13}C NMR (D_2O): δ 53.7 (OMe), 70.6, 71.7, 72.3 (C-2, C-4, C-5), 73.9 (C-6), 82.7 (C-3), 174.9 (C-1). ^1H NMR (D_2O): δ 3.55 (s, OMe), 3.60 (dd, $J_{6,5}$ 2.0, $J_{6,6'}$ 10.0, H-6), 3.85 (dd, $J_{6',5}$ 3.8, H-6'), 3.96 (dd, $J_{3,2}$ 2.0, $J_{3,4}$ 6.8, H-3), 4.08 (ddd, $J_{5,4}$ 4.6, H-5), 4.13 (dd, H-4), 4.25 (d, H-2).

3,6-Anhydro-D-altritol (1,4-anhydro-D-talitol) (**12**). Ethyl 3,6-anhydro-D-altronate (**11b**) (378 mg, 1.83 mmol) was dissolved in EtOH (30 ml) and treated with $NaBH_4$ (1.32 g, 34.7 mmol) as described above for **6** from **5b** to give a residue (295 mg) consisting of **12** and **11b** in a ratio of ≈ 10 : 1, as seen from a ^{13}C NMR spectrum. The ^{13}C NMR data of **12** were identical with those described in the literature.[16]

Attempt to prepare 6-bromo-6-deoxy-D-altritol (**10**) *by reduction of* **9a** *with* $NaBH_4$. The acetylated bromolactone **9a** (1.0 g, 2.85 mmol) was dissolved in EtOH (20 ml) and cooled with ice. After adding of IR-120 (H^+) resin (5 ml), $NaBH_4$ (650 mg, 17.1 mmol) was added in such a rate, that the pH was kept below 6. The reaction mixture was stirred for 30 min, then more resin (10 ml) was added to bring the pH to ≈ 3. After filtration and concentration *in vacuo* below 30 °C, the residue was co-destilled with MeOH (3 x 20 ml) to give a syrup, which was dissolved in MeOH (5 ml), and AcCl (1 ml) was added. The solution was kept overnight at +5 °C, and concentration *in vacuo* below 30 °C gave crude 6-bromo-6-deoxy-D-altritol (**10**) (690 mg). ^{13}C NMR (D_2O): δ 36.6 (C-6), 63.8 (C-1), 71.3, 71.8, 72.9, 73.0 (C-2, C-3, C-4, C-5). The product was not stable, giving **12** after 1 d at r.t.

*3,6-Anhydro-1,2-4,5-di-*O*-isopropyliden-D-altritol* (**13**). 3,6-Anhydro-D-altritol (**12**) (680 mg, 4.14 mmol) was dissolved in dry acetone (30 ml). MeOH (1 ml) and AcCl (0.2 ml) were added and the solution kept overnight (TLC: hexane - EtOAc 2:1, Rf = 0.53), after which time the solution was neutralized with diluted ammonia and concentrated. The residue was purified by column chromatography (20 g silica gel, hexane - EtOAc 8:1) to give **13** (556 mg, 2.28 mmol; 55 %) as a syrup. The syrup crystallized on storage to give colorless crystals, mp. 50-51 °C, $[\alpha]_D^{20}$ -36.5° (*c* 1.0, $CHCl_3$) [Lit.[19]: mp. 51 °C, $[\alpha]_D^{20}$ -37° (*c* 0.9, $CHCl_3$)]. ^{13}C NMR ($CDCl_3$): δ 24.8, 25.1, 26.0, 26.5 (4 x Me), 65.3 (C-1), 74.7, 76.8, 81.2, 82.9 (C-2, C-4, C-5, C-6), 83.4 (C-3), 109.4, 112.5 (2 x $\underline{C}Me_2$). ^1H NMR ($CDCl_3$, 500 MHz): δ 1.27, 1.28, 1.34, 1.44 (each s, Me), 3.83 (dd, $J_{1,1'}$ 8.0, H-1), 3.90 (dd, $J_{6,6'}$ 10.0, H-6), 3.92-3.97 (m, H-1', H-3), 4.03 (dd, H-6'), 4.08 (ddd, $J_{2,3}$ 3.6, $J_{2,1'}$ 6.5, $J_{2,1}$ 8.0, H-2), 4.65 (dd, $J_{4,3}$ 1.8, H-4), 4.78 (ddd, $J_{5,6'}$ 4.5, $J_{5,6}$ 1.5, $J_{5,4}$ 6.2, H-5).

6-Bromo-6-deoxy-D-mannono-1,4-lactone (**15**). To a solution of mannonolactone **14** (12.07 g, 67.7 mmol) in dry pyridine (500 ml), Ph_3P (36.25 g, 138.2 mmol) was added with stirring, followed by addition of freshly dried CBr_4 (22.70 g, 68.5 mmol) in portions in the course of 30 min. The solution was stirred for 2 h at r.t. (TLC: toluene - EtOH 3:1, Rf = 0.4). Then MeOH (100 ml) was added and stirring was continued for 30 min. The solution was concentrated and co-destilled with toluene (2 x 200 ml). To the residue H_2O (100 ml) was added and the mixture was extracted with CH_2Cl_2 (2 x 150 ml). The organic phase was re-extracted with H_2O (3 x 50 ml) and the combined H_2O-phases were concentrated to a volume of 100 ml. This solution was extracted with EtOAc (8 x 100 ml) and the combined organic layers were dried (Na_2SO_4). Concentration gave crystalline **15** (11.57 g, 48.0 mmol; 71 %), mp. 136-139 °C, which was sufficiently pure for further reactions. Recrystallization twice from EtOAc gave an analytical sample, mp. 145-146 °C, $[\alpha]_D^{20}$ +54.7° (*c* 1.1,

H_2O). *Anal.* Found: C, 30.06; H, 3.86; Br, 32.97. Calc. for $C_6H_9O_5Br$: C, 29.90; H, 3.76; Br, 33.15: ^{13}C NMR (D_2O): δ 37.5 (C-6), 66.7, 70.0, 71.5 (C-2, C-3, C-5), 80.6 (C-4), 178.5 (C-1).

From the H_2O-phase crude 6-deoxy-6-(N-pyridinium)-D-mannono-1,4-lactone bromide **16** (1.20 g, ≈ 3.75 mmol; 5 %) crystallized. ^{13}C NMR (D_2O): δ 64.1 (C-6), 67.3, 69.8, 71.3 (C-2, C-3, C-5), 79.9 (C-4), 129.9, 146.1, 147.3 (pyr-C), 177.9 (C-1). ^1H NMR (D_2O): δ 4.20-4.39 (m, 3H), 4.48 (m, 1H), 4.54-4.63 (m, under HDO peak), 4.86 (dd, H-6'), 7.96 (t, 2 H), 8.46 (t, 1 H), 8.70 (d, 2 H). It was not further characterized.

2,3,5-Tri-O-acetyl-6-bromo-6-deoxy-mannono-1,4-lactone (**15a**). Crude 6-bromo-mannonolactone **15** (3.38 g, 14.03 mmol), prepared as described above, was acetylated with $Ac_2O/HClO_4$ (10 ml/0.5 ml). After 2 h the solution was poured on ice and warmed to room temperature. Extraction with CH_2Cl_2 gave after drying (Na_2SO_4) and concentration crude **15a** (4.80 g, 13.07 mmol; 93 %) as a syrup. Further purification by column chromatography (200 g silica gel, hexane - EtOAc 3 : 1) gave homogeneous **15a** (3.00 g, 8.17 mmol; 58 %) as a syrup, $[\alpha]_D^{20}$ +16.9° (*c* 1.67, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 19.7, 19.9, 20.1 (3 x OAc), 32.1 (C-6), 66.3, 67.8, 68.3 (C-2, C-3, C-5), 75.7 (C-4), 168.6, 168.7, 168.8, 168.9 (C-1, 3 x OAc). ^1H NMR ($CDCl_3$): δ 1.97, 1.98, 2.02 (each s, OAc), 3.57 (dd, $J_{6,5}$ 4.0, $J_{6,6'}$ 11.9, H-6), 3.68 (dd, $J_{6',5}$ 2.6, H-6'), 4.76 (dd, $J_{4,3}$ 2.9, $J_{4,5}$ 9.6, H-4), 5.20 (ddd, H-5), 5.63 (dd, H-3), 5.70 (d, $J_{2,3}$ 4.8, H-2).

3,6-Anhydro-D-mannono-1,4-lactone (**17**). The 6-bromolactone **15** (1.00 g, 4.15 mmol) was dissolved in H_2O (20 ml) and heated under reflux for 4 h. The solution was concentrated and co-destilled with toluene (2 x 10 ml). The obtained syrup was dissolved in H_2O (10 ml) and filtered over ion exchange resin (IR-45, OH^-, 20 ml). Concentration gave **17** (365 mg, 2.28 mmol; 55 %) as a syrup, which crystallized slowly from EtOH - EtOAc, mp. 109-111 °C, $[\alpha]_D^{20}$+119.2° (*c* 1.0, H_2O) [Lit.[11]: mp. 108-110 °C, $[\alpha]_D^{20}$ +125° (*c* 2.8, H_2O)]. The ^{13}C NMR data were identical with those described.[11]

6-Bromo-6-deoxy-D-mannitol (**18**). Crude acetylated bromolactone **15a** (7.63 g, 20.78 mmol), prepared as described above, was dissolved in EtOH (180 ml) and ion exchange resin (IR-120, H^+, 50 ml) was added. The mixture was cooled with ice and $NaBH_4$ (6.06 g, 159.3 mmol) was added slowly (≈ 2 h), and the reaction mixture was stirred overnight. Then more resin (100 ml) was added to acidify the solution and stirring was continued for 30 min. After filtration and concentration, the residue was co-destilled with MeOH (2 x 50 ml) and deacetylated with EtOH (30 ml) and AcCl (3 ml). The solution was kept at +5 °C overnight and the product then precipitated by addition of Et_2O (500 ml). The precipitate was filtered off, washed with Et_2O and dried to give **18** (2.40 g, 9.79 mmol; 47 %), mp. 115-116 °C. The mother liquor was concentrated to give 3.92 g of a syrupy residue, which still contained partially acetylated product. It was dissolved in EtOH/AcCl (20 ml/2 ml) and deacetylated overnight at r.t. After addition of Et_2O (200 ml), a further amount of **18** crystallized (1.28 g, 5.23 mmol), raising the total yield to 72 %. Recrystallization from MeOH - $CHCl_3$ did not change the mp., $[\alpha]_D^{20}$+2.5° (*c* 1.0, H_2O). *Anal.* Found: C, 29.49; H, 5.41; Br, 32.31. Calc. for $C_6H_{13}O_5Br$: C, 29.40; H, 5.35; Br, 32.61. ^{13}C NMR (D_2O): δ 38.9 (C-6), 64.1 (C-1), 69.8 (C-3), 69.9 (C-5), 71.1 (C-4), 71.6 (C-2), assigned by C-H correlation. ^1H NMR (D_2O, 500 MHz): δ 3.53 (dd, $J_{1,2}$ 6.2, $J_{1,1'}$ 11.8, H-1), 3.59 (dd, $J_{6,5}$ 5.0, $J_{6,6'}$ 11.0, H-6), 3.61 (ddd, $J_{2,1'}$ 2.8, $J_{2,3}$ 8.6, H-2), 3.67 (dd, $J_{6',5}$ 2.6, H-6'), 3.67 (dd, $J_{3,4}$ 1.1, H-3), 3.71 (dd, $J_{4,5}$ 9.0, H-4), 3.72 (dd, H-1'), 3.76 (ddd, H-5).

1,4-Anhydro-D-mannitol (**19**). 6-Bromo-6-deoxy-D-mannitol (**18**) (785 mg, 3.20 mmol) was dissolved in H_2O (30 ml) and heated to reflux for 3 h. After concentration 780 mg of a brown, partially crystalline residue was obtained, which was dissolved by heating in EtOH (10 ml). After some hours the crystallized product was filtered off and dried to give **19** (311 mg, 1.89 mmol; 59 %), mp. 142.5-144.5 °C. The mother

liquor was concentrated to 5 ml and a further amount of **19** (47 mg, 0.28 mmol) crystallized, raising the yield to 68 %. Recrystallization from EtOH gave an analytical sample, mp. 143-144.5 °C, $[\alpha]_D^{20}$ -23.7° (*c* 1.0, H_2O), [Lit.[21]: m.p. 145-148 °C, $[\alpha]_D^{20}$ -24° (H_2O). ^{13}C NMR data were identical with those described in literature.[16] The mother liquor contained a 4:1 mixture of *1,5-anhydro-D-mannitol* **20** and **19**, the ^{13}C NMR data of **20** were identical with published data.[16]

6-Bromo-6-deoxy-D-idono-1,4-lactone (**22**). D-Idono-1,4-lactone (**21**)[22] (30.0 g, 168.4 mmol) was stirred with HBr/AcOH (225 ml) for 1.75 h. Then MeOH (400 ml) was added carefully through a reflux condenser and the solution was kept overnight. After concentration and co-concentration with H_2O (3 x 150 ml), the syrup was dissolved in H_2O (100 ml) and extracted with EtOAc (10 x 80 ml). The combined extracts were dried (Na_2SO_4), filtered over active carbon and concentrated. The H_2O-phase was concentrated and co-concentrated with 4N HCl (60 ml). The residue (13 g) was dissolved in H_2O (20 ml) and extracted again with EtOAc (5 x 50 ml). The combined organic phases were dried (Na_2SO_4) and mixed with the syrup obtained from the first extractions, followed by concentration to give a red syrup (35 g). The dibromolactones were removed by dissolving in H_2O (350 ml) followed by extraction with CH_2Cl_2 (2 x 30 ml) and EtOAc (5 x 30 ml). The H_2O-phase was concentrated to give **22** (22.95 g, 95.2 mmol; 56 %) as a yellow syrup. A sample was purified by column chromatography (silica gel, EtOAc) to give **22** as a colorless syrup, $[\alpha]_D^{20}$ -31.4° (*c* 1.0, H_2O). ^{13}C NMR (D_2O): δ 34.1 (C-6), 68.6, 72.6, 74.0 (C-2, C-3, C-5), 80.3 (C-4), 177.7 (C-1).

3,6-Anhydro-D-idono-1,4-lactone (**23**). The bromolactone **22** (2.73 g, 11.32 mmol) was dissolved in H_2O (30 ml) and heated to reflux for 2 h. A ^{13}C-NMR spectrum, measured directly on the solution, showed a 1:1 mixture of lactone **23** and acid **24** [^{13}C NMR of **24** (D_2O): δ 70.3, 73.5, 77.1, 77.7 (C-2, C-4, C-5, C-6), 80.9 (C-3), 175.7 (C-1)]. The solution was concentrated, then co-concentrated with 4N HCl (4 x 20 ml) and toluene (4 x 20 ml) to give **23** (1.45 g, 9.05 mmol; 80 %) as slightly yellow syrup, which crystallized slowly on storage. Recrystallization twice from EtOAc - hexane gave an analytical sample, mp. 90-92 °C, $[\alpha]_D^{20}$ -85.6° (*c* 1.0, acetone) [Lit[28]: mp. 111-112 °C, $[\alpha]_D^{20}$ +94.9° (*c* 1, acetone) for the L-enantiomer]. *Anal.* Found: C, 45.10; H, 5.50. Calc. for $C_6H_8O_5$: C, 45.00; H, 5.04. m/z (CI, NH_3), 178 ($M + NH_4^+$). ^{13}C NMR (D_2O): δ 72.4, 73.9, 74.0 (C-2, C-5, C-6), 83.4, 87.9 (C-3, C-4), 178.3 (C-1).

1,4-Anhydro-D-iditol (**26**). 6-Bromo-6-deoxy-D-idono-1,4-lactone **22** (3.16 g, 13.11 mmol) was dissolved in H_2O (50 ml) and ion exchange resin (IR-120, H^+, 10 ml) was added. $NaBH_4$ (996 mg, 26.22 mmol) was added in such a rate at 0 °C, that the pH was kept at ≈ 5-6. The same amount $NaBH_4$ was added, allowing the pH to increase to ≈ 9, and stirring was continued for 30 min, while the reaction mixture warmed up to room temperature. More resin (15 ml) was added to bring the pH to ≈ 3, followed by filtration and concentration at 30 °C. Co-concentration with MeOH (3 x 50 ml) left 3.16 g of a syrup, which contained 6-bromo-6-deoxy-iditol (**25**) [^{13}C NMR (D_2O): δ 35.6 (C-1), 63.5 (C-1), 71.8, 72.0, 72.1, 72.6 (C-2, C-3, C-4, C-5)] and 1,4-anhydro-D-iditol (3,6-anhydro-D-iditol) (**26**) in a ratio of 4 : 1. The mixture was dissolved in H_2O (50 ml) and heated to reflux for 2 h. After filtration over ion exchange resin (IR-45, OH^-, 50 ml) and concentration, **26** (1.50 g, 9.14 mmol; 70 %) was obtained as a syrup, which crystallized slowly (within weeks) from ^iPrOH - EtOAc, mp. 89-94 °C. Recrystallization from ^iPrOH gave an analytical sample, mp. 96.5-98 °C, $[\alpha]_D^{20}$ +18.2° (*c* 1.91, H_2O), [Lit.[29]: mp. 94-95 °C, $[\alpha]_D^{22}$+17.9° (*c* 3.5, H_2O)]. ^{13}C NMR data were identical with those described in literature.[16]

*3,6-Anhydro-2-deoxy-D-*arabino*-hexono-1,4-lactone* (**30**). 6-Bromo-2,6-dideoxy-D-*arabino*-hexono-1,4-lactone (**29**)[15c] (5.0 g, 22.22 mmol) was dissolved in H_2O (200 ml) and heated under reflux for 2 h.

Concentration and co-destillation with toluene (3 x 50 ml) gave crude **30** (3.97 g) as slightly brown, crystalline residue, which was pure enough for further reactions according to its ^{13}C NMR spectrum. Recrystallization from Et_2O - $CHCl_3$ gave pure **30** (1.96 g, 13.60 mmol; 61 %) as colorless needles, mp. 78.5-79 °C, $[\alpha]_D^{20}$ +88.7° (*c* 1.0, $CHCl_3$) [Lit.[30] mp. 77-78 °C, $[\alpha]_D^{20}$ +89° (*c* 1, $CHCl_3$)]. The ^1H and ^{13}C NMR data were identical with those described.[30,31]

3,6-Anhydro-2-deoxy-D-lyxo-hexono-1,4-lactone (**32**). 6-Bromo-2,6-dideoxy-D-*lyxo*-hexono-1,4-lactone (**31**)[15c] (1.0 g, 4.44 mmol) was dissolved in H_2O (20 ml) and heated under reflux for 2 h, followed by filtration over ion exchange resin (IR-67, OH^-, 10 ml). The filtrate was concentrated and co-destilled with toluene to give **32** (601 mg, 4.17 mmol; 94 %) as a slightly yellow syrup, which crystallized on storage. Recrystallization twice from EtOAc - pentane gave an analytical sample, mp. 85-86 °C , $[\alpha]_D^{20}$ -79.0° (*c* 1.05, $CHCl_3$) [Lit.[30] mp. 84-85 °C, $[\alpha]_D^{20}$+80° (*c* 1.07, $CHCl_3$) for the L-enantiomer]. The ^1H and ^{13}C NMR data were identical with those described.[30,31]

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