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A new efficient and stereospecific conversion of aminodeoxyalditols into aminoalkyl-substituted tetrahydrofurans

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Abstract

Reaction of a series of aminodeoxy-pentitols and -hexitols in anhydrous hydrogen fluoride with formic acid as catalyst gave the corresponding 2,5- and 3,6-anhydro-aminodeoxyalditols; namely, 1-amino-2,5-anhydro-1-deoxy-D-arabinitol, -D-xylitol, and -D-ribitol; 1-amino-3,6-anhydro-1-deoxy-D-glucitol, -D-mannitol, and -D-galactitol; and 2-amino-3,6-anhydro-2-deoxy-D-glucitol in yields of 95–100%. 1-Amino-1-deoxy-L-rhamnitol and its dimethylamino derivative gave 1-amino-2,5-anhydro-1,6-dideoxy-D-gulitol and 2,5-anhydro-1,6-dideoxy-1-dimethylamino-D-gulitol with configurational inversion at C-5. In all cases the reactive intermediate is believed to be a 4,5- or 5,6-dioxolenium ion, which can react intramolecularly with a hydroxy group to form a five-membered oxolane ring. The dimethylamino-D-*gulo*-oxolane was converted into a new 3-hydroxymuscarine isomer, namely, 2,5-anhydro-1,6-dideoxy-1-trimethylammonio-D-gulitol chloride. D-*arabino*-Hexosulose phenylosotriazole gave the corresponding 3,6-anhydro-D-*arabino*-hexosulose phenylosotriazole. Syntheses of the 1-amino-1-deoxyalditols were performed by reductive amination with benzylamine–sodium borohydride followed by catalytic hydrogenation over Pd–C. © 1996 Elsevier Science Ltd.

Keywords: Aminodeoxyalditol; Aminoalditol; Anhydroalditols; Hydrogen fluoride; Tetrahydrofurans

1. Introduction

Anhydrides of aminodeoxyalditols with a tetrahydrofuran core and an amino substituent in the side chain are important building blocks in the synthesis of more complex

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molecules. Despite earlier use, for example, in syntheses of C-nucleosides [1,2], as analogues of muscarine [3,4], as precursors of surface-active molecules [5], or as potential enzyme inhibitors [1] [6,7], no efficient and stereospecific synthesis of the aminoanhydroalditols has yet been published.

The chiral pool of sugars provides cheap and easily accessible starting materials, with several preorganized stereocenters. Several ways of transforming sugars and simple derivatives into various substituted tetrahydrofurans have already been published. Among these can be mentioned: (i) the displacement of furanosyl halides with cyanide ion [1]; (ii) the deamination of 2-amino-aldoses and -aldonic acids [8,9] and of 1-aminoalditols [10] with nitrous acid; (iii) the intramolecular S_N2 displacement of triflate [11], tosylate [9,12], or bromide [13] functionalities by either a hydroxy or benzyloxy group; (iv) the acid-catalyzed cyclization of alditols [14]; (v) the formic acid catalyzed dehydration of polyols in anhydrous hydrogen fluoride [15]; and (vi) the Michael-type addition of a hydroxy group to a double bond [16,17]. None of these methods allows the direct introduction of an amine functionality, but in several cases precursors of such compounds can be obtained. Problems arising from diastereomeric mixtures are a serious drawback for many of the methods listed above.

We now disclose a stereospecific synthesis of amine-substituted tetrahydrofurans in high yields directly from the corresponding aminoalditols.

2. Results

The aminoalditols (**1**, **3**, **5**, **7–9**, **15**) were obtained in good yields (Table 1) from the corresponding sugars by reductive amination with benzylamine–sodium borohydride and subsequent catalytic hydrogenation. The synthesis of 1-deoxy-1-dimethylamino-L-rhamnitol (**17**) was accomplished by treatment of L-rhamnose with 1 equivalent of dimethylamine in water to form the imine; addition of ethanol and 1 equivalent of acetic acid followed by sodium borohydride effected reduction of the iminium ion, which is an intermediate in the Amadori rearrangement [22], to give **17** (71%) and L-rhamnitol (21%) plus some minor products. 1-Deoxy-1-dimethylamino-L-rhamnitol (**17**) was isolated crystalline in 43% yield.

Treatment of the aminodeoxyalditols in anhydrous HF with 1 equivalent of formic acid yielded the 2,5- (**2**, **4**, **6**) and 3,6-anhydrides (**10–12**, **14**) of the amino-pentitols (**1**, **3**, **5**) and -hexitols (**7–9**, **13**), respectively [2] (Schemes 1 and 2). 1-Amino-1-deoxy-L-rhamnitol hydrochloride (**15**) gave the 2,5-anhydride **16** (Scheme 3). 1-Deoxy-1-dimethylamino-L-rhamnitol (**17**) formed the 2,5-anhydride **18** which was methylated to give the previously unknown 3-hydroxymuscarine isomer **19** in 65% yield from **18**. In one case, the osotriazole **20** was converted into the corresponding 3,6-anhydride **21** (Scheme 4). Yields of the crude hydrofluorides (**2a**, **4a**, **6a**, **10a**, **11a**, **12a**, **14a**, **16a**,

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[1] Recent studies have shown the corresponding pyranosyl derivatives, namely, the 1-amino-2,6-anhydro-1-deoxyheptitols, to be potential enzyme inhibitors. See ref. [6].

[2] This work has in part been published in ref. [23].

Table 1
Data for amino- and benzylamino-deoxyalditols

	^{13}C Chemical shifts [a] (δ) (not assigned)						Cryst. yield (%)	Mp (°C)	Lit. mp (°C)	$[\alpha]_D^{25}$ (°)	Lit. $[\alpha]_D$ (°)	Ref.
										In H_2O		
1-Amino-1-deoxy-D-arabinitol · HCl (**1**)	72.1	71.4	67.2	63.6	43.5	–	78	135–136	136.5–137.5	+12.8 (*c* 2.3)	+15	[18]
									135–135.5			[10]
									166–167 [d]		+11 [d]	[19]
1-Benzylamino-1-deoxy-D-arabinitol · HCl	72.0	71.4	66.5	63.6	50.6	–	50	198–199		+12.4 (*c* 2.3)	–	
									122–123 [c]			[20]
1-Amino-1-deoxy-D-xylitol · HBr (**3**)	72.5	72.4	68.6	63.2	42.9	–	71	164–166	167–168	–12.2 (*c* 2.4)	–13	[19]
									139–140 [e]			[10]
1-Benzylamino-1-deoxy-D-xylitol · HBr	72.4	72.4	67.9	63.3	50.0	–	83	113–115	(oil) [c]	–13.3 (*c* 2.1)	–	[20]
1-Amino-1-deoxy-D-ribitol · HCl (**5**)	73.6	72.5	68.7	63.3	42.0	–	~100 (oil) [b]	–	126–128	–		[10]
									132.5–134		–8	[18]
1-Benzylamino-1-deoxy-D-ribitol · HCl	73.7	72.5	67.9	63.4	49.0		65	125–126	102–103 [c]	–14.9 (*c* 2.3)	–	[20]
1-Amino-1-deoxy-D-glucitol (**7**)	74.5	71.8	71.4	67.4	63.7	43.6	82	127–130	124.5–130	–6.5 (*c* 2.2)	–	[20]
1-Benzylamino-1-deoxy-D-glucitol · HCl	71.7	71.4	69.0	67.4	63.5	49.6	66	190–191	138–139 [c]	–16.4 (*c* 2.4)	–	[20]
1-Amino-1-deoxy-D-mannitol · HCl (**8**)	71.7	71.4	69.7	68.0	63.9	43.4	67	159–161	163–165	+5.5 (*c* 2.0)	+5	[18]
									134–135 [c]		+1 [c]	[18]
1-Benzylamino-1-deoxy-D-mannitol · HCl	71.8	71.4	69.7	67.3	63.9	50.7	76	174–175	–	+10.5 (*c* 2.0)	–	–
1-Amino-1-deoxy-D-galactitol · HCl (**9**)	71.2	70.7	70.0	67.2	64.0	43.6	85	161–163	146–148 [c]	–12.4 (*c* 2.1)	–1 [c]	[20]
									136 [d]		–10.5 [d]	[19]
1-Benzylamino-1-deoxy-D-galactitol · HCl	71.3	70.8	70.1	66.6	64.1	50.8	66	224–225	157–159 [c]	–10.8 (*c* 1.0)	–6 [c]	[20]
2-Amino-2-deoxy-D-glucitol · HCl (**13**)	71.6	71.3	66.8	63.6	59.7	56.2	74	158–160	159–161	–6.5 (*c* 1.6) [f]	–6.8 [f]	[21]
1-Amino-1-deoxy-L-rhamnitol · HCl (**15**)	73.9	71.8	68.2	67.7	43.3	19.8	85	133–134	–	+5.9 (*c* 2.0)	–	–
1-Benzylamino-1-deoxy-L-rhamnitol · HCl	73.8	71.9	67.7	67.4	50.5	19.8	80	187–189	–	–2.1 (*c* 2.3)	–	–

[a] Chemical shifts in D_2O of alditol part of the molecules. Referenced to internal dioxane, δ 67.4.

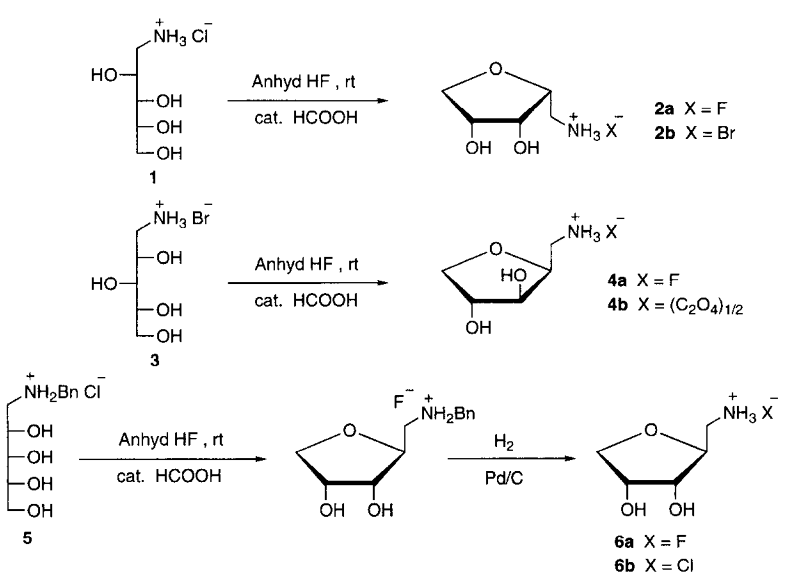
[b] Not obtained as crystalline material.

[c] Free amine.

[d] Hydrobromide.

[e] Hydrochloride.

[f] $[\alpha]_{365}^{25}$.

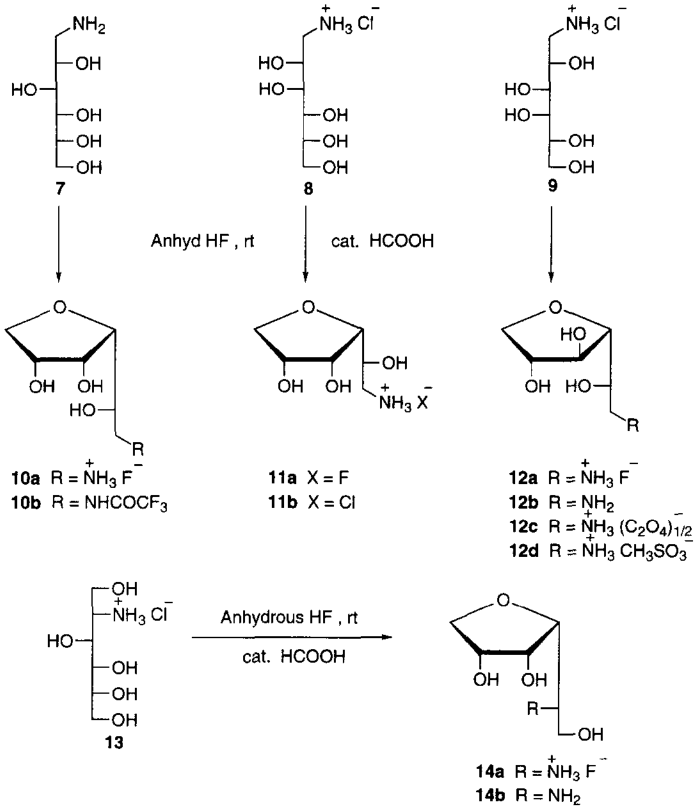


Scheme 1.

18a) and of the neutral **21** were in all cases 95–100%, as judged by ^{13}C NMR spectroscopy. All compounds could be crystallized in overall yields of 66–81% either as their salts or, for **14b** and **21**, as the neutral compounds and in the case of **10** as the trifluoroacetamide **10b**. The hydrofluorides, of which many could be crystallized, had a varying content of amine-complexed HF, which could only be accounted for by titration. Melting points were always broad due to loss of HF on heating. In some cases isolation of the hydrofluorides was prevented by formation of formamides which required boiling in dilute acid or treatment with a basic ion-exchange resin to be hydrolyzed.

3. Discussion

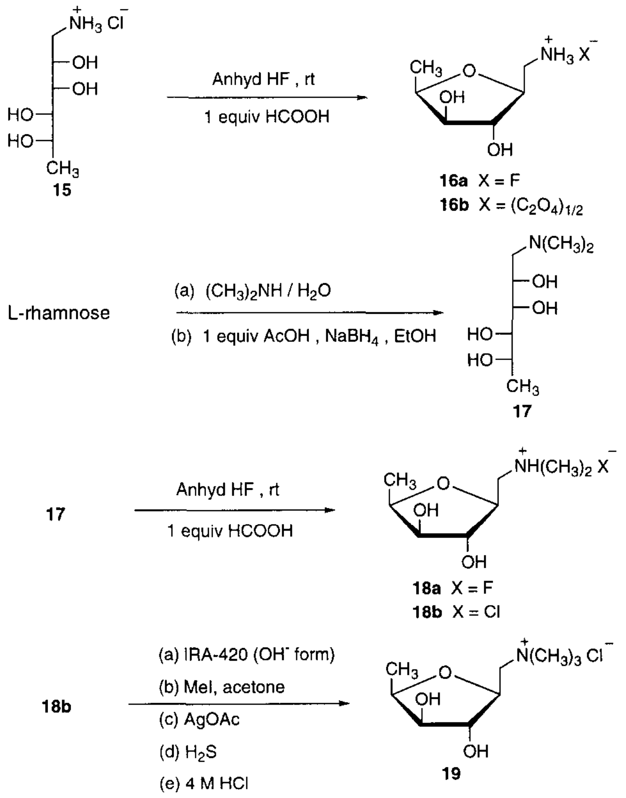
The reactions of sugars, lactones, alditols, and polysaccharides in anhydrous HF have been thoroughly investigated [24]. As early as 1962, Hedgley and Fletcher [25] proposed cyclic dioxolenium ions as intermediates in the isomerization of acetylated cyclitols in HF. Ions of this type had been isolated by Meerwein a few years earlier. Meerwein also showed that these ions could react with alcohols to give ethers [26]. In 1990 Defaye et al. [15] showed how alditols, hexoses, and hexonolactones could be transformed into tetrahydrofuran derivatives by the formic acid catalyzed reaction in HF. Cyclic formoxonium ions were detected in the reaction mixture by ^{13}C NMR spectroscopy, and a mechanism analogous to that depicted in Scheme 5 was proposed. The formoxonium ions were shown to have a much higher reactivity compared to the acetoxonium ions in accordance with Burt et al. [27]. In the case of alditols the reaction led to mixtures of mono- and di-anhydrides, but reaction conditions could be changed to favour one of the products.



Scheme 2.

The aminopentitols (**1**, **3**, **5**) gave only 2,5-anhydrides by reaction of HO-2 with a 4,5-formoxonium ion. In the case of the aminohexitols (**7**–**9**, **13**), only the 3,6-anhydrides were formed from reaction of HO-3 with a 5,6-formoxonium ion. In both cases, the opening of the formoxonium ion took place in an endo fashion [28]. The reaction is believed to take place with inversion at the primary carbon atom (see Scheme 5). Due to difficulties in crystallizing 1-amino-1-deoxy-D-ribitol hydrochloride, the benzylamine **5** was used for the cyclization in HF in the synthesis of **6** (see Scheme 1). Reaction of the benzylamines in HF–formic acid was shown in all cases to yield the corresponding benzylamino-substituted anhydrides in almost quantitative yields.

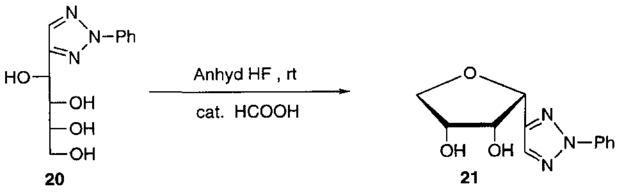
The hexitols formed only the five-membered anhydrides, which are the kinetically more favoured. In some cases, less than 5% of the 2,5-anhydrides resulting from attack of HO-2 at C-5 were observed. These compounds were never isolated and only detected by their ^{13}C NMR spectra. This selectivity can mainly be ascribed to less steric hindrance at the primary carbon atom. In addition, attack by HO-2 would bring the positive charge from the amino function close to the charge of the formoxonium ion, resulting in repulsion. However, this effect does not result in an observable lower reactivity of the aminopentitols and the 2-amino-2-deoxyhexitol **13** compared to the



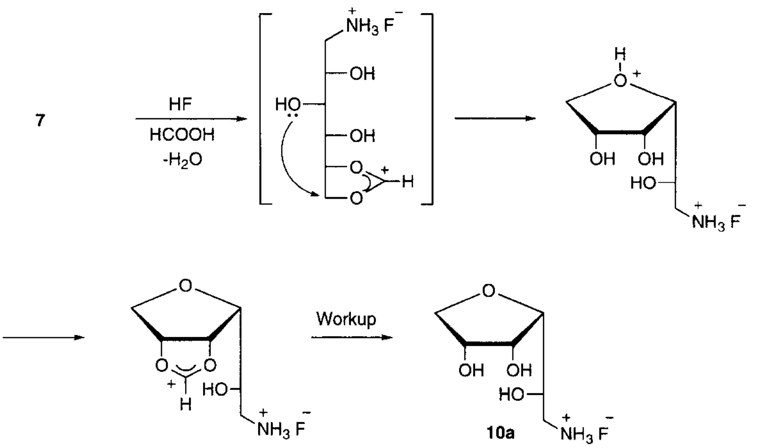
Scheme 3.

1-amino-1-deoxyhexitols. The repulsion of the two positive charges may nevertheless account for the missing products expected from the 2,3-formoxonium ions. It could be argued that differences in protonation of HO-2 and HO-5 could result in reactivity differences, which could account for the observed products, but this effect is believed to be of minor importance.

The importance of the repulsion is also supported by the products obtained from compounds **15** and **17**. Only products from a 4,5-formoxonium ion are obtained. The stereochemistry of **16** and **18** (Scheme 3) confirms that the reaction takes place with



Scheme 4.



Scheme 5. The proposed mechanism for the formic acid catalyzed reaction in HF, exemplified with 1-amino-1-deoxy-D-glucitol (**7**).

configurational inversion at C-5. The stereochemistry of these two products has been confirmed by ^{13}C NMR spectroscopy (see later) and by comparison with the previously prepared enantiomeric species (see experimental section). The *N-tert*-butoxycarbonyl derivative of **16** has previously been isolated in low yield from a mixture with its C-2 epimer in a synthesis starting from 5-deoxy-D-xylose [16]. The D-*gulo* compound **18** was converted into the 3-hydroxymuscarine isomer **19**. The enantiomer of **19** has previously been described by Kuszmann and Dvortsák [4], who found no muscarine-like activity for that isomer. The reaction of **20** to yield the known **21** [29,30] is a special case which shows the potential of the HF–formic acid method for *C*-nucleoside synthesis.

The structures of the products in this work have, in the cases of known compounds (**6**, **11**, **18** [3], and **21**), all supported the proposed mechanism. The structures of the remaining compounds have been deduced from the predictions of the mechanism. It is well known that ^{1}H NMR coupling constants give very limited information about the structures of five-membered rings due to their great flexibility [31]. On the other hand, useful information could in some cases be extracted from the ^{13}C NMR spectra. In the cases of **16** and **18** the cis relationship between Me-6 and HO-4 resulted in a shielding of Me-6 by ~ 5 ppm [32] (δ 13.9 and 13.8, respectively).

The synthesis of **17** is to our knowledge the first example of the synthesis of a dialkylaminoalditol by reduction of the intermediate iminium ion of the Amadori rearrangement. This method has also been applied for the synthesis of the corresponding D-mannitol and D-glucitol derivatives in moderate yields [4]. Only two other anhydrides of a similar structure have been published. These are 1-amino-3,6-anhydro-D-allitol [33] and 5-amino-1,4-anhydro-5,6-dideoxy-L-galactitol [34].

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[3] The enantiomer of **18b** was synthesized by Kuszmann and Dvortsák [4].

[4] J.C. Norrild, C. Pedersen, and J. Defaye, unpublished results.

4. Experimental

General methods.—The ^{13}C and ^{1}H NMR spectra were recorded on Bruker 250 and AM 500 spectrometers, respectively. Chemical shifts (δ) were measured in ppm and coupling constants (J) in Hz. Dioxane (δ 67.4) was used as the internal standard for ^{13}C NMR in D_2O. For spectra in methanol-d_4, the solvent signal was used as the internal standard (δ 49.0). In Me_2SO-d_6, the solvent signal was set to δ 39.5. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Melting points are uncorrected. Ion-exchange resins used were of commercially available Amberlite types. Evaporations were performed in vacuo on a rotary evaporator at 40–50 °C. All reactions in anhydrous HF were carried out in polyethylene bottles equipped with a screw cap. Microanalyses were performed by Leo Microanalytical Laboratory.

General synthesis of aminoalditols **1**, **3**, **5**, **7–9**, **15**.—1-Amino-1-deoxy-pentitols and -hexitols were prepared from the corresponding sugars by a method analogous to that of Kagan et al. [20]. Instead of hydrogenation of the benzylimines over Pt, reduction was accomplished using $NaBH_4$ (1.2 equiv) for 1 h at room temperature in MeOH to yield the benzylamines. Acidification (HCl or HBr), evaporation, and coevaporation three times with MeOH, to remove boric acid as $B(OMe)_3$, was followed by extraction of the residue with EtOH or MeOH to remove inorganic salts. Evaporation and recrystallization of the residue from an appropriate solvent yielded the crystalline benzylammonium salts (Table 1). The aminoalditols were obtained in a quantitative yield (confirmed by ^{13}C NMR) by catalytic hydrogenation: H_2 (50 atm), Pd–C(5%) in water (pH adjusted to ~ 8–9 with aq NH_3) at 70 °C, 15 h. The compounds were crystallized in yields as given in Table 1 which also contains physicochemical data and comparison with the literature.

*2-Amino-2-deoxy-*D*-glucitol hydrochloride* (**13**) [35,21].—2-Amino-2-deoxy-D-glucose · HCl (21.50 g, 0.10 mol) was dissolved in H_2O (100 mL) and cooled to 5 °C. $NaBH_4$ (10.0 g, 0.26 mol) was added in portions keeping the temperature below 10 °C. The solution was stirred for 1 h and carefully acidified with concd HCl, keeping the temperature below 10 °C to avoid vigorous foaming. The water was evaporated and the residue was coevaporated three times with MeOH. The residue was extracted with boiling MeOH (200 mL) and the NaCl was filtered off. The MeOH was evaporated and the white solid recrystallized from MeOH (~ 75 mL) and water (~ 20 mL) to yield colourless cubic crystals (16.0 g, 74%); mp 158–160 °C, lit. 159–161 °C [21]; $[\alpha]_{365}^{25}$ $-6.5°$ (c 1.57, H_2O), lit. $-6.8°$ (c 0.76, H_2O) [21]; ^{13}C NMR (D_2O): δ 71.6, 71.3, 66.8, 63.6, 59.7, 56.2. Anal. Calcd for $C_6H_{16}ClNO_5$: C, 33.11; H, 7.41; Cl, 16.29; N, 6.44. Found C, 33.03; H, 7.38; Cl, 16.24; N, 6.36.

*1-Deoxy-1-dimethylamino-*L*-rhamnitol* (**17**).—L-Rhamnose · H_2O (10.0 g, 60.9 mmol) and dimethylamine (40% in water) (7.0 g, 62 mmol) were stirred for 30 min at 35 °C to yield a viscous light-yellow solution. Absolute EtOH (100 mL) was added followed by cooling to 0 °C. Glacial AcOH (3.7 mL, 59 mmol) was added in one portion immediately followed by addition of $NaBH_4$ (3.5 g, 93 mmol) in small portions in the course of 15 min keeping the temperature below 15 °C. After an additional 15 min of stirring, the solution was acidified with concd HCl. The solvent was evaporated and the residue was coevaporated three times with MeOH. The resulting semicrystalline oil was extracted with abs EtOH (100 mL) to remove NaCl, the solution filtered, and the filtrate evaporated to dryness. ^{13}C NMR showed a major compound ($\sim$ 71%), a minor compound ($\sim$ 21%) (which could be recognized as L-rhamnitol), and some undefined minor peaks ($\sim$ 8%). The crude oil was dissolved in a small amount of water and absorbed on a column (90 mL) of IR-120 (H^+) ion-exchange resin. The resin was washed with water (500 mL) and then eluted with NH_3–water ($\sim$ 600 mL). The concentration of NH_3 was gradually increased from 1 to 6 M to avoid warming of the column. Evaporation of the eluate yielded a crude crystalline material (6.5 g); ^{13}C NMR showed only one compound. The residue was extracted with hot EtOAc (100 mL), and the extract was treated with activated charcoal and filtered through Celite. Evaporation of the filtrate to dryness yielded a crystalline residue (5.5 g) which was recrystallized from EtOAc (30 mL). Slow cooling yielded, after scratching of the first oily precipitate, a colourless crystalline compound. The crystals were isolated at 0 °C, washed with cold EtOAc, and dried in vacuo. The yield was 4.93 g (43%). A sample was recrystallized from EtOAc for analysis; mp 77–94 °C. Further recrystallizations did not change the rotation nor the mp; $[\alpha]_D^{25}$ $-5.9°$ (*c* 1.48, H_2O); ^{13}C NMR (D_2O): δ 19.9, 45.3, 61.5, 67.8, 69.5, 72.7, 74.5. Anal. Calcd for $C_8H_{19}NO_4$: C, 49.72; H, 9.91; N, 7.25. Found C, 49.47; H, 9.94; N, 7.13.

*1-Amino-2,5-anhydro-1-deoxy-*D*-arabinitol hydrobromide* (**2b**).— 1-Amino-1-deoxy-D-arabinitol · HCl (**1**; 3.00 g, 16.0 mmol) was dissolved in anhyd HF (15 mL) while cooling in an ice–acetone bath; HCl was evolved. Formic acid (0.15 mL, 4.0 mmol) was added and the mixture was left for 4 h at room temperature. The HF was evaporated in a stream of air, yielding a colourless oil. The remaining HF was removed by coevaporation three times with MeOH (10 mL) followed by evaporation at 50 °C in a stream of air. The resulting oil (1-amino-2,5-anhydro-1-deoxy-D-arabinitol · $(HF)_x$ as the only product observable in the ^{13}C NMR spectrum) was dissolved in a small amount of water and adsorbed on a column (75 mL) of IRA-420 (OH^-) ion-exchange resin. The amine was eluted with water until a neutral eluate (750 mL). Concentration followed by evaporation twice with abs EtOH yielded 2.1 g (98%) of 1-amino-2,5-anhydro-1-deoxy-D-arabinitol as a colourless solid. The amine was turned into the bromide salt by dissolving in MeOH and adding 1 equiv of HBr (48%). Evaporation of the solvent and recrystallization from abs EtOH (23 mL) + H_2O (0.5 mL) yielded 2.76 g (81% overall) of the hydrobromide as colourless flakes; mp 128–129 °C. A second fraction, from addition of ether to the filtrate, yielded an additional 0.34 g (10%); mp 127–128 °C. A sample was recrystallized for analysis; mp 128–129 °C; $[\alpha]_D^{25}$ $+8.6°$ (*c* 1.25, H_2O); ^{13}C NMR (D_2O): δ 40.1, 71.6, 71.9, 72.5, 76.3. Anal. Calcd for $C_5H_{12}BrNO_3$: C, 28.06; H, 5.65; Br, 37.33; N, 6.54. Found C, 28.15; H, 5.66; Br, 36.68; N, 6.58.

*1-Amino-2,5-anhydro-1-deoxy-*D*-xylitol oxalate* (**4b**)[5] [23,36].— 1-Amino-1-deoxy-D-xylitol · HBr (**3**; 3.00 g, 12.9 mmol) was dissolved in anhyd HF (15 mL) while cooling in an ice–acetone bath. Hydrogen bromide was evolved. Formic acid (0.24 mL, 0.5 equiv) was added and the mixture was left for 20 h at room temperature. Workup and ion exchange as for **2** yielded 1.8 g of the amine as a colourless oil (still containing

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[5] First described as the racemic mixture of the hydrochloride in refs. [21,35].

some EtOH). The crude oil (pure as seen from ^{13}C NMR) was dissolved in abs EtOH (25 mL) and oxalic acid (~ 0.58 g, 0.5 equiv) in EtOH (25 mL) was added. It was not possible to obtain crystals from the EtOH–water mixture, so the solvent was evaporated and the resulting oil was dissolved in boiling MeOH (20 mL), from which colourless crystals were formed immediately. The yield of 1-amino-2,5-anhydro-1-deoxy-D-xylitol · 0.5 oxalate after drying was 1.75 g (76%); mp 152–154 °C; $[\alpha]_D^{25}$ +1.4° (*c* 1.43, H_2O); ^{13}C NMR (D_2O): δ 39.7, 73.9, 76.9, 77.5, 77.6, 174.1. Anal. Calcd for $C_6H_{12}NO_5$: C, 40.45; H, 6.79; N, 7.82. Found C, 40.38; H, 6.76; N, 7.82.

1-Amino-2,5-anhydro-1-deoxy-D-ribitol hydrochloride (**6b**).—1-Benzylamino-1-deoxy-D-ribitol · HCl (**5**; 3.00 g, 10.8 mmol) was dissolved in anhyd HF (21 mL) while cooling in an ice–acetone bath. Hydrogen chloride was evolved. Formic acid (0.21 mL, 0.5 equiv) was added and the mixture was left for 5 h at room temperature. Workup to give the hydrofluoride, as for **2**, gave a colourless oil which was dissolved in H_2O (70 mL) and Pd–C(5%) (250 mg) was added. The anhydro-benzylamine was hydrogenolyzed (H_2, 50 atm/55 °C) overnight. The resulting solution was filtered through Celite and concentrated. The resulting oil (1-amino-2,5-anhydro-1-deoxy-D-ribitol · HF, **6a**) was treated with anion-exchange resin as above. The eluate was concentrated almost to dryness and redissolved in EtOH. Acidification with concd HCl resulted in precipitation of the hydrochloride. Evaporation of the solvent followed by recrystallization from EtOH–water yielded **6b** as long colourless needles. A sample was recrystallized for analysis; mp 166–168 °C, lit. 164–168 °C [37]; $[\alpha]_D^{25}$ −57.3° (*c* 1.56, H_2O); ^{13}C NMR (D_2O): δ 42.2, 71.7, 73.5, 74.3, 77.9. Anal. Calcd for $C_5H_{12}ClNO_3$: C, 35.41; H, 7.13; Cl, 20.90; N, 8.26. Found C, 35.46; H, 7.15; Cl, 20.67; N, 8.34.

3,6-Anhydro-1-deoxy-1-trifluoroacetamido-D-glucitol (**10b**) [23].—1-Amino-1-deoxy-D-glucitol (**7**; 2.00 g, 11.0 mmol) was dissolved in anhyd HF (10 mL) while cooling in an ice–acetone bath. Formic acid (0.21 mL, 5.5 mmol) was added and the mixture was left for 4 h at room temperature. After workup and ion exchange as for **2b**, 1-amino-3,6-anhydro-1-deoxy-D-glucitol was obtained as a colourless oil which crystallized slowly after seeding. The partly crystalline product was dissolved in dry MeOH (75 mL), and NEt_3 (0.3 g) and CF_3COOMe (1.63 g, 12.7 mmol) were successively added. The clear solution was stirred for 22 h. Evaporation of the solvent and recrystallization from EtOAc (20 mL) + hexane (15 mL) yielded after cooling long colourless needles. The crystals were isolated after standing at −10 °C overnight, washed with EtOAc–hexane, and dried in vacuo over concd H_2SO_4; 2.16 g (76% overall yield); mp 114–121 °C. The product was pure as judged by its ^{13}C NMR spectrum. Recrystallization of 0.55 g from EtOAc–hexane gave **10b** (0.50 g); mp 122–124 °C; $[\alpha]_D^{25}$ −12.8° (*c* 1.50, H_2O); ^{13}C NMR (CD_3OD): δ 43.9, 69.3, 72.7, 72.8, 73.2, 81.9, 117.5 (q, 287 Hz), 159.2 (q, 37 Hz). Anal. Calcd for $C_8H_{12}F_3NO_5$: C, 37.07; H, 4.67; N, 5.40. Found C, 37.18; H, 4.73; N, 5.57.

1-Amino-3,6-anhydro-1-deoxy-D-mannitol hydrochloride (**11b**).—1-Amino-1-deoxy-D-mannitol · HCl (**8**; 3.00 g, 13.8 mmol) was dissolved in anhyd HF (15 mL) while cooling in an ice–acetone bath. Hydrogen chloride was evolved. Formic acid (0.26 mL, 1 equiv) was added and the mixture was left for 4 h at room temperature. Workup and ion exchange were performed as above. The yield of the crude amine was 1.85 g (> 95% pure) as a colourless oil, which slowly crystallized as needles on standing. The amine was dissolved in abs EtOH (25 mL) and the solution was acidified with concd HCl (~ 0.9 mL, 1 equiv). The white crystalline precipitate of **11b** was isolated at 0 °C and washed twice with ice-cold abs EtOH; 1.65 g (75% overall yield); mp 162–164 °C. A sample was recrystallized and dried for analysis: mp 164–166 °C, lit. 166–167 °C [38], lit. 165–167 °C [23]; $[\alpha]_D^{25}$ $-10.7°$ (c 1.57, H_2O), lit. $-11.5°$ (H_2O) [38], lit. $-8.5°$ (H_2O) [23]; ^{13}C NMR (D_2O): δ 43.1, 66.4, 71.3, 71.6, 71.9, 82.3. Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07; Cl, 17.76; N, 7.02. Found C, 36.16; H, 7.07; Cl, 17.61; N, 7.04.

*1-Amino-3,6-anhydro-1-deoxy-*D*-galactitol* (**12b**).—1-Amino-1-deoxy-D-galactitol · HCl (**9**; 3.00 g, 13.8 mmol) was dissolved in anhyd HF (15 mL) while cooling in an ice–acetone bath. Hydrogen chloride was evolved. Formic acid (0.26 mL, 0.5 equiv) was added and the mixture was left for 20 h at room temperature. Workup and ion exchange as above yielded 2.2 g (98%) of the crude amine as a colourless oil which crystallized on standing. A sample of **12b** (0.5 g) was recrystallized from abs EtOH (15 mL). The hot solution was filtered through a small pad of Celite to remove some undissolved salts. By cooling, colourless crystals were formed. The crystals were isolated and washed with cold abs EtOH. The yield after drying in vacuo over concd H_2SO_4 was 0.39 g (78% from 0.5 g crude amine); mp 140–141 °C; $[\alpha]_D^{25}$ $+14.0°$ (c 1.52, H_2O); ^{13}C NMR (D_2O): δ 44.2, 73.0, 73.5, 77.7, 79.1, 86.6. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.17; H, 8.03; N, 8.58. Found C, 44.38; H, 8.10; N, 8.52.

Oxalate **12c**.—The crude amine **12b** (0.5 g, 3.1 mmol) was dissolved in hot EtOH–water and oxalic acid (0.14 g, 1.55 mmol) was added (pH ≈ 3). The precipitate was crystallized by evaporation of the solvent and the oily residue was redissolved in boiling MeOH (20 mL) + H_2O (3 mL). Filtering through a small pad of Celite followed by slow cooling yielded **12c** (0.45 g, 71%) as colourless crystals; mp 142–144 °C; $[\alpha]_D^{25}$ $+3.6°$ (c 1.16, H_2O); ^{13}C NMR (D_2O): δ 43.0, 67.7, 73.7, 77.5, 78.6, 86.3, 174.2. Anal. Calcd for $C_7H_{14}NO_6$: C, 40.38; H, 6.78; N, 6.73. Found C, 40.36; H, 6.76; N, 6.69.

Mesylate **12d**.—The free amine **12b** (1.39 g, 8.5 mmol) was dissolved in abs EtOH (7 mL) and the solution was acidified with CH_3SO_3H. The resulting warm solution was allowed to cool and to crystallize at 0 °C. The crystals were isolated, washed with cold abs EtOH, and dried. The yield of **12d** was 1.68 g (76%); mp 90–96 °C. A sample was recrystallized from abs EtOH for analysis: mp 94–96 °C; $[\alpha]_D^{25}$ $+3.3°$ (c 1.44, H_2O); ^{13}C NMR (D_2O): δ 39.3, 43.0, 67.6, 73.8, 77.5, 78.7, 86.3. Anal. Calcd for $C_7H_{17}NO_7S$: C, 32.43; H, 6.61; N, 5.40; S, 12.37. Found C, 32.22; H, 6.68; N, 5.31; S, 12.43.

*2-Amino-3,6-anhydro-2-deoxy-*D*-glucitol* (**14b**).—2-Amino-2-deoxy-D-glucitol · HCl (**13**; 2.00 g, 9.19 mmol) was dissolved in anhyd HF (15 mL) while cooling in an ice–acetone bath. Hydrogen chloride was evolved. Formic acid (0.17 mL, 0.5 equiv) was added and the mixture was left for 4 h at room temperature. Workup and ion exchange as above yielded **14b** as a colourless oil that crystallized during 2 days (1.5 g). The crude **14b** was dissolved in boiling abs EtOH (10 mL) and the solution filtered through a small pad of Celite. The Celite was washed with EtOH (5 mL) and the filtrate was allowed to cool. The solution was seeded and left at −10 °C for 2 days. The crystals were isolated, washed with cold EtOH and ether, and dried in vacuo. The yield of **14b** was 1.00 g (67%); mp 97–102 °C; $[\alpha]_D^{25}$ $+4.5°$ (c 1.64, H_2O); ^{13}C NMR (D_2O):

δ 51.7, 64.3, 71.6, 72.0, 72.2, 81.1. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.17; H, 8.03; N, 8.58. Found C, 44.23; H, 8.08; N, 8.83.

*1-Amino-2,5-anhydro-1,6-dideoxy-*D*-gulitol oxalate* (**16b**) [4].—1-Amino-1-deoxy-L-rhamnitol · HCl (**15**; 3.00 g, 14.9 mmol) was dissolved in anhyd HF (21 mL) and formic acid (0.56 mL, 14.9 mmol) was added. The mixture was left at room temperature for 16 h. Workup and ion exchange to give the free amine were performed as above. The resulting semicrystalline oil was extracted with abs EtOH (50 mL) at room temperature and the solution filtered through a small pad of Celite. Evaporation of the solvent gave a colourless oil (2.58 g), which was not dried further. The oil was again dissolved in EtOH (50 mL) and oxalic acid (~ 0.7 g, 0.5 equiv) dissolved in EtOH was added until pH ~ 3–4. The precipitate was recrystallized from a total of 210 mL of abs EtOH. After seeding and slow cooling to room temperature followed by standing for several days at − 10 °C, colourless crystals (fine needles) were isolated. The crystals were washed with cold EtOH and ether, and dried in vacuo. The yield of **16b** was 1.90 g (66% overall); mp 143–145 °C (slightly hygroscopic); $[\alpha]_D^{25}$ −41.1° (*c* 1.72, H_2O), lit. for the enantiomeric hydrochloride (syrup) $[\alpha]_D^{20}$ +46° (H_2O) [4]; ^{13}C NMR (D_2O): δ 13.8, 42.2, 78.3, 79.1, 80.5, 81.6, 174.2. Anal. Calcd for $C_7H_{14}NO_5 \cdot 0.3\ H_2O$: C, 42.55; H, 7.45; N, 7.09. Found C, 42.51; H, 7.45; N, 7.13.

*2,5-Anhydro-1,6-dideoxy-1-dimethylamino-*D*-gulitol hydrochloride* (**18b**).—1-Deoxy-1-dimethylamino-L-rhamnitol (**17**; 2.00 g, 10.3 mmol) was dissolved in anhyd HF (15 mL) while cooling in an ice–acetone bath. Formic acid (0.43 mL, 11 mmol) was added, and the mixture was left for 16 h at room temperature. Workup and ion exchange as above yielded the free amine as a colourless oil that was dissolved in abs EtOH. The solution was filtered to remove some insoluble impurities, then acidified with HCl (4 M) and evaporated to yield a colourless crystalline material. Recrystallization from abs EtOH yielded colourless crystals which were isolated at 0 °C, washed twice with cold EtOH, and dried in vacuo. The yield of **18b** was 1.77 g (81%). A sample was recrystallized for analysis; mp 154–155 °C, lit. for the enantiomeric species 152–154 °C [4]; $[\alpha]_D^{25}$ −59.5° (*c* 1.70, H_2O), lit. for the enantiomeric species $[\alpha]_D^{20}$ +57.7° (H_2O) [4]; ^{1}H NMR (500 MHz, D_2O, ref. sodium 4,4-dimethyl-4-silapentane-1-sulfonate, DSS): δ 1.26 (d, 3 H, H-6), 2.94 (s, 6 H, *N*-methyl), 3.37 (dd, H-1a), 3.42 (dd, H-1b), 4.00 (dd, H-3), 4.04 (dd, H-4), 4.06 (dt, H-2), 4.26 (dq, H-5); $J_{1a,1b}$ 13.3, $J_{1a,2}$ 10.0, $J_{1b,2}$ 3.3, $J_{2,3}$ 3.3, $J_{3,4}$ 1.5, $J_{4,5}$ 3.5, $J_{5,6}$ 6.3 Hz; ^{13}C NMR (D_2O): δ 13.9, 42.5, 45.3, 60.3, 78.6, 79.2, 79.3, 80.8. Anal. Calcd for $C_8H_{18}ClNO_3$: C, 45.39; H, 8.57; Cl, 16.75; N, 6.62. Found C, 45.39; H, 8.56; Cl, 16.42; N, 6.72.

*2,5-Anhydro-1,6-dideoxy-1-trimethylammonio-*D*-gulitol chloride* (**19**).—The dimethylamine hydrochloride **18b** (0.50 g, 2.36 mmol) was converted into the free amine by passing through a column of IRA-420 (OH^-) resin (20 mL). Elution with water until the eluate was neutral and evaporation to dryness yielded 0.38 g (93%). The crude product was treated with MeI (0.62 g, 2 equiv) in acetone (10 mL) for 4 days at room temperature. Evaporation followed by evaporation with abs EtOH left the trimethylammonium iodide as a yellow oil. The oil was dissolved in water (20 mL) and treated with AgOAc (0.39 g, 2.36 mmol). After stirring for 2 h, AgI was filtered off, and the filtrate was saturated with H_2S and filtered with activated charcoal. The filtrate was acidified with 4 M HCl and evaporation followed by coevaporation with EtOH yielded

0.49 g (92% from the free amine) of **19** as a colourless oil which slowly crystallized. The crystals were filtered off using 1:2.5 2-propanol–ether and dried in vacuo; 0.40 g (65% overall); mp 137–139 °C, lit. for the enantiomeric species 118–120 °C [4]; $[\alpha]_D^{25}$ $-47.2°$ (*c* 1.13, H_2O), lit. for the enantiomeric species $[\alpha]_D^{20}$ $+44.4°$ (H_2O) [4]; ^{13}C NMR (D_2O): δ 81.9, 79.5, 79.0, 78.1, 69.1, 54.8, 14.1. Anal. Calcd for $C_9H_{20}ClNO_3$: C, 47.89; H, 8.93; N, 6.21. Found C, 47.63; H, 8.55; N, 6.11.

*3,6-Anhydro-*D-arabino*-hexosulose phenylosotriazole* (**21**).—D-*arabino*-Hexosulose phenylosotriazole [39] (**20**; 2.00 g, 7.54 mmol) was dissolved in anhyd HF (15 mL) while cooling in an ice–acetone bath. Formic acid (0.14 mL, 3.7 mmol) was added and the solution left for 12 h at room temperature. The HF was evaporated in a stream of air followed by coevaporation of the residue three times with MeOH. Addition of water to the resulting light-tan oil caused precipitation of **21** as a white powder. The product was transferred to a polyethylene Büchner funnel, washed with cold water, and air-dried. The yield of the crude product was 1.82 g (~ 98%). Recrystallization from EtOH–water yielded colourless needles which were isolated at 0 °C, washed with cold water, and dried in vacuo over concd H_2SO_4; 1.49 g (81%); mp 99.5–101 °C, lit. 102–103 °C [29], lit. 101–102 °C [30]. A sample was recrystallized for analysis; mp 100–100.5 °C; $[\alpha]_D^{25}$ $-36.5°$ (*c* 0.95, $CHCl_3$), lit. $-37°$ (*c* 0.9, $CHCl_3$) [29,30]; ^{13}C NMR (Me_2SO-d_6): δ 71.0, 71.6, 72.0, 75.9, 118.1, 127.4, 129.7, 136.5, 139.2, 148.5. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found C, 58.05; H, 5.44; N, 16.83.

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References

[1] E.M. Acton, A.N. Fujiwara, L. Goodman, and D.W. Henry, *Carbohydr. Res.*, 33 (1974) 135–151.

[2] J. Cleophax, J. Defaye, and S.D. Gero, *Bull. Soc. Chim. Fr.*, (1967) 104–107.

[3] J. Kuszmann, *Carbohydr. Res.*, 142 (1985) 71–84.

[4] J. Kuszmann and P. Dvortsák, *Carbohydr. Res.*, 123 (1983) 209–229.

[5] V.I. Veksler, L.N. Kovalenko, I.K. Lagert, and A.V. Markovich, *J. Gen. Chem. USSR*, 41 (1971) 1404–1407.

[6] W. Lai and O.R. Martin, *Carbohydr. Res.*, 250 (1993) 185–193; H. Dietrich and R.R. Schmidt, *Carbohydr. Res.*, 250 (1993) 161–176.

[7] P.M. Myerscough, A.J. Fairbanks, A.H. Jones, I. Bruce, S.S. Choi, G.W.J. Fleet, S.S. Al-Daher, I.C. di Bello, and B. Winchester, *Tetrahedron*, 48 (1992) 10177–10190.

[8] D. Horton and K.D. Philips, *Carbohydr. Res.*, 30 (1973) 367–374.

[9] J. Defaye, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 181–228.

[10] D.D. Heard, B.G. Hudson, and R. Barker, *J. Org. Chem.*, 35 (1970) 464–467.

[11] B.-H. Yang, J.-Q. Jiang, K. Ma, and H.-M. Wu, *Tetrahedron Lett.*, 36 (1995) 2831–2834; P.A. Fowler, A.H. Haines, R.J.K. Taylor, E.J.T. Chrystal, and M.B. Gravestock, *J. Chem. Soc., Perkin Trans. 1*, (1993) 1003–1005; S.J. Mantell, P.S. Ford, D.J. Watkin, G.W.J. Fleet, and D. Brown, *Tetrahedron*, 49 (1993) 3343–3358, and references therein.

[12] A. Wisniewski, E. Skorupowa, J. Sokolowski, D. Glod, and G. Descotes, *J. Carbohydr. Chem.*, 8 (1989) 59–72; H. Frank and I. Lundt, *Tetrahedron*, 51 (1995) 5397–5402.

[13] I. Lundt and H. Frank, *Tetrahedron*, 50 (1994) 13285–13298.

[14] R. Barker, *J. Org. Chem.*, 35 (1970) 461–464; L.F. Wiggins, *Adv. Carbohydr. Chem.*, 5 (1950) 191–228.

[15] J. Defaye, A. Gadelle, and C. Pedersen, *Carbohydr. Res.*, 205 (1990) 191–202, and references therein.

[16] T. Sakakibara, T. Takamoto, T. Matsuzaki, H. Omi, U.V. Maung, and R. Sudoh, *Carbohydr. Res.*, 95 (1981) 291–298.

[17] H. Ohrui, G.H. Jones, J.G. Moffatt, M.L. Maddox, A.T. Christensen, and S.K. Byram, *J. Am. Chem. Soc.*, 97 (1975) 4602–4613.

[18] J.K.N. Jones, M.B. Perry, and J.C. Turner, *Can. J. Chem.*, 40 (1962) 503–510.

[19] M.L. Wolfrom, F. Shafizadeh, J.O. Wehrmüller, and R.K. Armstrong, *J. Org. Chem.*, 23 (1958) 571–575.

[20] F. Kagan, M.A. Rebenstorf, and R.V. Heinzelman, *J. Am. Chem. Soc.*, 79 (1957) 3541–3544.

[21] H. Kuzuhara, M. Kimura, and S. Emoto, *Carbohydr. Res.*, 45 (1975) 245–255.

[22] J.E. Hodge, *Adv. Carbohydr. Chem.*, 10 (1955) 169–205.

[23] J. Defaye, A. Gadelle, and C. Pedersen, EP 0 491 593 A1 (1991); World Patent Index (Derwent Publishers), ATC No. 92-161277/20.

[24] J. Defaye and C. Pedersen, *Hydrogen fluoride, solvent and reagent for carbohydrate conversion technology*, in F.W. Lichtenthaler (Ed.), *Carbohydrates as Organic Raw Materials*, VCH, Weinheim, 1991, pp 247–265, and references therein; J. Defaye and C. Pedersen, *Zuckerindustrie*, 116 (1991) 271–276.

[25] E.J. Hedgley and H.G. Fletcher, Jr., *J. Am. Chem. Soc.*, 84 (1962) 3726–3731.

[26] H. Meerwein, K. Bodenbenner, P. Borner, F. Kunnert, and K. Wunderlich, *Justus Liebigs Ann. Chem.*, 632 (1960) 38–55.

[27] R.A. Burt, C.A. Chambers, Y. Chiang, C.S. Hillock, A.J. Kresge, and J.W. Larsen, *J. Org. Chem.*, 49 (1984) 2622–2624.

[28] J.E. Baldwin, *J. Chem. Soc., Chem. Commun.*, (1976) 734–736.

[29] E. Hardegger and E. Schreier, *Helv. Chim. Acta*, 35 (1952) 232–247.

[30] G. Hanisch and G. Henseke, *Chem. Ber.*, 100 (1967) 3225–3230.

[31] S.J. Angyal, *Carbohydr. Res.*, 77 (1979) 37–50.

[32] M. de Amici, C. de Micheli, G. Molteni, D. Pitrè, G. Carrea, S. Riva, S. Spezia, and L. Zetta, *J. Org. Chem.*, 56 (1991) 67–72; R.G.S. Ritchie, N. Cyr, B. Korsch, H.J. Koch, and A.S. Perlin, *Can. J. Chem.*, 53 (1975) 1424–1433.

[33] I. Lundt, R. Madsen, S. Al Daher, and B. Winchester, *Tetrahedron*, 50 (1994) 7513–7520.

[34] K. Adelhorst and G.M. Whitesides, *Carbohydr. Res.*, 232 (1992) 183–187.

[35] P. Karrer and J. Meyer, *Helv. Chim. Acta*, 20 (1937) 626–627.

[36] N.S. Tikhomirova-Sidorova and G.E. Ustiuzhanin, *J. Gen. Chem. USSR*, 28 (1958) 3238–3241.

[37] J. Cleophax, J. Hildesheim, R.E. Williams, and S.D. Gero, *Bull. Soc. Chim. Fr.*, (1968) 1415–1417.

[38] G.S. Skinner, L.A. Henderson, and C.G. Gustafson, Jr., *J. Am. Chem. Soc.*, 80 (1958) 3788–3790.

[39] R.M. Hann and C.S. Hudson, *J. Am. Chem. Soc.*, 66 (1944) 735–738.