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Carbohydrate Research 297 (1997) 261–272

CARBOHYDRATE RESEARCH

A highly stereoselective synthesis of 1-amino-2,5-anhydro-1-deoxyhexitols via 2-trifluoromethyl-oxazolinium intermediates [1,2]

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Received 2 September 1996; accepted 26 October 1996

Abstract

A series of 1-amino-2,5-anhydro-1-deoxyalditols, namely derivatives of 1-amino-2,5-anhydro-1-deoxy-D-glucitol, -D-mannitol and -D-talitol was prepared from the corresponding 1-deoxy-1-trifluoroacetamidohexitols by treatment with anhydrous hydrogen fluoride. The reaction was also performed on 1,3-dideoxy-1-trifluoroacetamido-D-*ribo*-hexitol and 1-deoxy-1-trifluoroacetamido-L-rhamnitol which both gave the expected C-2 inverted anhydrides. The reaction mechanism involves 2-trifluoromethyl-oxazolinium intermediates, which further undergo intramolecular attack of HO-5 at C-2 with inversion of the configuration. The reaction is stereospecific and highly regioselective. The crystal structure of 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride is presented. © 1997 Elsevier Science Ltd.

Keywords: Anhydrohexitols; Hydrogen fluoride; Aminodeoxyalditols; Tetrahydrofurans

1. Introduction

The preparation and isolation of 2,5-anhydrohexitols has previously been accomplished by a number of methods. One of the most simple and efficient syntheses is probably the transformation of 2-amino-2-deoxy-D-glucose into 2,5-anhydro-D-mannose followed by reduction of the aldehyde function to give 2,5-anhydro-D-mannitol in 74% overall yield [1,2]. Here, the formation of a highly unstable 2-diazonium ion causes the intramolecular attack by HO-5 at C-2 with inversion of configuration.

We have recently prepared a number of alkylamino substituted 2,5- and 3,6-anhydrides from aminodeoxy-pentitols and -hexitols, respectively, by treatment with anhydrous hydrogen fluoride (HF) under formic acid catalysis [3]. The anhydrides are formed through an intramolecular opening of a 1,3-dioxolenium ion by a hydroxyl group. The result of this study was that only 3,6-anhydrides were formed from aminodeoxyhexitols. In a few cases, less than 5% 2,5-anhydrides could be detected. As expected, 1-

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[1] Dedicated to Professor Hans Paulsen on the occasion of his 75th birthday.

[2] Part of J.C. Norrild, "*Reactivity of aminodeoxyalditols and derivaties in hydrogen fluoride*", Ph.D. Thesis, The Technical University of Denmark, 1996.

PII S0008-6215(96)00278-9

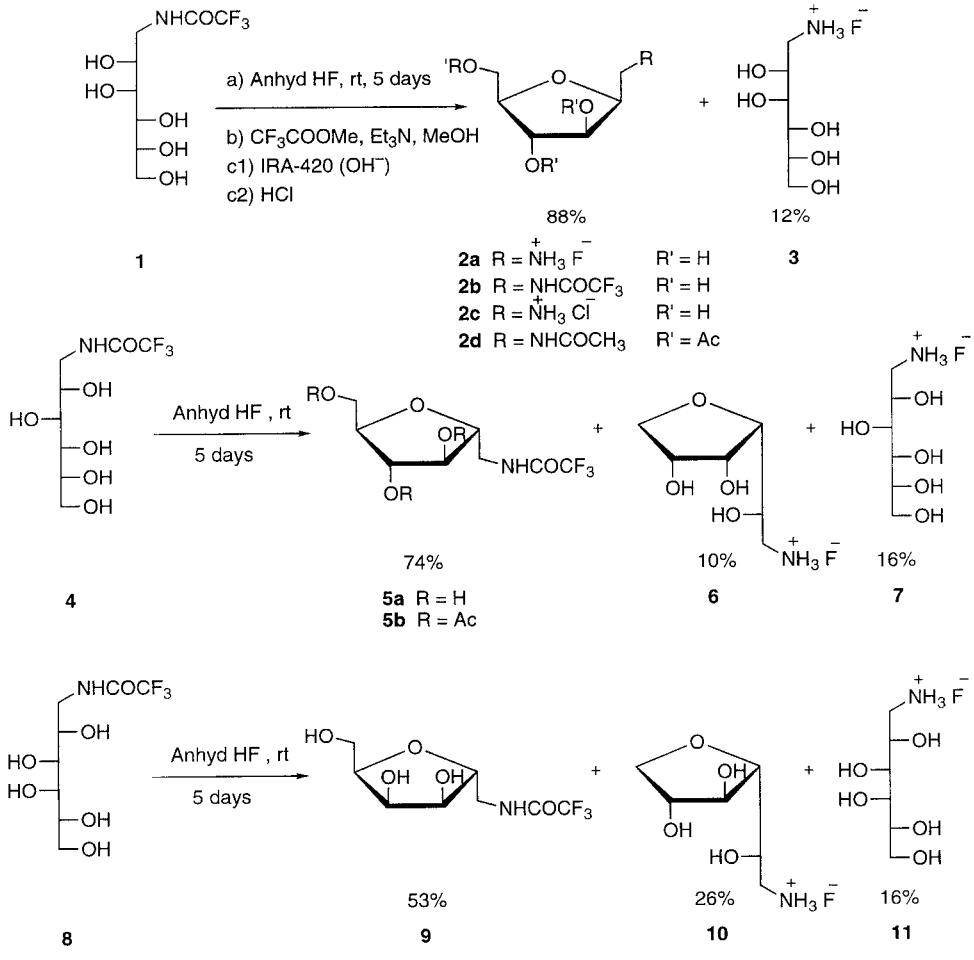
amino-1-deoxy-L-rhamnitol gave the corresponding C-5 inverted 2,5-anhydride.

Searching for a general method to synthesize 1-amino-2,5-anhydro-1-deoxyhexitols starting from aminodeoxyhexitols, an intramolecular opening of a 1,2-fused oxazolinium ion by HO-5 was considered. It is known that 1,3-oxazolinium salts can open at C-5 with oxygen nucleophiles [4]. Early work by Paulsen et al. [5] established that the stability of 2-methyloxazolinium ions strongly exceeds that of the analogous acetoxonium ions. Because acetoxonium ions, in anhydrous HF, react more reluctantly than formoxonium ions in the dehydration reactions of alditols and hexonolactones [6], 2-methyloxazolinium ions were expected to be even less reactive.

It was found that, treating the easily obtainable 1-deoxy-1-trifluoroacetamidohexitols with HF, the corresponding 2-trifluoromethyloxazolinium ions were formed. These activated oxazolinium intermediates reacted further to yield the C-2 inverted 2,5-anhydrides in high yield and with full stereochemical control.

2. Results

The 1-deoxy-1-trifluoroacetamidohexitols **1**, **4**, **8**, **12**, **17**, **19** were prepared in high yield, from the corresponding aminodeoxyhexitols [3], by treatment with methyl trifluoroacetate and triethylamine in methanol. Treatment of 1-deoxy-1-trifluoroacetamido-D-mannitol (**1**) with anhydrous HF for 5 days gave 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrofluoride (**2a**, 88%) in admixture with hydrolyzed starting material, namely 1-amino-1-deoxy-D-mannitol hydrofluoride (**3**, 12%) (Scheme 1) as seen from the ^{13}C NMR spectrum of the mixture. Reconversion of the mixture into the trifluoroacetamides, and separation by column chromatography, gave almost pure 2,5-anhydro-1-deoxy-1-trifluoroacetamido-D-glucitol (**2b**). Subsequent hydrolysis to the free



Scheme 1.

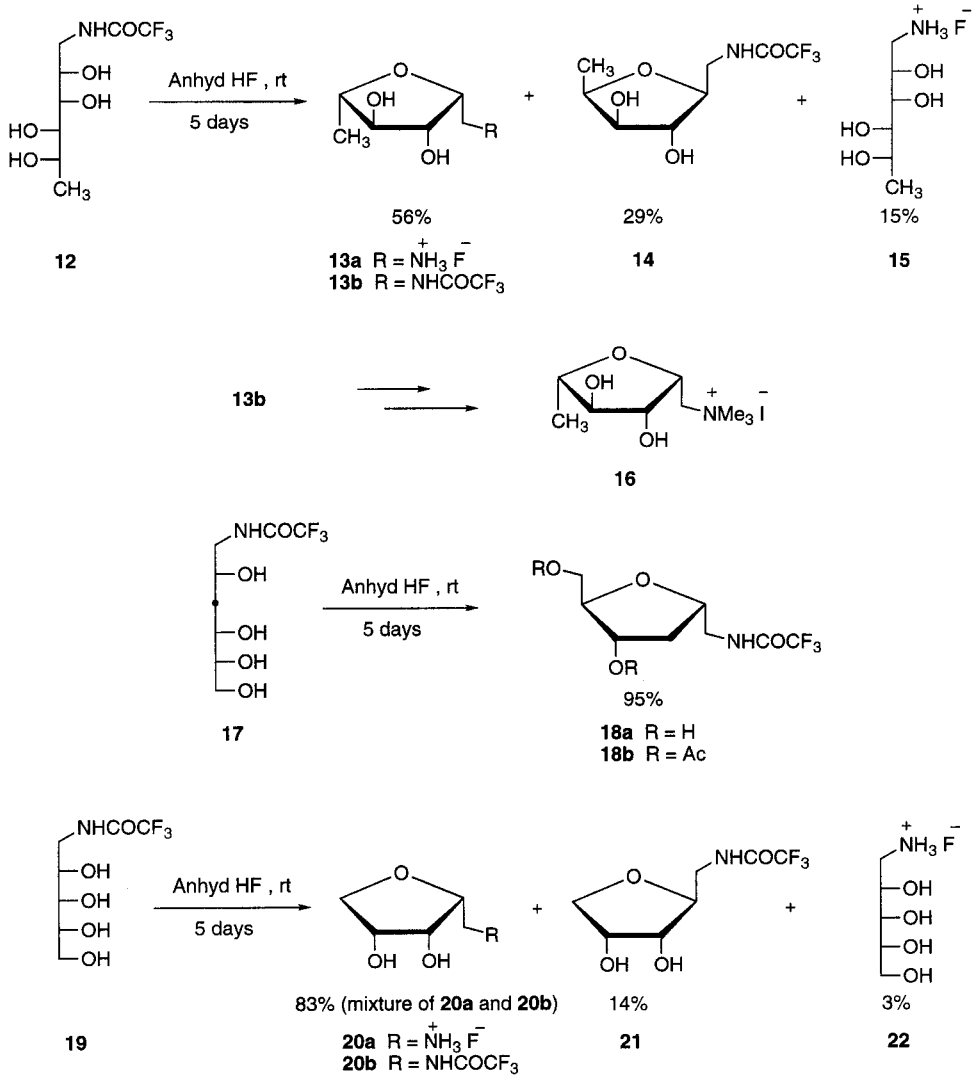
amine and acidification with hydrochloric acid gave the crystalline hydrochloride **2c** in 69% overall yield. The absolute stereochemistry of **2c** was determined by X-ray crystallography to be 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride as shown in Fig. 2.

Analogously, treatment of 1-deoxy-1-trifluoroacetamido-D-glucitol (**4**) with anhydrous HF for 5 days gave 2,5-anhydro-1-deoxy-1-trifluoroacetamido-D-mannitol (**5a**, 74%), in admixture with 1-amino-1-deoxy-3,6-anhydro-D-glucitol hydrofluoride (**6**, 10%) and hydrolyzed starting material, namely 1-amino-1-deoxy-D-glucitol hydrofluoride (**7**, 16%). In this case, the by-products were removed by simple treatment with a cationic ion-exchange resin. Acetylation of the oily **5a** gave, after column chromatography, 3,4,6-tri-*O*-acetyl-2,5-anhydro-1-deoxy-1-trifluoroacetamido-D-mannitol (**5b**) as a colourless oil in 66% overall yield.

Treatment of 1-deoxy-1-trifluoroacetamido-D-galactitol (**8**) with HF gave 2,5-anhydro-1-deoxy-1-trifluoroacetamido-D-talitol (**9**, 53%) in admixture with the hydrofluorides of 1-amino-3,6-anhydro-1-deoxy-D-galactitol (**10**, 26%) and 1-amino-1-deoxy-D-galactitol (**11**, 16%). Workup, as for **5a**, gave **9** in 42% yield after recrystallization.

In the case of the L-rhamnitol derivative **12**, treatment with HF gave a mixture of **13a** (56%) and **14** (29%) together with 15% hydrolyzed starting material (Scheme 2). Reconversion of the mixture to the trifluoroacetamides, followed by chromatography, gave a mixture of **13b** and **14** in 78% yield. Fractional crystallization from ethyl acetate–hexane gave pure **13b** in 40% overall yield.

1,3-Dideoxy-1-trifluoroacetamido-D-*ribo*-hexitol (**17**) gave the expected 2,5-anhydro-1,3-dideoxy-1-trifluoroacetamido-D-*arabino*-hexitol (**18a**) in 95%



Scheme 2.

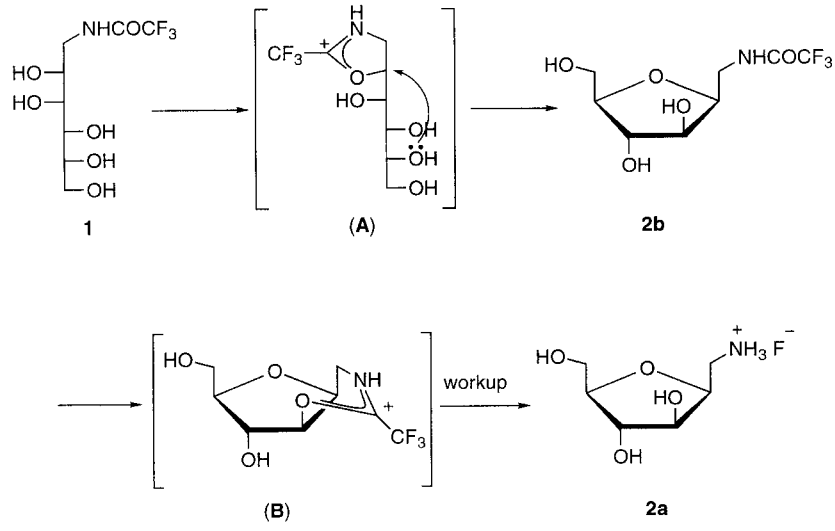


Fig. 1. Proposed mechanism for the transformation of 1-deoxy-1-trifluoroacetamido-alditols into C-2 inverted 2,5 anhydrides, as exemplified with 1-deoxy-1-trifluoroacetamido-D-mannitol (**1**).

yield, which was isolated as its diacetate **18b** in 88% overall yield.

The structures of **5b**, **9**, **13b**, **18b** are based on mechanistic considerations and NMR spectroscopy data (as discussed below).

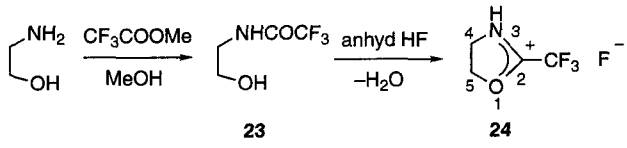
3. Discussion

The present study of the reactivity of oxazolinium ions in HF was initiated by investigations of the reactions of 1-acetamido-1-deoxy-D-glucitol and 1-acetamido-1-deoxy-D-mannitol in HF. The reactions were followed by ^{13}C NMR spectroscopy; we expected to observe the formation of stable 2-methyl-oxazolinium ions, analogous to the 2-acetamido-2-deoxy-D-glucose system [7,8]. However, the only species observed after several days in HF were the protonated amides. Replacement of the acetamido group with a trifluoroacetamido group drastically changed the reactivity of the initially protonated amides. Within 4–5 h, the 1,2-fused 2-trifluoromethyloxazolinium ions [3] were formed. The differences in reactivity of the acetamido and trifluoroacetamido groups can be ascribed to the strong electron withdrawing effect of the trifluoromethyl group which increases the electrophilicity of the carbonyl carbon atom, resulting in the observed ring-closure. Thus, by treatment of 1-deoxy-1-trifluoroacetamido-alditols **1**, **4**, **8**, **12**, **17**, **19** with HF, the corresponding 2-trifluoromethyl-oxazolinium ions were formed. These ions, being much more reactive for nucleophilic ring-opening than the 2-methyl analogues [10,11], reacted slowly in the expected way to give the C-2 inverted 2,5-anhydrides [4]. The reactions were, in the case of 1-deoxy-1-trifluoroacetamido-D-mannitol (**1**) and -D-glucitol (**4**), followed by ^{13}C NMR spectroscopy. The proposed reaction mecanism is illustrated for **1** in Fig. 1. The signal of C-5 in the oxazolinium ions was observed at ~ 90–95 ppm (a deshielding of 15–21 ppm compared to the protonated amides), and C-4 was shifted ~ 4 ppm downfield. The high $\Delta\delta$ of C-5 is in accordance with earlier results [13,14] and with recent data on protonated methyl trifluoroacetate [15] if accounting for the additional ring-closure in the present system. The difference in shielding in the two positions can be correlated to the higher partial positive charge in the 5-position [14,16] and thereby to the higher electrophilicity of C-5 compared to C-4 in the protonated heterocycle.

In the case of 1-deoxy-1-trifluoroacetamido-D-mannitol (**1**), the resulting 2,5-anhydride **2a** has a *cis* relationship between the aminomethyl and the hydroxyl group at C-3. The ^{13}C NMR spectrum of the

[3] The 2-trifluoromethyl-oxazolinium ion was first proposed as an intermediate by Brown and Wetzel [9] in the synthesis of *N*-(2-chloroethyl)trifluoromethyl amides.

[4] In a synthesis of substituted *N*-alkyl-2(1H)-pyridones, activation of the intermediate pyridinium-[2,1-b]-oxazolinium ions with electron withdrawing groups such as nitro- or trifluoromethyl- was needed in order to get a nucleophilic opening of the ion [12].



Scheme 3.

reaction mixture, before workup, indicated the formation of the six membered oxazinium ion (**B**, Fig. 1) which hydrolysed on workup. The ^{13}C chemical shifts of (**B**) are 89.8, 86.4, 78.2, 70.6, 63.5, 42.6 (62.5 MHz, internal acetone, δ 30.5 ppm). Hydrolysis of the trifluoroacetamido group is also seen for compound **13** and partly for compound **20** (Scheme 2) and seems to be general for 2,3-*cis* configurated compounds. In the case of 1-deoxy-1-trifluoroacetamido-D-glucitol (**4**), which gave the corresponding *trans* configurated trifluoroacetamide **5a** (Scheme 1), no further reaction in HF and no hydrolysis of the amide during workup could be observed. Analogously, for compounds **9**, **14**, **18a**, **21**, the corresponding ammonium fluorides were not observed.

In order to study further the ^{13}C NMR spectra of these ions, 2-trifluoroacetamido-ethanol (**23**) was prepared (Scheme 3). Treatment of this compound with HF gave the expected 2-trifluoromethyl-2-oxazolinium ion **24**, which could not undergo further reaction (Scheme 3). The measured ^{13}C chemical shift values (62.5 MHz, external acetone-d_6 δ 29.8) were 46.9 (C-4), 78.5 (C-5), 113.6 (q, CF_3, $^1J_{CF}$ 278 Hz), 166.3 (q, C-2, $^2J_{CF}$ 56 Hz). The values of C-4 and C-5 can be compared with those of the 3-*N*-methyl-2-(pentafluoroethyl)-oxazolinium ion [11]. The $\Delta\delta$ of C-4 and C-5, compared to the initial amide, were 4 and 16 ppm, respectively. The $^2J_{CF}$ coupling constant is considerably larger in the oxazolinium ion than in the neutral trifluoroacetamides (56 Hz compared to 38 Hz). This increase is expected because this system is more electron deficient [17].

The investigated 1-deoxy-1-trifluoroacetamidoalditols all gave the expected products, but some variations in the regioselectivity of the reaction was observed. In the case of 1-deoxy-1-trifluoroacetamido-D-mannitol (**1**), the reaction gave only the expected 2,5-anhydro derivative **2a** in admixture with 12% of 1-amino-1-deoxy-D-mannitol hydrofluoride (**3**). The *gluco*, *galacto* and *rhamno* derivatives **4**, **8**, **12** gave, in addition, products from the general acid catalyzed reaction, namely the 3,6-anhydro-D-*gluco* **6**, 3,6-anhydro-D-*galacto* **10** and 2,5-anhydro-D-*gulo* **14** derivatives, respectively (Schemes 1 and 2). With a reaction time of 5 days, this slow reaction becomes important. The water formed in the reactions does not hydrolyze the trifluoroacetamides directly during the reaction as this would result in a fast trifluoroacetic acid catalyzed reaction to the 3,6-anhydrides.

In the case of the 1,3-dideoxy-1-trifluoroacetamido-D-*ribo*-hexitol (**17**), the expected 2,5-anhydride **18a** was formed in more than 97% yield as judged from the ^{13}C NMR of the crude product.

For further studies of the selectivity of the reaction, 1-deoxy-1-trifluoroacetamido-D-ribitol (**19**) was investigated. It gave 83% of the C-2 inverted product with the D-*arabino* configuration **20a** and **20b**, in admixture with 14% of the D-*ribo* configurated anhydride **21** and 3% of hydrolyzed starting material **22**. However, this is not the most convenient synthesis of 1-amino-2,5-anhydro-1-deoxy-D-arabinitol, as it can easily be obtained from the formic acid catalyzed dehydration of 1-amino-1-deoxy-D-arabinitol with full stereoselectivity [3].

The structure of **2c** was proven by X-ray crystallography (see below). In case of compounds **5b**, **9**, **13b**, **18b**, it was found that, using ^{13}C chemical shift values, assignment of the relative stereochemistry between C-2 and C-3 and between C-4 and C-5 within a series of comparable compounds could be achieved. In the case of a *cis* relationship of the hydroxyl group and the alkyl substituent, we observed a relative shielding of C-2 or C-5 of ~ 5 ppm compared to the *trans* configurated compounds. This is in agreement with earlier results [3,18,19]. Shielding in the *cis* configurated compounds is also seen at

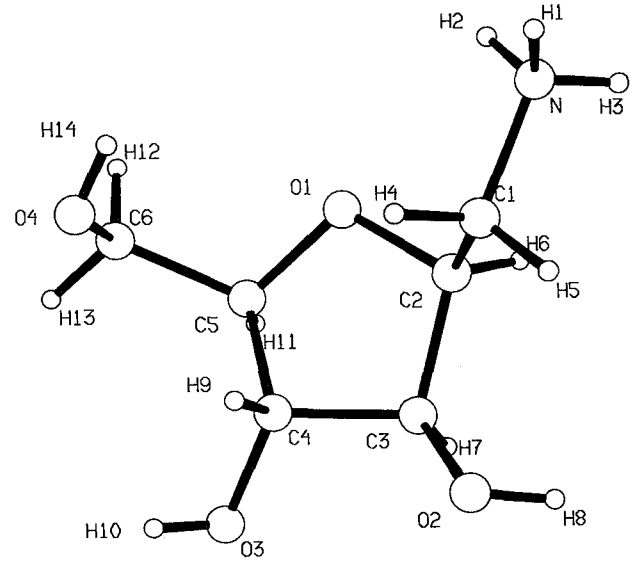


Fig. 2. Molecular structure and atomic numbering of 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride (**2c**).

C-1 and C-6, but the effect is only ~2 ppm for amino or hydroxyl substituted carbons. In the case of the 6-deoxy compound **13b**, the shielding of C-6 is ~5 ppm [18]. To prove further the structure of **13b**, it was converted, in solution, to the known 3-hydroxymuscarine analogue **16** [20] (Scheme 2). The ^{13}C NMR chemical shifts matched those previously published for the tosylate of **16** within ±0.4 ppm. The structure of **14** was confirmed by hydrolysis of the amide functionality to the previously published ammonium compound, obtained from the formic acid catalyzed dehydration of 1-amino-1-deoxy-L-rhamnitol in HF [3].

Crystal structure determination.—The crystal structure of 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride (**2c**) was determined. The structure of the cation and numbering of the atoms is shown in Fig. 2. The bond lengths and bond angles are listed in Table 2. A list of selected torsional angles are listed in Table 3. The compound consists of $C_6H_{14}NO_4^+$

Table 1
Crystal and experimental data for 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride **2c**

Formula	$C_6H_{14}NO_4^+,Cl^-$
Formula weight	199.6
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit-cell dimension (Å)	$a = 6.949(4)$ $b = 7.111(5)$ $c = 17.761(8)$
Unit-cell volume V (Å^3)	877.6(9)
Formula units per unit cell, Z	4
F(000)	424
Calculated density D_x (g cm^{-3})	1.51
Radiation	MoK α
Wavelength, λ (Å)	0.71073
Linear absorption coefficient (cm^{-1})	4.1
Temperature, T (K)	120
Crystal description	colourless
Crystal size (mm)	0.09 × 0.13 × 0.26
Diffractometer	Enraf–Nonius CAD-4F
Unit-cell determination	
No. of reflections used	25
θ-range (°)	9.4–17.4
Intensity data collection	
θ_{max} (°)	30
Range of h	−9–9
Range of k	0–10
Range of l	0–25
Scan mode	ω
Scan range, $\Delta\omega$	1.30 + 0.35 tan θ
Total number of reflections	2539
No. of independent reflections, [$I > 2\sigma(I)$]	2218
Corrections	Lorenz-polarization
Structure refinement:	
Minimization of	$\Sigma w(\|F_o\| - \|F_c\|)^2$
Anisotropic thermal parameters	All non-hydrogen atoms
Isotropic thermal parameters	Hydrogen atoms
No. of refined parameters	165
Weighting scheme	$[\sigma^2\|F_o\| + 0.0002\|F_o\|^2]^{-1}$
$R = \Sigma\|F_o\| - \|F_c\|/\Sigma\|F_o\|$	0.032
$R_w = [\Sigma w(\|F_o\| - \|F_c\|)^2/\Sigma w\|F_o\|^2]^{1/2}$	0.032
$S = [\Sigma w(\|F_o\| - \|F_c\|)^2/(N_{obs} - N_{var})]^{1/2}$	1.25
Final $(\Delta/\sigma)_{max}$	0.26
Final $\Delta\rho_{min}$ and $\Delta\rho_{max}$ (e Å^{-3})	−0.31 and 0.58

Table 2
Bond lengths (in Å) and bond angles (in °) for 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride **2c**

O-1–C-2	1.441(2)
O-1–C-5	1.442(2)
O-2–C-3	1.415(2)
O-3–C-4	1.430(2)
O-4–C-6	1.421(2)
N–C-1	1.492(2)
C-1–C-2	1.515(2)
C-2–C-3	1.546(2)
C-3–C-4	1.513(3)
C-4–C-5	1.522(3)
C-5–C-6	1.510(3)
C-2–O-1–C-5	109.89(11)
N–C-1–C-2	110.07(13)
O-1–C-2–C-1	108.40(13)
O-1–C-2–C-3	106.01(12)
C-1–C-2–C-3	112.97(13)
O-2–C-3–C-2	114.73(13)
O-2–C-3–C-4	110.93(13)
C-2–C-3–C-4	102.29(14)
O-3–C-4–C-3	110.78(15)
O-3–C-4–C-5	113.36(14)
C-3–C-4–C-5	102.25(12)
O-1–C-5–C-4	104.77(12)
O-1–C-5–C-6	109.75(14)
C-4–C-5–C-6	114.49(15)
O-4–C-6–C-5	113.32(15)

cations and Cl^- anions. The bond lengths and bond angles are in agreement with those found in similar compounds [21–23].

Table 3
Selected torsion angles (in °) for 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride **2c**

N–C-1–C-2–O-1	−72.10(18)
N–C-1–C-2–C-3	170.73(16)
O-1–C-5–C-6–O-4	−68.46(17)
C-4–C-5–C-6–O-4	49.00(19)
H-4–C-1–C-2–H-6	167.1(19)
H-5–C-1–C-2–H-6	−71.3(19)
H-6–C-2–C-3–H-7	−22.6(19)
H-7–C-3–C-4–H-9	165.8(18)
H-9–C-4–C-5–H-11	−160.3(18)
H-11–C-5–C-6–H-12	−65.3(18)
H-11–C-5–C-6–H-13	54.5(18)

The furanoid ring adopts an envelope ^3E conformation slightly distorted towards $^3T_2$, the pseudorotation parameters P and τ_m being 15.0(2) and 38.7(1), respectively [24]. An envelope conformation of the ring is also found in 2,5-anhydro-1-*O*-(*p*-tolylsulfonyl)-D-mannitol [21] and in 3,4-di-*O*-acetyl-2,5-anhydro-1,6-dideoxy-1,6-diiodo-D-mannitol [22]. The orientation of the nitrogen atom about the C-1–C-2 bond is *gauche* to O-1 with the torsion angle N–C-1–C-2–O-1 being −72.10(18)° and *trans* to C-3 with the torsion angle N–C-1–C-2–C-3 being 170.73(16)°. The orientation of O-4 about the C-5–C-6 bond is *gauche–gauche* to O-1 and C-4, with the torsions angles O-1–C-5–C-6–O-4 and C-4–C-5–C-6–O-4 being −68.46(17)° and 49.00(19)°, respectively. These conformations of the side chains are

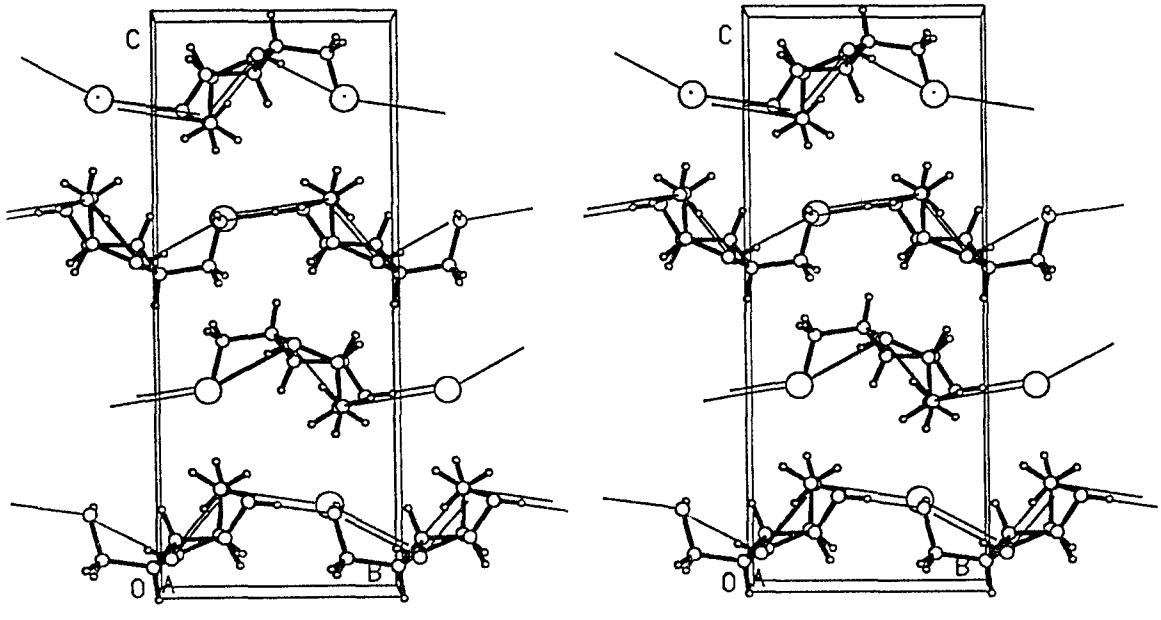


Fig. 3. Stereoscopic representation of the crystal packing for 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride (**2c**). Hydrogen bonds are added as narrow solid lines.

Table 4
Hydrogen bond geometry in 1-amino-2,5-anhydro-1-deoxy-D-glucitol hydrochloride (**2c**)

Donor (O/N)	Acceptor (O/Cl^-)	$H \cdots O/Cl^-$	$N/O \cdots O/Cl^-$	Angle $O/N-H \cdots O/Cl^-$
O-2–H-8	O-4 (x, $1+y$, z)	2.060(20)	2.875(3)	158.0(20)
O-3–H-10	Cl ($1+x$, $-1+y$, z)	2.320(20)	3.086(3)	172.0(20)
O-4–H-14	Cl (x, $-1+y$, z)	2.370(20)	3.140(3)	161.0(20)
N^+–H-1	Cl ($1-x$, $-1/2+y$, $1/2-z$)	2.230(20)	3.163(3)	168.0(18)
N^+–H-2	O-3 ($-1+x$, y, z)	2.010(30)	2.867(3)	161.0(20)
N^+–H-3	Cl (x, y, z)	2.330(30)	3.193(3)	162.0(20)

also found in 3,4-di-*O*-acetyl-2,5-anhydro-1,6-dideoxy-1,6-diiodo-D-mannitol [22]. In isotiazofurin [23], the orientation of O-5′ in the primary OH group around the C–C bond is *gauche* and *trans* to O-1 and C-3, respectively, whereas in 2,5-anhydro-1-*O*-(*p*-tolylsulfonyl)-D-mannitol [21], the orientation of the corresponding oxygen is *gauche–gauche*.

The crystal packing is influenced by hydrogen bonds, which are shown in Fig. 3 and Table 4.

4. Experimental

General methods.—^{13}C NMR spectra were recorded on a Bruker 250 instrument and ^1H NMR spectra on a Bruker AM 500 at 20 °C, unless otherwise stated. ^{13}C NMR spectra in anhydrous HF were measured at 20 °C in Teflon sample tubes, which were placed in a 5 mm glass tube. 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 CD_3OD, the solvent signal was used as the internal standard (δ 49.0). In benzene-d_6, the solvent signal was set to δ 128.0 and Me_2SO-d_6 to δ 39.7. ^1H NMR spectra in benzene-d_6 and $CDCl_3$ were referenced internally to the solvents: 7.16 and 7.27 ppm, respectively. ^1H NMR spectra in D_2O were referenced to DSS. Assignments of spectra were obtained from COSY and C–H correlated experiments. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Melting points are uncorrected. Ion-exchange resins were commercially available Amberlite types. Evaporations were performed under reduced pressure 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, and the Research Institute for Pharmacy and Biotechnology, Prague.

X-ray techniques.—Crystals were obtained from EtOH. A colourless needle was used for data collection. Crystal and experimental data for the compound are listed in Table 1. The possible space groups were established from rotation and Weissenberg photographs using Cu radiation. The crystals were cooled to 120 K using the Cryostream nitrogen gas cooler system [25]. The unit cells were derived from least-squares fit of refined diffractometer setting angles for 25 reflections. Four standards were measured for intensity and orientation control after every 4 h. No fading was observed. The intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined by a full-matrix least-squares technique. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms could all be located in the difference maps and are refined with isotropic thermal parameters. There is a significant difference between the *R*-values of the two possible enantiomorphic structures. The crystallographic computations were performed with SHELXS86 [26] and SHELX76 [27]. The atomic scattering factors were taken from the literature [28]. The PLUTO program [29] was used for the illustrations and PLATON [30] for molecular geometry calculations. The final positional parameters are listed in Table 5. Anisotropic thermal parameters, positional parameters for the hydrogen atoms and list of observed and calculated structure factors may be obtained from the authors on request.

1-Deoxy-1-trifluoroacetamido-D-mannitol (**1**).—1-Amino-1-deoxy-D-mannitol · HCl (12.00 g, 55.4 mmol) was dissolved in a small amount of water and adsorbed on a column (200 mL) of IRA 420 (HO^-) ion-exchange resin. The free amine was eluted with water until a neutral eluate was obtained. Evaporation to dryness yielded 9.87 g (98%) of the amine as a white solid. The amine (8.50 g, 46.9 mmol) was suspended in dry MeOH (200 mL). Triethylamine (0.5 g) and CF_3COOMe (7.21 g, 1.2 equiv) were added successively. The suspension was stirred at room temperature overnight. The solvent was evaporated and the residue was recrystallized from abs EtOH (~ 200 mL). 1-Deoxy-1-trifluoroacetamido-D-

Table 5
Fractional atomic coordinates and equivalent isotropic thermal parameters (in Å^2)

Atom	x	y	z	U_{eq} [a]
O-1	0.84968(16)	0.07869(18)	0.07147(8)	0.0169(3)
O-2	1.18916(18)	0.37794(19)	0.16601(7)	0.0179(4)
O-3	1.36915(16)	0.06464(19)	0.07283(7)	0.0166(3)
O-4	0.98705(17)	0.27420(19)	0.14248(7)	0.0186(3)
N	0.59250(19)	0.2733(3)	0.17983(9)	0.0172(4)
C-1	0.8067(2)	0.2626(3)	0.18337(9)	0.0177(5)
C-2	0.8900(2)	0.2595(2)	0.10458(9)	0.0132(4)
C-3	1.1114(2)	0.2808(3)	0.10351(9)	0.0127(4)
C-4	1.1783(2)	0.0784(3)	0.10243(9)	0.0127(4)
C-5	1.0274(3)	0.0153(2)	0.05291(9)	0.0142(4)
C-6	1.0059(2)	0.2243(3)	0.06534(10)	0.0182(4)
Cl	0.53586(6)	0.71309(7)	0.15104(2)	0.0188(1)

[a] $U_{eq} = 1/3\Sigma U_{ij} a_i^* a_j^* \boldsymbol{a}_i \boldsymbol{a}_j$.

mannitol was isolated at 0 °C and washed with cold EtOH. Yield of **1** after drying was 10.12 g (78%); mp 171–172 °C; $[\alpha]_D^{25}$ +14.2° (*c* 1.71, H_2O); ^{13}C NMR (D_2O) δ 160.1 (q, $^2J_{CF}$ 37 Hz), 116.7 (q, $^1J_{CF}$ 286 Hz), 71.6, 71.2, 69.9, 69.6, 64.0, 44.0. Anal. Calcd for $C_8H_{14}F_3NO_6$: C, 34.66; H, 5.09; N, 5.05. Found: C, 34.72; H, 5.13; N, 5.04.

1 - Amino - 2, 5 - anhydro - 1 - deoxy - D - glucitol hydrochloride (**2c**).—1-Trifluoroacetamido-1-deoxy-D-mannitol (**1**; 3.00 g, 10.8 mmol) was dissolved in anhyd HF (30 mL), while cooling in an ice-acetone bath, and left for 5 days at room temperature. The HF was evaporated in a stream of air. The resulting colourless oil was coevaporated three times with MeOH in a stream of air at 50 °C to remove residual HF. The crude oil, containing **2a** (88%) plus **3** (12%) as judged by ^{13}C NMR, was transferred to a round bottomed flask with MeOH–water and the solvents were removed by evaporation in vacuo followed by repeated coevaporation with toluene to remove residual water. The oil was dissolved in dry MeOH (30 mL); Et_3N (4.40 g) and methyl trifluoroacetate (2.5 g) were added, and the solution was stirred overnight at room temperature. Evaporation yielded an oil which was chromatographed on a silica gel column (3 × 30 cm, 5:4:0.9 CH_2Cl_2–EtOAc–MeOH). The fractions containing the major component were evaporated to yield **2b**, containing 3% of **3**, as a colourless oil (2.45 g). This was dissolved in water (50 mL) and stirred with IRA-420 (HO^-) ion-exchange resin (40 mL) for 1 h. The resin was added to a column of fresh resin (30 mL) and eluted with water until a neutral eluate was obtained. Evaporation of the eluate yielded 1-amino-2,5-anhydro-1-deoxy-D-glucitol as an oil. It was redissolved in 50% EtOH (50 mL), neutralized with 1 M HCl (~ 7.2 mL) and concentrated (if acidic on evaporation, a pink coloured product was obtained). Addition of EtOH caused the precipitation of **2c**. The crystals were isolated and washed with cold EtOH. The yield of **2c** was 1.48 g (69%); mp 171–173 °C; $[\alpha]_D^{25}$ +21.4° (*c* 2.0, H_2O); ^{13}C NMR (D_2O): δ 85.8 (C-5), 78.7 (C-4), 78.4 (C-3), 77.0 (C-2), 62.4 (C-6), 40.0 (C-1); ^1H NMR (D_2O): δ 4.30 (ddd, H-2), 4.27 (dd, H-3), 4.05 (dd, H-4), 3.90 (ddd, H-5), 3.80 (dd, H-6b), 3.71 (dd, H-6a), 3.35 (dd, H-1b), 3.27 (dd, H-1a); $^3J_{H,H}$ (Hz): $J_{1a,1b}$ 13.6, $J_{1a,2}$ 6.5, $J_{1b,2}$ 3.9, $J_{2,3}$ 4.5, $J_{3,4}$ 2.4, $J_{4,5}$ 4.1, $J_{5,6a}$ 6.4, $J_{5,6b}$ 3.7, $J_{6a,6b}$ 12.1. Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07; Cl, 17.76; N, 7.02. Found: C, 36.01; H, 7.06; Cl, 17.61; N, 6.92. A sample was acetylated in Ac_2O-pyridine to give 1-acetamido-3,4,6-tri-*O*-acetyl-2,5-anhydro-1-deoxy-D-glucitol (**2d**): ^{13}C NMR (125 MHz, benzene-d_6): 170.4, 170.3, 169.7, 169.5 (4 × carbonyl), 81.9 (C-5), 79.5 (C-2), 79.0 (C-4), 76.9 (C-3), 63.8 (C-6), 38.5 (C-1), 22.7 (amide CH_3), 20.4, 20.23, 20.18 (3 × CH_3); ^1H NMR (benzene-d_6): δ 5.28 (dd, H-3), 5.08 (dd, H-4), 4.40 (dd, H-6b), 4.27 (dd, H-6a), 4.11 (ddd, H-2), 3.96 (ddd, H-5), 3.64 (ddd, H-1b), 3.39 (ddd, H-1a); $^3J_{H,H}$ (Hz): $J_{1a,1b}$ 13.8, $J_{1a,2}$ 6.8, $J_{1b,2}$ 5.3, $J_{2,3}$ 3.75, $J_{3,4}$ 1.25, $J_{4,5}$ 3.25, $J_{5,6a}$ 6.5, $J_{5,6b}$ 4.9, $J_{6a,6b}$ 11.5, $J_{1a,NH}$ 6.0, $J_{1b,NH}$ 6.0.

1 - Deoxy - 1 - trifluoroacetamido - D - glucitol (**4**).—1-Amino-1-deoxy-D-glucitol (5.00 g, 27.6 mmol) was suspended in dry MeOH (100 mL) at room temperature. Triethylamine (0.5 g) and CF_3COOMe (4.24 g, 1.2 equiv) were added successively, and the suspension was stirred overnight at room temperature. The solvent was evaporated and the residue was recrystallized from abs EtOH (150 mL). The product was isolated at 0 °C and washed twice with ice-cold EtOH. Yield of **4** after drying was 7.19 g (94%); mp 170–171 °C; $[\alpha]_D^{25}$ −17.7° (*c* 1.69, H_2O); ^{13}C NMR (D_2O) δ 160.2 (q, $^2J_{CF}$ 37 Hz), 116.7 (q, $^1J_{CF}$ 286 Hz), 72.1, 71.8, 71.3, 71.0, 63.5, 43.2. Anal. Calcd for $C_8H_{14}F_3NO_6$: C, 34.66; H, 5.09; N, 5.05. Found: C, 34.62; H, 5.07; N, 4.98.

3, 4, 6 - Tri - O - acetyl - 2, 5 - anhydro - 1 - deoxy - 1 - trifluoroacetamido-D-mannitol (**5b**).—1-Deoxy-1-trifluoroacetamido-D-glucitol (**4**; 2.00 g, 7.22 mmol) was dissolved in anhyd HF (20 mL) as above and left for 5 days at room temperature then concd as for **2c**. The resulting oil was dissolved in 1:1 H_2O–MeOH (50 mL) at 0 °C and stirred with IR-120 (H^+) ion-exchange resin (20 mL) for 10 min. The resin was filtered off and washed with MeOH. Evaporation of the filtrate gave **5a** as a colourless oil (1.32 g,

71%). Acetylation of **5a** with Ac_2O (10 mL) in pyridine (15 mL) overnight followed by evaporation and coevaporation with toluene gave, after chromatography on a silica gel column (1.5 × 35 cm, 2:3 EtOAc–pentane), **5b** as a colourless oil. The yield of **5b** was 1.73 g (62% overall); $[\alpha]_D^{25}$ +11.5° (*c* 3.3, $CHCl_3$); ^{13}C NMR (125 MHz, benzene-d_6): δ 170.3, 170.0, 169.6 (3 × carbonyl), 157.5 (carbonyl, q, $^2J_{CF}$ 37 Hz), 116.6 (CF_3, q, $^1J_{CF}$ 288 Hz), 81.9 (C-2), 81.7 (C-5), 79.6 (C-3), 78.6 (C-4), 62.7 (C-6), 41.1 (C-1), 20.2, 20.1, 20.0 (3 × CH_3); ^1H NMR (benzene-d_6): δ 6.89 (bs, NH), 5.20 (t, H-4), 4.98 (dd, H-3), 4.24 (dd, H-6b), 4.18 (dt, H-5), 4.11 (dd, H-6a), 3.96 (dt, H-2), 3.42 (bt, H-1); $^3J_{H,H}$ (Hz): $J_{1,2}$ 6.1, $J_{2,3}$ 3.2, $J_{3,4}$ 2.0, $J_{4,5}$ 2.7, $J_{5,6a}$ 5.0, $J_{5,6b}$ 6.1, $J_{6a,6b}$ 11.1, $J_{1,NH}$ 6.0. Anal. Calcd for $C_{14}H_{18}F_3NO_8$: C, 43.64; H, 4.71; N, 3.64. Found: C, 43.24; H, 4.71; N, 3.32.

*1-Deoxy-1-trifluoroacetamido-*D*-galactitol* (**8**).—1-Amino-1-deoxy-D-galactitol · HCl (4.00 g, 18.4 mmol) was dissolved in water and adsorbed on a column (80 mL) of IRA-420 (HO^-) ion-exchange resin. The free amine was eluted with water until a neutral eluate was obtained. Evaporation to dryness yielded 2.84 g (85%) of the amine, as a white solid which was suspended in dry MeOH (50 mL). Triethylamine (0.32 g) and CF_3COOMe (2.41 g, 18.8 mmol) were added successively. The suspension was stirred at room temperature overnight. The solvent was evaporated and the residue was recrystallized from MeOH (~ 300 mL). The crystals were isolated at 0 °C and washed with cold MeOH. The yield of **8** after drying was 3.58 g (82%); mp 205–206 °C; $[\alpha]_D^{25}$ −26.5° (*c* 2.0, Me_2SO); ^{13}C NMR (Me_2SO-d_6) δ 156.7 (q, $^2J_{CF}$ 36 Hz), 116.3 (q, $^1J_{CF}$ 288 Hz), 70.5, 70.2, 69.5, 67.6, 63.4, 43.6. Anal. Calcd for $C_8H_{14}F_3NO_6$: C, 34.66; H, 5.09; N, 5.05. Found: C, 34.57; H, 5.04; N, 4.70.

*2,5-Anhydro-1-deoxy-1-trifluoroacetamido-*D*-talitol* (**9**).—1-Deoxy-1-trifluoroacetamido-D-galactitol (**8**; 1.00 g, 3.61 mmol) was dissolved in HF (10 mL) as above and left for 5 days at room temperature. Evaporation of HF as for **2c** resulted in a colourless oil which was dissolved in 50% aqueous MeOH (30 mL) at 0 °C and stirred with IR-120 (H^+) ion-exchange resin (10 mL) for 10 min. The resin was filtered off and washed with MeOH. The filtrate was concentrated and evaporated twice with EtOH yielding **9** as a colourless oil (0.48 g) which slowly crystallized. The crude product was dissolved in hot EtOAc and filtered through a 0.5 μ filter to remove some solid impurities. Heating and addition of hexane gave, after cooling, **9** as colourless crystals (0.39 g, 42%); mp 109–110 °C; $[\alpha]_D^{25}$ +25.9° (*c* 2.4, H_2O); ^{13}C NMR (125 MHz, D_2O): δ 160.1 (carbonyl, q, $^2J_{CF}$ 38 Hz), 116.7 (CF_3, q, $^1J_{CF}$ 286 Hz), 81.5, 79.5, 74.4, 72.4, 61.1, 42.3. Anal. Calcd for $C_8H_{12}F_3NO_5$: C, 37.07; H, 4.67; N, 5.40. Found: C, 36.96; H, 4.74; N, 5.34.

*1-Deoxy-1-trifluoroacetamido-*L*-rhamnitol* (**12**).—1-Amino-1-deoxy-L-rhamnitol · HCl (8.00 g, 39.7 mmol) was dissolved in dry MeOH (100 mL), and Et_3N (4.82 g, 1.2 equiv) and CF_3COOMe (6.10 g, 1.2 equiv) were added. The clear solution was stirred for 22 h at room temperature and the solvent evaporated yielding a white powder. The product (containing Et_3N · HCl) was redissolved in MeOH (75 mL) and treated with IR-120 (H^+) ion-exchange resin (75 mL) at 0 °C for 15 min. The resin was filtered off and washed with MeOH. Evaporation of the combined filtrates yielded 10.8 g (^{13}C-NMR showed less than 5% salt left). The crude product was recrystallized from EtOH–EtOAc. The yield of **12** was (8.35 g, 81%); mp 167–168 °C; $[\alpha]_D^{25}$ −8.6° (*c* 1.34, H_2O); ^{13}C NMR (D_2O) δ 160.1 (q, $^2J_{CF}$ 37 Hz), 116.8 (q, $^1J_{CF}$ 286 Hz), 74.0, 71.4, 69.8, 67.8, 43.8, 19.7. Anal. Calcd for $C_8H_{14}F_3NO_5$: C, 36.79; H, 5.40; N, 5.36. Found: C, 36.89; H, 5.46; N, 5.44.

*2,5-Anhydro-1,6-dideoxy-1-trifluoroacetamido-*L*-glucitol* (**13b**).—1-Deoxy-1-trifluoroacetamido-L-rhamnitol (**12**; 1.75 g, 6.70 mmol) was dissolved in HF (15 mL) and left for 5 days at room temperature. Evaporation of the HF as above yielded a reddish oil which was treated with charcoal in MeOH and re-evaporated yielding a light yellow oil. The oil was dissolved in dry MeOH (25 mL) and treated with Et_3N (2.7 g), followed by CF_3COOMe (1.20 g, 9.40 mmol), and the solution was stirred at room temperature overnight. Evaporation of the solvent yielded a reddish oil, which was chromatographed on a silica gel column (4 × 22 cm, 16:1 EtOAc–EtOH) to give a mixture of **13b** and **14**. Fractions containing a mixture of these two compounds were collected and evaporated to yield 1.27 g of a crystalline 2:1 mixture of **13b** and **14**. Fractional crystallization from EtOAc–hexane yielded **13b** as colourless flakes (0.65 g, 40%); mp 124–126 °C; $[\alpha]_D^{25}$ +30.5° (*c* 1.39, acetone); ^{13}C NMR (CD_3OD): δ 159.2 (carbonyl, q, $^2J_{CF}$ 37 Hz), 117.5 (CF_3, q, $^1J_{CF}$ 287 Hz), 84.8, 82.3, 79.6, 79.5, 40.9, 19.4. Anal. Calcd for $C_8H_{12}F_3NO_4$: C, 39.51; H, 4.97; N, 5.76. Found: C, 39.44; H, 5.09; N, 5.79.

*1,3-Dideoxy-1-trifluoroacetamido-*D*-ribo-hexitol* (**17**).—Crude 1-amino-1,3-dideoxy-D-*ribo*-hexitol (see below) (**25**; 3.40 g, 20.6 mmol) was dissolved in dry MeOH (50 mL) and Et_3N (0.4 g) and CF_3COOMe

(3.4 g) were added. After stirring overnight at room temperature, the solution was concentrated under reduced pressure to yield crude **17** (3.4 g, ~ 100%) as a white powder. Recrystallization from 2-propanol afforded **17** as a white microcrystalline powder. The yield was 2.40 g (71%); mp 122–124 °C. One further recrystallization gave a compound with mp 123–124 °C; $[\alpha]_D^{25}$ −14.6° (*c* 2.4, H_2O); ^{13}C NMR (CD_3OD): δ 159.3 (carbonyl, q, $^2J_{CF}$ 37 Hz), 117.6 (CF_3, q, $^1J_{CF}$ 287 Hz), 76.2, 71.8, 69.5, 64.4, 46.6, 38.2. Anal. Calcd for $C_8H_{14}F_3NO_5$: C, 36.79; H, 5.40; N, 5.36. Found: C, 36.81; H, 5.38; N, 5.36.

*4,6-Di-O-acetyl-2,5-anhydro-1,3-dideoxy-1-trifluoroacetamido-*D-arabino-*hexitol* (**18b**).—1,3-Dideoxy-1-trifluoroacetamido-D-*ribo*-hexitol (**17**; 1.00 g, 3.83 mmol) was dissolved in anhyd HF (10 mL) and left for 5 days at room temperature. Evaporation of HF was carried out as above. The resulting oil was acetylated in pyridine (15 mL) and acetic anhydride (10 mL) at room temperature overnight. The pyridine and acetic anhydride was evaporated under reduced pressure and the residual pyridine was removed by repeated evaporation with toluene. The oil was purified by column chromatography (silica gel, EtOAc). The yield was 1.10 g (88%); $[\alpha]_D^{25}$ +13.2° (*c* 2.9, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 170.6, 170.4 (2 × carbonyl), 157.3 (carbonyl, q, $^2J_{CF}$ 37 Hz), 116.6 (CF_3, q, $^1J_{CF}$ 287 Hz), 81.9 (C-5), 76.7, 75.5 (C-2, C-4), 63.6 (C-6), 43.2 (C-1), 34.5 (C-3), 20.7, 20.6, (2 × CH_3);^1H NMR ($CDCl_3$): δ 6.88 (bs, NH), 5.14 (dt, H-4), 4.33 (m, H-2), 4.22 (ddd, H-5), 4.11 (d, H-6), 3.59 (dq, H-1b), 3.44 (p, H-1a), 2.49 (p, H-3b), 1.79 (dq, H-3a); $^3J_{H,H}$ (Hz): $J_{1a,1b}$ 14.5, $J_{1a,2}$ 7.0, $J_{1b,2}$ 3.5, $J_{2,3a}$ 5.0, $J_{2,3b}$ 8.0, $J_{3a,4}$ 2.8, $J_{3b,4}$ 7.0, $J_{4,5}$ 2.3, $J_{5,6}$ 5.0, $J_{1a,NH}$ 6.0, $J_{1b,NH}$ 5.0. Anal. Calcd for $C_{12}H_{16}F_3NO_6$: C, 44.04; H, 4.93; N, 4.28. Found: C, 43.68; H, 4.93; N, 4.04.

2 - Trifluoroacetamido - ethanol (**23**).—Ethanolamine (2.50 g, 40.9 mmol) was dissolved in dry MeOH (25 mL) and CF_3COOMe (6.29 g, 1.2 equiv) was added at room temperature with slight exothermic reaction. After stirring overnight, the solvent was evaporated under reduced pressure at 30 °C. The yellow residue was distilled at 85–90 °C (1 mmHg) yielding 4.86 g (76%) of a thick colourless oil which crystallized on cooling. ^{13}C NMR (CD_3OD) δ 159.3 (q, $^2J_{CF}$ 37 Hz), 117.5 (q, $^1J_{CF}$ 286 Hz), 60.7 (C-1), 43.2 (C-2).

*1-Amino-1,3-dideoxy-*D-ribo-*hexitol* (**25**).—3-Deoxy-β-D-*ribo*-hexopyranose [31,32] (crystalline mp 135–137 °C [33]) (4.00 g, 24.4 mmol), benzylamine (2.87 g, 26.8 mmol) and water (1.0 mL) were mixed and stirred at 60 °C for 45 min. Methanol (30 mL) was added to the resulting thick light-yellow oil, and the solution was cooled to 8 °C. Sodium borohydride (1.20 g, 31.7 mmol) was added during 5 min at 8–10 °C. The solution was stirred for 1 h at 25 °C and, after cooling to 5 °C, the colourless solution was carefully acidified with concd HCl. The solvent was evaporated and the residue evaporated four times with MeOH to remove boric acid as $B(OMe)_3$. The residue was extracted with EtOH (100 mL) at room temperature and NaCl was filtered off. Evaporation of the solvent gave 1-benzylamino-1,3-dideoxy-D-*ribo*-hexitol hydrochloride as a semicrystalline oil (~ 10 g). The ^{13}C NMR spectrum showed a purity of 85%, the major impurity being ~ 15% benzylamine hydrochloride. The raw product was dissolved in H_2O (100 mL) and Pd–C (5%) (250 mg) was added. The pH was adjusted to 9 with 12 M NH_4OH and debenzylation was achieved by hydrogenolysis (H_2/50 atm, 60 °C, 15 h). Filtration and evaporation yielded a colourless oil that crystallized partly by evaporation with EtOH. The ^{13}C NMR spectrum showed 95% pure 1-amino-1,3-dideoxy-D-*ribo*-hexitol hydrochloride (D_2O δ 75.3, 69.9, 66.7, 63.1, 45.1, 37.5). The product was dissolved in water and stirred with IR-120 (H^+) ion-exchange resin (50 mL) for 10 min. The resin was added on top of a column of fresh resin (50 mL) and washed with water (500 mL). The free amine was eluted with 2 M NH_4OH. Evaporation of the eluate gave an oil which was redissolved in abs EtOH (150 mL), treated with activated charcoal, filtered and evaporated to dryness to yield **25** as a light-yellow oil (3.40 g, 84% overall); ^{13}C NMR (CD_3OD) δ 76.3, 72.1, 71.7, 64.4, 48.1, 38.3 (only peaks observable). Anal. Calcd for $C_6H_{15}NO_4$: C, 43.63; H, 9.15; N, 8.48. Found: C, 43.55; H, 9.45; N, 7.17. The oil did not crystallize during several days, and it was used without further purification in the synthesis of **17**.

Acknowledgements

Financial support of this project by the Danish Technical Research Council is gratefully acknowledged.

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