On the Way to Glycoprocessing Inhibitors: A General One-Pot Synthesis of Imidazolosugars

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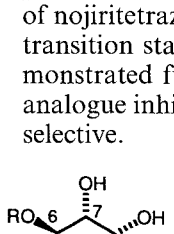
Dedicated to Professor Manfred Regitz on the occasion of his 60th birthday

Reaction of several monosaccharides with formamidine acetate afforded the corresponding imidazolosugars **5–11** in 30–50% yield.

The enzymatic glycosidase mechanism of pyranosic polysaccharides is believed to involve a transient half-chair oxocarbonium ion, which is stabilized by a complementary carboxylate anion of an active site catalytic residue.[1,2] Structural aza analogues of these glycosyl cations have long represented attractive synthetic targets for the design of potent glycoprocessing inhibitors. As a matter of fact, half-chair piperidinose derivatives with an intracyclic imine double bond, e.g. amidines proved to be the goal of choice for those[3,4] who were looking for competitive glycosidase inhibitors. Along this line of thought we described in 1991 the rather lengthy synthesis of the D-arabinoimidazole **1** from the D-fructose derivative **5**.[5] This chiral half-chair piperidinose transition state analogue, when tested against a dozen human liver glycosidases, proved to be a potent mannosidase inhibitor.[6] Azasugar **1** is of interest as, unlike other azasugar derivatives, it selectively inhibits α-D-mannosidase but does not inhibit α-fucosidase.[4]

In the meantime Vasella, Withers and their co-workers published the synthesis of mannonojiritetrazole **(3)** and of nojiritetrazole **(4)**, both of which proved to be potent transition state analogue inhibitors.[7] These authors demonstrated furthermore that these true transition state analogue inhibitors of glycosidases are configurationally selective.



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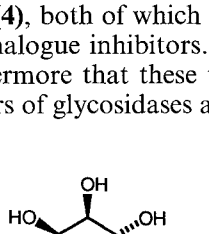

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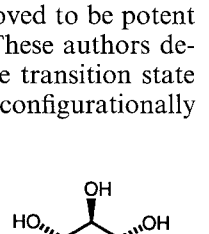

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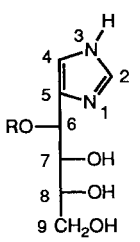
Since **1** is of interest as a specific glycoprocessing inhibitor, we looked for a shorter and more expeditious synthesis for it. Furthermore, in our first synthesis,[5] the starting material **5** was obtained in poor yield (10%) from D-fructose, according to the Parrod,[8] and Weidenhagen–Herrmann procedures[9]: the α-hydroxyketone moiety of D-fructose was oxidized with copper(II) acetate and cyclized with ammonia and formaldehyde in water. The drawback of this procedure is that the imidazole derivatives formed as copper(I) salts had to be decomposed with hydrogen sulfide. Furthermore, most of the D-fructose underwent retroaldolisation which led ultimately to 4(5)-hydroxymethyleneimidazole **(12)** as the major reaction product. As a matter of fact this procedure represents a convenient access to the cleavage product **12** on a preparative scale.[10]

Therefore we turned our attention to the double condensation of formamidine with ketoses and aldoses by applying a procedure which was initiated by Schunack, e.g. for the synthesis of **12** from dihydroxyacetone[11] in ammonia in a pressure bottle.

Formamidine acetate and the appropriate monosaccharide were treated with ammonia in a pressure vessel (75 °C, ca. 40 atm, overnight) whereby the expected imidazole derivatives formed in yields, ranging as a rule from 30 to 50%. These azasugars were characterized by ^1H and ^{13}C NMR as well as by electrospray mass spectroscopy. To the best of our knowledge, this rather simple synthesis of imidazolosugars has not been described previously. It represents a general method which is useful on a preparative scale. For example imidazole **6** was obtained in ca. 50% yield using this method from the known 3-*O*-benzyl-D-glucose.[12]



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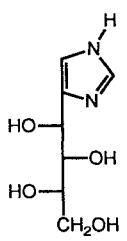

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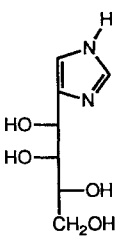

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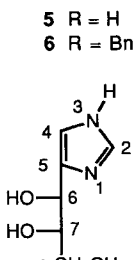

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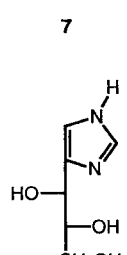

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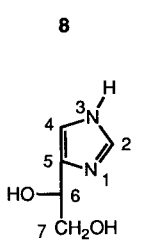

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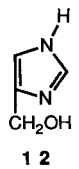

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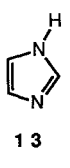

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Reaction of **6** with triphenylphosphine and carbon tetrabromide, followed by treatment with triethylamine, according to Appel's procedure,[13] gave the bicyclic derivative **2** in 57% yield without protection of the two secondary alcohol functions. This latter procedure is very similar to the one described by Rassu and his co-workers for a piperidine having a polyhydroxylated sidechain in the α-position.[14] Eventually hydrogenolysis [H_2/$Pd(OH)_2$/C] of **2** led to the known D-arabinoimidazole **1**.

Table 1. ^{1}H NMR (250 MHz) Data of Imidazolocarbohydrates **5–10** Prepared [δ, J (Hz)][a]

Product	Assignments								Coupling Constants[b]								
	H-2	H-4	H-6	H-7	H-8	H-8′	H-9	H-9′	$J_{4,2}$	$J_{4,6}$	$J_{6,7}$	$J_{7,8}$	$J_{7,8'}$	$J_{8,8'}$	$J_{8,9}$	$J_{8,9'}$	$J_{9,9'}$
5	7.79 (d)	7.17 (dd)	4.96 (dd)	3.88 (dd)	3.73 (td)	–	3.80 (dd)	3.62 (dd)	1.2	0.7	4.0	6.6	–	–	2.7	6.5	11.0
6 · HCl[c]	8.84 (d)	7.47 (d)	5.01 (d)	3.57 (dd)	3.86 (ddd)	–	3.79 (dd)	3.65 (dd)	1.5	–	2.1	8.6	–	–	2.9	5.3	11.2
7	7.75 (d)	7.17 (d)	4.84 (d)	3.94 (dd)	3.52 (td)	–	3.66 (ddABx)	3.62 (ddABx)	1.2	–	7.3	2.8	–	–	5.1	7.2	11.6
8	7.74 (d)	7.17 (d)	4.78 (d)	3.94 (dd)	3.98 (m)	–	3.72 (ddAB)	3.67 (ddAB)	1.2	–	7.9	2.5	–	–	4.9	7.3	11.4
9	7.74 (d)	7.15 (d)	4.73 (d)	3.63 (td)	4.02 (dd)	3.80 (dd)	–	–	1.2	–	6.8	3.3	6.8	11.9	–	–	–
10	7.73 (d)	7.15 (d)	4.72 (d)	3.99 (td)	3.60 (dd)	3.48 (dd)	–	–	1.2	–	6.6	3.8	6.7	11.8	–	–	–

[a] The ^{1}H NMR spectra of compounds **5, 7–10** were recorded in D_2O with $TSPD_4$ as the internal standard. The spectrum of **6** · HCl was measured in CD_3OD (reference peak $\delta = 3.30$).

[b] The coupling constants $J_{6,7}$, $J_{7,8}$, $J_{8,9}$, $J_{8,9'}$ and $J_{9,9'}$ for **6** · HCl, **7** and **8** were determined by simulation with the PANIC program from Bruker.

[c] Benzyl groups: 4.57, 4.52 (AB pattern, $C\underline{H}_2Ph$, $J_{A,B} = 11.7$ Hz), 7.26–7.33 (m, H_{arom}).

Imidazolosugars 5–11; General Procedure:
In a 200 mL stainless steel pressure vessel protected from moisture and cooled in a dry ice/acetone bath, was condensed ammonia (ca. 20 mL) followed by the addition of the appropriate sugar (30 mmol) and formamidine acetate (5.02 g, 36 mmol). The bomb was sealed and heated at 75 °C (pressure reaches ca. 40 atm) with stirring for 15 h. The bomb was then cooled in a dry ice/acetone bath, opened, taken out of the cold, and the ammonia was left to evaporate between −70 °C and r.t. The resulting brownish oil was dissolved in MeOH (50 mL) the solution evaporated to dryness and the residue stripped off of ammonia in a rotary evaporator for 4 h at reduced pressure (0.05 Torr). The remaining oil was taken up in H_2O and treated over a CP 2110 Rohm and Haas resin (acidic form, 40 g) to remove AcOH. Desorption was performed with 10% aq ammonia, the solution evaporated to dryness and the residue separated by flash chromatography (Et_2O/MeOH, 5:5–4:6 containing 2% conc. ammonia).

4(5)-(D-Arabinotetritol-1-yl)imidazole **(5)**: The general procedure applied to D-fructose led to a 3:7 mixture (according to ^{1}H NMR) of the known hydroxymethyleneimidazole **12** and **5** from which the latter (2.13 g, 38%) was isolated by flash chromatography (FC) as a white powder, mp 155 °C dec; $[\alpha]_D^{20} - 12$ ($c = 1.0$, H_2O) (Tables 1 and 2).

MS: m/z (%) = 189 (0.4, $M^+ + H$), 157 (1, $M^+ - CH_2OH$), 139 (0.8), 123 (0.7), 127 (6), 111 (10), 109 (6), 98 (30), 97 (100, ($M^+ - CHOHCHOHCH_2OH$)), 95 (6), 81 (10), 69 (13), 42 (14), 31 (6).

Table 2. ^{13}C NMR (62.9 MHz) Data of Imidazolocarbohydrates **5–10** Prepared (δ)[a]

Product	C-2	C-4	C-5	C-6	C-7	C-8	C-9
5	137.8	119.1	139.1	68.7	76.3	73.9	65.5
6 · HCl[b]	135.2	118.5	133.8	73.1	75.1	72.2	64.5
7	139.1	119.7	140.1	71.1	76.1	73.9	65.8
8	139.1	120.2	140.6	69.6	75.3	73.3	65.9
9	139.0	120.0	140.1	70.6	76.6	65.4	–
10	138.3	119.2	139.2	70.0	76.8	65.2	–

[a] The ^{13}C NMR spectra of compounds **5, 7–10** were recorded in D_2O with $TSPD_4$ as the internal standard. The spectrum of **6** · HCl was measured in CD_3OD (reference peak $\delta = 49.02$).

[b] Benzyl group: 73.3 ($C\underline{H}_2Ph$), 128.8, 129.2, 129.3, 138.7 (C_{arom}).

$C_7H_{12}N_2O_4$ (188.2)	calc.	C 44.68	H 6.43	N 14.88
	found	44.4	6.2	14.9

4(5)-(L-Xylotetritol-1-yl)imidazole **(7)**: The general procedure applied to L-sorbose led to a mixture from which **12** (1.14 g, 39%) and **7** (3.01 g; 53%) were isolated by FC. Compound **7**: hygroscopic resin, $[\alpha]_D^{20} - 9$ ($c = 1.0$, H_2O) (Tables 1 and 2). MS identical to that of **5**.

4(5)-(D-Lyxotetritol-1-yl)imidazole **(8)**: The general procedure applied to D-galactose led to a mixture from which the known imidazole **13** (310 mg, 15%) and **8** (1.49 g, 26%) were isolated. Compound **8**: hygroscopic resin; $[\alpha]_D^{20} - 9$ ($c = 1.0$, H_2O) (Tables 1 and 2). MS: identical to that of **5**.

4(5)-(L-(Erythrotriitol-1-yl)imidazole **(9)**: The general procedure applied to L-arabinose gave a mixture from which imidazole **13** (350 mg, 17%), hydroxymethyleneimidazole **12** (476 mg, 16%), and **9** (1.43 g, 30%) were isolated. Compound **9**: hygroscopic resin; $[\alpha]_D^{20} - 14$ ($c = 1.0$, H_2O) (Tables 1 and 2).

MS: m/z (%) = 159 (2.5, $M^+ + H$), 141 (1.7), 140 (0.6), 127 (2.4, ($M^+ - CH_2OH$)), 123 (0.7), 111 (10), 109 (8), 98 (30), 97 (100, ($M^+ - CHOHCH_2OH$)); the other peaks are identical to those of **5**.

ent-**9**: The general procedure applied to D-arabinose gave likewise *ent*-**9** (1.48 g, 31%) as a resin; $[\alpha]_D^{20} + 13$ ($c = 1.0$, H_2O). ^{1}H and ^{13}C NMR spectra were identical with those of **9** (Tables).

4(5)-D-Threotriitol-1-yl)imidazole **(10)**: The general procedure applied to D-xylose gave a mixture whose FC led to **10** (2.34 g, 49%) as a hygroscopic resin; $[\alpha]_D^{20} - 16$ ($c = 1.0$, H_2O) (Tables 1 and 2). MS identical to that of **9**.

4(5)-(L-Glycerodiitol-1-yl)imidazole **(11)**: The general procedure applied to L-erythrulose (2.23 g, 16.0 mmol) with formamidine acetate (1.68 g, 16.0 mmol) led to **11** (1.71 g, 83%) as colourless crystals mp 156–157 °C (EtOH/H_2O); $[\alpha]_D^{20} - 19$ ($c = 1.0$, H_2O).

^{1}H NMR (D_2O) second order spectrum: $\delta = 7.73$ (H-2), 7.14 (H-4), 4.83 (H-6), 3.86 (H-7), 3.81 (H-7′) ($J_{6,7} = 4.7$ Hz, $J_{6,7'} = 7.2$ Hz, $J_{7,7'} = 11.4$ Hz).

^{13}C NMR (D_2O): $\delta = 140.7$ (C-5), 139.1 (C-2), 118.9 (C-4), 70.9 (C-6), 67.6 (C-7).

MS: m/z (%) = 128 (6, M^+), 98 (20), 97 (100, ($M^+ - CH_2OH$)); the other peaks were identical to those of **5**.

$C_5H_8N_2O_2$ (128.1)	calc.	C 46.87	H 6.29	N 21.87
	found	46.6	6.2	22.0

6-O-Benzyl-4(5)-(D-arabinotetritol-1-yl)imidazole **(6)**: The general procedure applied to 3-*O*-benzyl-D-glucose (6.82 g, 25.2 mmol) with

formamidine acetate (3.66 g, 35.1 mmol) gave **6** (3.72 g, 53 %) as a resin; $[\alpha]_D^{20}$ − 53 (c = 1.0, MeOH), which was characterized as its hydrochloride **6** · HCl (resin) (Tables 1 and 2).

MS: m/z (%) = 217 (4, $M^+ - CHOHCH_2OH$), 187 (35, $M^+ - CHOHCHOHCH_2OH$), 111 (12), 108 (10), 97 (40), 91 (100, Bn^+).

(6*R*,7*R*,8*R*)-6-Benzyloxy-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-6,7,8-triol (2):

To a stirred mixture of **6** (1.067 g, 3.83 mmol) in DMF (8 mL) kept at 0 °C under Ar was added CBr_4 (2.35 g, 7.09 mmol). After 15 min, PPh_3 (2.19 g, 8.17 mmol) was added portionwise. After 4 h at 0 °C, NEt_3 (1.6 mL, 11.5 mmol) was added and the mixture left overnight to warm up to r.t. DMF was removed in vacuum and the residue purified by FC (EtOAc + trace amounts of MeOH) to yield **2** (569 mg, 57 %) as a crystalline material; mp 170.5–172 °C (EtOAc/MeOH), $[\alpha]_D^{20}$ − 73 (c = 1.0, MeOH).

^{1}H NMR (CD_3OD): δ = 7.59 (s large, H-2), 7.33–7.26 (m, H_{arom}), 6.98 (s large, H-4), 4.63 (d, J = 4.5, H-6), 4.64 and 4.58 (AB-spectrum, J = 11.7 Hz, $\underline{CH}_2Ph$), 4.38 (ddd, J = 8.9, 5.5, 2.1 Hz, H-8), 4.20 (dd, J = 12.1, 5.5 Hz, H-9), 4.16 (dd, J = 4.5, 2.1 Hz, H-7) 3.94 (dd, J = 12.1, 8.9 Hz, H-9′).

^{13}C NMR (CD_3OD): δ = 139.5, 129.4, 129.0, 128.8 (C_{arom}), 137.6 (C-2), 128.2 (C-4), 127.8 (C-5), 72.8 (C-6), 72.2 (C-7), 72.0 ($\underline{C}H_2Ph$), 66.6 (C-8), 45.8 (C-9).

$C_{14}H_{16}N_2O_3$	calc.	C 64.60	H 6.20	N 10.76
(260.3)	found	64.6	6.4	10.8

(6*R*,7*R*,8*R*)-5,6,7,8-Tetrahydroimidazo[1,5-a]pyridine-6,7,8-triol (1):

A stirred mixture of **2** (116.3 mg, 0.447 mmol) in AcOH (3 mL) containing a small amount of $Pd(OH)_2/C$ was kept under H_2 atmosphere and left to react overnight under 1 atm. pressure. After filtration over Celite and rinsing with MeOH the solvents were evaporated in vacuum leaving a viscous residue which became powdery; mp 180 °C (dec); $[\alpha]_D^{20}$ − 9 (c = 1.08, MeOH) (Lit.[5] $[\alpha]_D^{20}$ − 11 (c = 1.12, MeOH). ^{1}H and ^{13}C NMR spectra were identical with those of **1**.[5]

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