Synthesis of iminopolyols *via* Henry reaction: a short route to the α-mannosidase inhibitor 1,4-dideoxy-1,4-imino-D-mannitol and to amino analogues†,[1]

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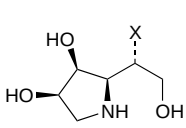
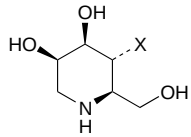
The α-mannosidase inhibitor 1,4-dideoxy-1,4-imino-D-mannitol (DIM) as well as amino analogues of DIM and of deoxy-*manno*-nojirimycin, respectively, have been prepared using a diastereoselective nitroaldol addition as the key step.

Many polyhydroxy-pyrrolidines and -piperidines (iminoglycitols) act as strong and specific inhibitors of glycosidases,[2–4] *e.g.* 1,4-dideoxy-1,4-imino-D-mannitol **1**[3] or deoxy-*manno*-nojirimycin **2**.[4] Due to their potential as anti-diabetic, anti-viral or anti-tumour agents,[2c] many efforts have been directed towards syntheses of this class of compounds, usually based on modification of carbohydrate precursors or cycloaddition methods.[5]



1 X = OH
3 X = NH_2

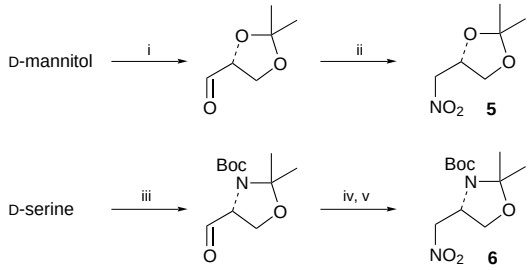


2 X = OH
4 X = NH_2

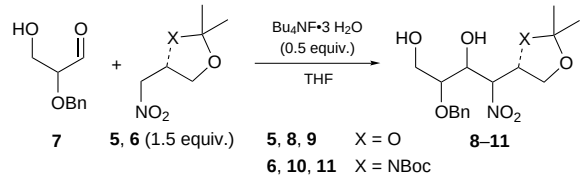
For some time, we have been studying the diastereoselectivity of the nitroaldol addition (Henry reaction),[6] with a view to efficient construction of nitro- and amino-polyols and further uses in the preparation of various amino- and imino-polyols.[7] We now report a simple synthesis of DIM **1**, and of new amino analogues **3**, **4** of DIM and of **2**, respectively, based on diastereoselective nitroaldol additions catalyzed by tetrabutylammonium fluoride trihydrate.[7,8] (C_3 + C_3)-Assembly of nitro compounds, bearing an α-oxy or α-amino function, and the glyceraldehydes **7** leads to nitrohexitols (see Scheme 2), which can be reduced to the corresponding amino compounds. Cyclization would then give access to iminopolyols. Thus, the question should be addressed whether the 4- or 5-OH group could be replaced by an amino function, to retain or alter inhibition of glycosidases.

The optically active nitro compounds **5**, **6** were prepared from the corresponding aldehydes[9,10] by oximation,[9d,10c] followed by oxidation with trifluoroperacetic acid[11] (Scheme 1).

For the aldehyde part, 2-*O*-benzylglyceraldehyde **7** was chosen, readily available in both enantiomeric forms from



Scheme 1 *Reagents and conditions*: i, ref. 9(*a*), (*b*), 53%; ii, ref. 9(*d*), 11, 67%; iii, ref. 10(*a*), (*b*), 84%; iv, NH_2OH·HCl, K_2CO_3, MeOH, H_2O, 0 °C, 2 h; [ref. 10(*c*)]; v, H_2O_2 (85%), $(CF_3CO)_2O$, Na_2HPO_4, MeCN, 0 °C, 2 h, 76% (iv, v)



7 **5**, **6** (1.5 equiv.) **5**, **8**, **9** X = O **8–11**
6, **10**, **11** X = NBoc

Scheme 2

Table 1 Nitroaldol addition of **5** and **6** to **7**

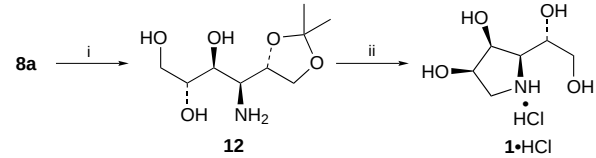
Reactants	Conditions	Products	Yield[a] (%)	Dr[b]	Major isomer
D-**7** + **5**	−20 °C, 6 d	**8a,8b,8c**	90	67 : 22 : 11	D-*manno*
L-**7** + **5**	−20 °C, 6 d	**9a,9b,9c**	92	69 : 18 : 13	D-*gulo*
D-**7** + **6**	0 °C, 7 d	**10a,10b**	88	90 : 10	D-*manno*
L-**7** + **6**	0 °C, 7 d	**11a,11b**	81	90 : 10	D-*gulo*

[a] Pure material after flash chromatography on silica. [b] From ^{13}C NMR and/or HPLC analyses of crude mixture; other diastereomers < 5%.

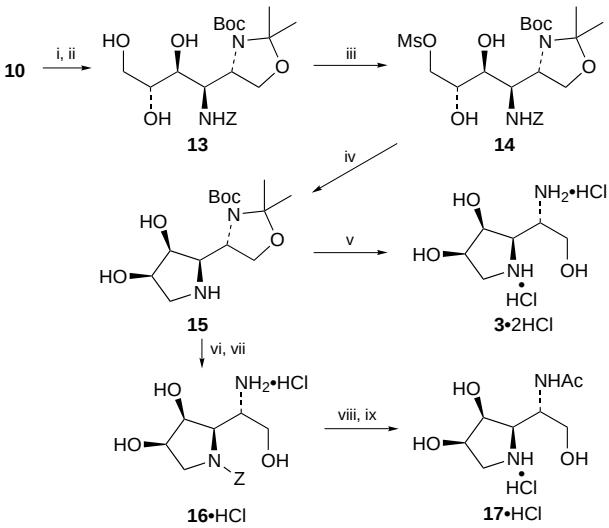
tartrates,[12] which had given the best diastereomer ratios in related cases.[7] The addition of **5** to D- or L-**7** afforded the nitro alcohols **8** and **9** in high yields as mixtures of diastereomers,[7c] from which the major isomers **8a** (D-*manno*) and **9a** (D-*gulo*) were separated by chromatography (Scheme 2, Table 1). As seen earlier,[7] 1,2-induction from the aldehyde stereocentre strongly favoured 2,3-*erythro* formation, and the non-induced stereoselection concerning C3/C4 preferentially led to a *threo* relationship. Double stereodifferentiation, as observed in related cases,[1,7b,c] was not operative here.

The nitroaldol **8a** was converted into the amine **12** by catalytic hydrogenation.[13] Cyclization of **12** with the Appel reagent (Ph_3P, CCl_4, Et_3N),[14] followed by ion exchange chromatography and hydrochloric acid treatment, afforded the D-iminomannitol **1** in 74% yield after conversion into the hydrochloride (Scheme 3); the overall yield from D-mannitol was 10% (seven steps). Starting from **9a**, the D-*gulo* isomer[15] was accessible likewise, as confirmed by crystal structure analysis.[16]

Addition of the nitro compound **6** to D-**7** occurred with a considerably higher diastereomer ratio: the 5-amino-4-nitrohexitol **10** was preferred by 90 : 10 (D-*manno* : D-*talo*; from L-**7**: **11a** and **11b**, D-*gulo* and D-*allo* were formed; Table 1). The nitro alcohol mixture **10** was converted to the corresponding amines



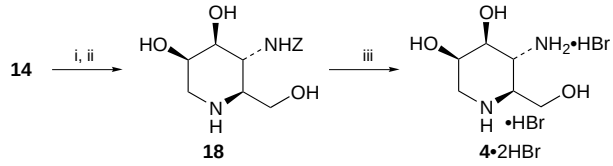
Scheme 3 *Reagents and conditions*: i, H_2 (4 bar), Pd–C, MeOH (*cf.* ref. 13), 25 °C, 21 h, 84%; ii, Ph_3P, CCl_4, Et_3N, pyridine, 25 °C, 2 d; Lewatit S 100 (H^+ form); 1 M HCl; 74% **1**·HCl, mp 147–148 °C, $[\alpha]_D^{20}$ −15.8 (*c* 0.97, H_2O) {lit.[3] mp 148–149 °C, $[\alpha]_D^{20}$ −16.3 (*c* 1.00, H_2O)}



Scheme 4 *Reagents and conditions*: i, H_2 (4 bar), Pd–C, MeOH, 25 °C, 22 h; ii, ZCl, $NaHCO_3$, dioxane, H_2O, 0 to 25 °C, 24 h, then crystallization (hexanes–EtOAc), 61% (**10**→**13**); iii, MsCl, NEt_3, CH_2Cl_2, −10 to 25 °C, 22 h, 84%; iv, H_2 (4 bar), Pd–C, MeOH, 25 °C, 18 h, 96%; v, 5 M HCl, 0 °C, 2 h, 90%; vi, ZCl, $NaHCO_3$, dioxane, H_2O, 0 to 25 °C, 20 h, 91%; vii, 3 M HCl, MeOH, 0 to 25 °C, 3 h, 98%; viii, Ac_2O, $KHCO_3$, dioxane, H_2O, 0 to 25 °C, 3 h, 87%; ix, H_2, Pd–C, 0.1 M HCl, MeOH, 18 h, 96%

by hydrogenation, followed by *N*-protection with benzyl chloroformate (ZCl) (Scheme 4). The major diastereomer **13** (D-*manno*) was separated by crystallization. Regioselective mesylation of the primary hydroxy group then led to the methanesulfonate **14**. Hydrogenolysis of the Z group was accompanied by *N*-cyclization[7] to afford the pyrrolidine **15**. On treatment of **15** with hydrochloric acid, the amino analogue of DIM **3** was obtained as the bis(hydrochloride). The configuration of **3** was again secured by X-ray crystallography.[7c] Due to orthogonal protection, the two amino groups of **14** could be functionalized individually, as is shown by the syntheses of the 5-acetylaminopyrrolidine **17** and the 4-aminopiperidine **4**. After Z protection of the ring nitrogen in **15**, the 5-amino function was liberated with aqueous acid to yield **16**. *N*-Acetylation and finally removal of Z furnished the 5-acetamido target compound **17** in the form of its hydrochloride (Scheme 4).

Next, the isomeric structure of the piperidine **4** was sought from the methanesulfonate **14**, by changing the order of steps. After removal of both the Boc and the acetonide protecting groups with acid, cyclization to the piperidine **18** took place on treatment with base. Catalytic hydrogenation under acidic conditions, followed by ion exchange chromatography, and subsequent reaction with hydrobromic acid led to the piperidine **4** in form of the bis(hydrobromide) (Scheme 5). The L-*manno* enantiomers of **3** and **4** were prepared according to the same protocol, starting with D-**6**, readily accessible from L-serine.



Scheme 5 *Reagents and conditions*: i, 3 M HCl, MeOH, 0 to 25 °C, 6 h, quant.; ii, $KHCO_3$, H_2O, 25 °C, 18 h, 92%; iii, H_2, Pd–C, 1 M HCl, MeOH, 25 °C; 2.5 h; Dowex 50 W (H^+ form); 1 N HBr; 94%

The iminopolyols were tested concerning their inhibitory activity on 24 glycosidases.[17] While DIM **1**, in accord with the literature,[3] showed strong and very selective inhibition of α-mannosidases [jack bean, IC_{50}/μM 3, K_i /μM 1.6; almond, IC_{50} 6, K_i 1.6], the 5-amino analogues **3** and **17** were inactive; this emphasizes the crucial role of the 5-hydroxy function in **1**.[18] The piperidines **4** and **18** showed no activity either, nor did the L-enantiomers of **3**, **4** and **18**. In contrast, the *N*-protected intermediates **16**, **18** proved moderately active towards β-galactosidases [**16**: bovine liver, IC_{50}/μM 460, K_i/μM 228; *Aspergillus orizae*, IC_{50} 540, K_i 705; **18**: bovine liver, 31% inhibition at 1 mM].

In summary, short and efficient syntheses of 1,4-imino-D-mannitol and -D-gulitol as well as of new amino analogues of DIM and of deoxy-*manno*-nojirimycin are presented, demonstrating the potential of the Henry reaction for the diastereoselective assembly of iminopolyols.

Financial support by the Landesgraduiertenförderung Baden-Württemberg (doctoral fellowship to F.-M. K.) and by the Fonds der Chemischen Industrie is gratefully acknowledged.

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Received in Liverpool, UK, 23rd September 1997; 7/06915D