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New stereocontrolled transformations in the imidazolosugar series

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Abstract—The isomeric imidazolopyrrolidinose **1**, imidazolopiperidinose **2** and imidazoloazepanose **3**, potential glycosidase inhibitors, were obtained in several steps from D-glucose.

Imidazolosugars as potential glycosidase inhibitors have been a subject of interest for several research groups.[1–6] The only known natural imidazolosugar–nagstatine is an effective inhibitor of *N*-acetylamino-β-D-glucosaminidase of bovine kidney.[7,8] We present herein the synthesis of three new isomeric imidazolosugars of the structures **1**, **2** and **3** (Fig. 1), potential glycosidase inhibitors.

This synthesis is based on stereocontrolled transformations of two epimeric dibenzylditritylimidazolyl-pentitols **10a** and **10b** which were obtained in several steps from dialdofuranose **4**, a compound readily available from D-glucose.[9]

The two epimeric imidazolosugars **6a** and **6b** were prepared in a 3:5 ratio by nucleophilic addition of the 5-lithiated derivative of 2-*t*-butyldimethylsilyl-1-dimethylsulphamoylimidazole (**5**)[10] to dialdofuranose **4**[9] according to the Kurihara procedure.[11] These two diastereomers were separated by flash chromatography and hence subjected to analogous reaction sequences.

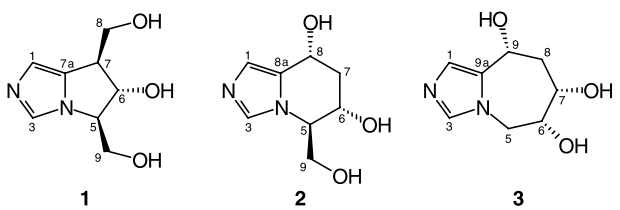

Figure 1.

Thus, benzylation of **6a** and **6b** resulted in the formation of the compounds **7a** and **7b** which, after removing acid-labile protecting groups, gave imidazolyl-pentoses **8a** and **8b**, each as a mixture of anomers. Subsequent reduction of **8a** and **8b** yielded imidazolyl-pentitols **9a** and **9b**, respectively, which were then tritylated to form the dityrityl derivatives **10a** and **10b** (Scheme 1).

Phenylmethanesulphonylation of the OH groups in **10a** and successive removal of the trityl groups by acid hydrolysis afforded the imidazolyl-pentitol **11a**. The same reaction sequence starting from **10b** gave the imidazolyl-pentitol **11b** and the imidazolo-*manno*-piperidinose **12** in a 2:1 ratio (Scheme 2).

Under treatment with $NaNH_2$ the compound **11a** rearranged to the tricyclic structure **13**,[14] which was consecutively catalytically debenzylated and the resulting aldehyde was immediately reduced to produce the imidazolopyrrolidinose **1**.[14] Imidazolopiperidinose **12**, treated with $NaNH_2$, underwent a *trans*-elimination reaction to provide its unsaturated derivative **14**,[14] which was catalytically debenzylated and reduced to give the imidazolopiperidinose **2**.[14] When the imidazolyl-pentitol **11b** was treated with $NaNH_2$, the cyclisation and elimination reaction sequence led to the dibenzyl unsaturated imidazoloazepanose **15**.[14] Catalytic debenzylation and reduction of **15** resulted in the formation of the imidazoloazepanose **3**[14] (Scheme 3).

The stereochemical outcome of the above reactions proves the configurations at the newly occurring chiral centre of the two epimeric adducts **6a** and **6b**. Thus, we believe the strong base promotes the S_N2 type cyclisation of **11a** to afford the imidazolopiperidinose **16**

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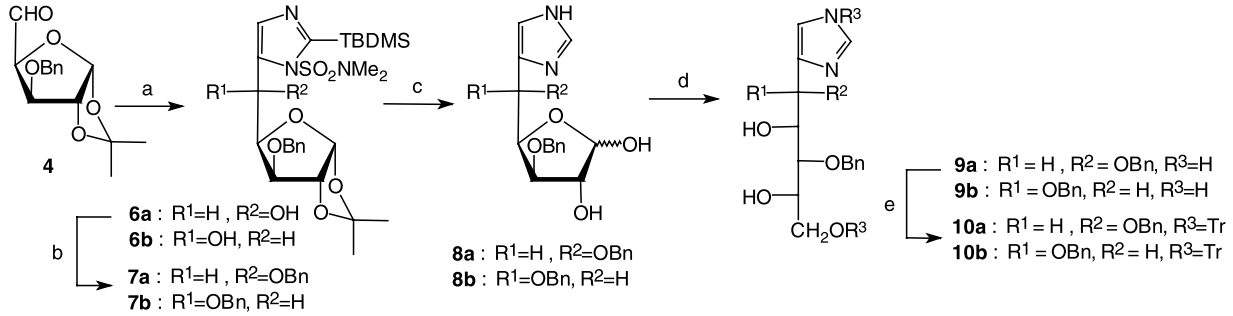
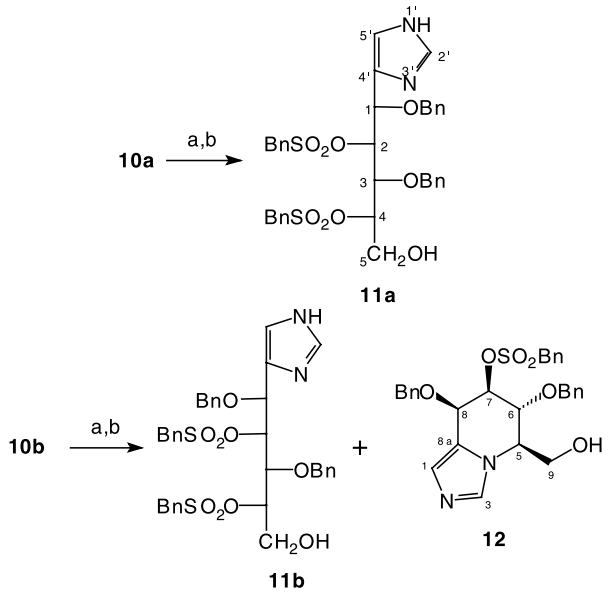
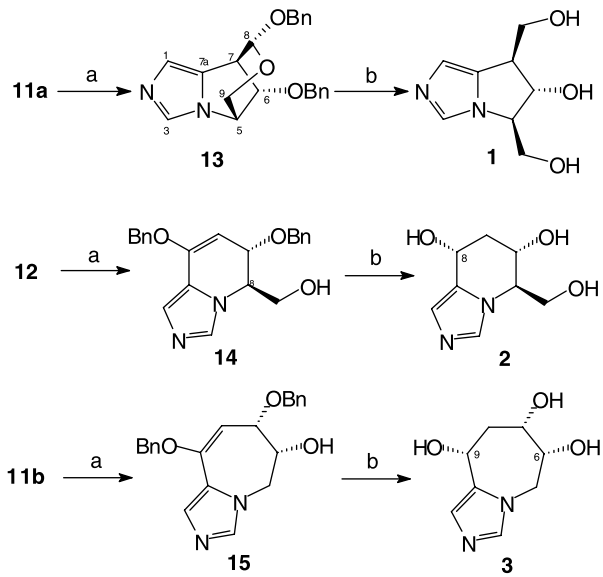


Scheme 1. *Reagents and conditions*: (a) 2-*t*-butyldimethylsilyl-1-dimethylsulphamoylimidazole (**5**), BuLi, THF, −70°C, 78%; (b) BnBr, NaH, DMF, rt; (c) 1.5N HCl, THF, reflux, **8a**: 65% (two steps), **8b**: 60% (two steps); (d) $NaBH_4$, MeOH, 0°C→rt, **9a**: 88%, **9b**: 87%; (e) TrCl, Py, DMAP, 80°C, **10a**: 56%, **10b**: 48%.



Scheme 2. *Reagents and conditions*: (a) $BnSO_2Cl$, Py, −30°C→rt; (b) 6N HCl, THF, reflux, **11a**: 70% (two steps); **11b**: 34%, **12**: 18% (two steps).



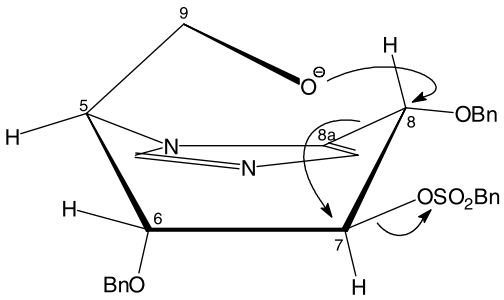
Scheme 3. *Reagents and conditions*: (a) $NaNH_2$, DMF, rt, **13**: 56%, **14**: 84%, **15**: 85%; (b) H_2/Pd/C, EtOH, rt, **1**: 81%, **2**: 35%, **3**: 24%.

(Scheme 4). The rearrangement of **16** into **13** involves piperidine ring contraction, relying on the departure of the equatorial phenylmethanesulphonate group from C-7 and the 1,2-migration of the antiperiplanar [C-8/C-8a] bond, assisted by an attack of the alcoholate ion at C-9 on C-8, which is possible only in the boat conformation of the piperidine ring. The formation of **13** as only one isomer with the *S*-configuration at C-8 suggests both the above processes are simultaneous (Scheme 4). The epimeric imidazolopiperidinose **12**, however, in the same reaction conditions yields the *trans*-elimination product **14**, thanks to the hydrogen atom at C-8 in **12** which is situated *anti* towards the leaving group.

The conversion of the imidazolyl-pentitol **11b** into the imidazoloazepanose **15** in basic conditions proceeds probably via the epoxide **17** (compare Lohray et al.[13]), with seven-membered ring closing and *trans*-elimination of phenylmethanesulphonic acid residue (Scheme 5).

The *trans* stereochemistry of the elimination reactions converting **12** into **14** and **11b** into **15** proves the *R*-configuration on the carbon atom adjacent to the imidazole ring in both **12** and **11b**.

The configuration of **13** and the boat conformation of its pyranose ring (Scheme 3) were deduced by nuclear Overhauser effect (NOE) measurements. Thus, irradiation of H-9 generated nuclear Overhauser enhancement at H-9′ (26%) and H-5 (6%). When H-9′ was irradiated, a 22% NOE at H-9, 8% NOE at H-8 and 4% at H-5 were observed. Irradiation of H-7 gave enhancement of H-8 (3%) and H-6 (8%). The irradiation of H-6 led only to NOE enhancement of the proton H-7 (10%). The experimental results were confirmed by molecular modelling with the SYBYL 6.5 software from TRIPOS Inc.



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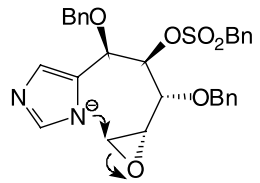
Scheme 4. Proposed course of rearrangement of **16** into **13**.



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Scheme 5. Proposed course of the seven-membered ring closing in **17**.

The configuration at C-8 in compound **2** was assigned on the basis of the ROE signal between H-6 and H-8 in the ROESY spectrum. The ROE signal between H-7 and H-9 was helpful in the configuration assignment at C-9 for compound **3**.

The configuration at C-6 in **3** can be deduced from the analysis of vicinal coupling constants. The proton H-6 occupies the *pseudo*-equatorial position, corresponding to the *R*-configuration, because its vicinal coupling constants with the *pseudo*-axial H-5 and H-7 (0 and 1.75 Hz, respectively) correspond to H–C–C–H torsion angles close to 90°.[12]

Acknowledgements

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14. All new compounds gave satisfactory NMR and MS spectroscopy data. The most important data are listed below.
1: $[\alpha]_D$ −16 (*c* 0.3, MeOH); ^{1}H NMR (D_2O) δ: 3.43 (ddd, 1H, *J* 5.1, 6.2, 6.6 Hz, H-5), 3.85 (dd, 1H, *J* 6.2, 11.3 Hz, H-9), 3.90 (dd, 1H, *J* 6.6, 12.4 Hz, H-8), 4.00 (dd, 1H, *J* 5.1, 11.3 Hz, H-9′), 4.22 (dd, 1H, *J* 3.7, 12.4 Hz, H-8′), 4.50 (dt, 1H, *J* 3.7, 6.6 Hz, H-7), 4.61 (1H, t, *J* 6.6 Hz, H-6), 7.24 (s, 1H, H-1), 8.61 (s, 1H, H-3); ^{13}C NMR (D_2O) δ: 45.0 (C-5), 58.2 (C-8), 58.3 (C-9), 65.5 (C-7), 75.0 (C-6), 111.6 (C-1), 127.0 (C-3), 134.6 (C-7a); FAB MS: 185 ([M+H]$^+$); HRMS: calcd for [M+H]$^+$ ($C_8H_{13}N_2O_3$) 185.0926, found 185.0926
2: $[\alpha]_D$ −32 (*c* 0.35, MeOH); ^{1}H NMR (D_2O) δ: 1.86 (ddd, 1H, *J* 7.5, 8.75, 13.0 Hz, H-7), 2.32 (ddd, 1H, *J* 3.0, 5.75, 13.0 Hz, H-7'), 3.78 (dd, 1H, *J* 4.25, 12.25 Hz, H-9), 3.97 (dd, 1H, *J* 3.5, 12.25 Hz, H-9′), 4.03 (ddd, 1H, *J* 3.5, 4.25, 6.5 Hz, H-5), 4.12 (ddd, 1H, *J* 3.0, 6.5, 8.75 Hz, H-6), 4.89 (1H, dd, *J* 5.75, 7.5 Hz, H-8), 6.95 (s, 1H, H-1), 7.73 (s, 1H, H-3); ^{13}C NMR (D_2O) δ: 35.9 (C-7), 60.2 (C-9), 60.3 (C-8), 61.0 (C-5), 64.0 (C-6), 124.0 (C-1), 131.2 (C-3), 143.0 (C-8a); FAB MS: 185 ([M+H]$^+$); HRMS: calcd for [M+H]$^+$ ($C_8H_{13}N_2O_3$) 185.0926, found 185.0923
3: $[\alpha]_D$ −17 (*c* 0.4, MeOH); ^{1}H NMR (D_2O) δ: 2.03 (ddd, 1H, *J* 10.5, 10.75, 12.5 Hz, H-8), 2.14 (ddd, 1H, *J* 3.0, 4.0, 12.5 Hz, H-8′), 3.99 (d, 1H, *J* 15.0 Hz, H-5), 4.06 (ddd, 1H, *J* 1.75, 4.0, 10.75 Hz, H-7), 4.15 (dd, 1H, *J* 1.75, 6.5 Hz, H-6), 4.37 (dd, 1H, *J* 6.5, 15.0 Hz, H-5′), 4.89 (dd, 1H, *J* 3.0, 10.5 Hz, H-9), 6.95 (s, 1H, H-1), 7.73 (s, 1H, H-3); ^{13}C NMR (D_2O) δ: 35.8 (C-8), 45.3 (C-5), 61.6 (C-9), 66.9 (C-7), 69.4 (C-6), 120.6 (C-1), 126.8 (C-3), 134.1 (C-9a); FAB MS: 185 ([M+H]$^+$); HRMS: calcd for [M+H]$^+$ ($C_8H_{13}N_2O_3$) 185.0926, found 185.0929
13: $[\alpha]_D$ −82 (*c* 1.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 3.48 (bd, 1H, *J* 2.5 Hz, H-7), 3.60 (dd, 1H, *J* 3.25, 11.25 Hz, H-9), 3.85 (d, 1H, *J* 11.25 Hz, H-9′), 4.40 (d, 1H, *J* 3.25 Hz, H-5), 4.51, 4.73 (2d, 2H, *J* 12 Hz, OBn), 4.54, 4.62 (2d, 2H, *J* 11.5 Hz, OBn), 4.88 (d, 1H, *J* 2.5 Hz, H-8), 4.89 (s, 1H, H-6), 6.86 (s, 1H, H-1), 7.19–7.42 (m, 10H, arom.), 7.51 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$) δ: 43.5 (C-7), 59.2 (C-5), 63.5 (C-9), 69.5 (O$\underline{C}H_2$Ph), 70.7 (O$\underline{C}H_2$Ph), 85.2 (C-6), 98.6 (C-8), 121.2 (C-1), 128.0–129.0 (m, arom.), 131.1 (C-3), 135.2 (C-7a), 138.8, 138.9 (s-arom.); FAB MS: 363 ([M+H]$^+$)

14: $[\alpha]_D$ +172 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 3.47 (dd, 1H, *J* 8.75, 11.25 Hz, H-9), 3.60 (dd, 1H, *J* 5.0, 11.25 Hz, H-9′), 4.24 (dd, 1H, *J* 1.25, 6.25 Hz, H-6), 4.41 (ddd, 1H, *J* 1.25, 5.0, 8.75 Hz, H-5), 4.42, 4.47 (2d, 2H, *J* 12.25 Hz, OBn), 4.88 (d, 1H, *J* 6.25, H-7), 4.95 (s, 2H, OBn), 6.94 (s, 1H, H-1), 7.20–7.40 (m, 10H, arom.), 7.50 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$) δ: 60.5 (C-5), 62.8 (C-9) 69.2 ($O\underline{C}H_2Ph$), 69.3 ($O\underline{C}H_2Ph$), 71.2 (C-6), 89.8 (C-7), 124.8 (C-1), 127.5–129.0 (m, arom.), 138.3 (C-3), 139.2 (C-8a), 140.0 (C-8); FAB MS: 363 ($[M+H]^+$)

15: $[\alpha]_D$ +57 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$+C_6D_6) δ: 3.51 (dd, 1H, *J* 2.6, 13.2 Hz, H-5), 3.74 (ddd, 1H, *J* 2.6, 3.1, 9.0 Hz, H-6), 3.83 (dd, 1H, *J* 9.0, 13.2 Hz, H-5′), 3.88 (dd, 1H, *J* 3.1, 6.0 Hz, H-7), 4.21, 4.36 (2d, 2H, *J* 11.5 Hz, OBn), 4.58, 4.61 (2d, 2H, *J* 12 Hz, OBn), 4.70 (d, 1H, *J* 6.0, H-8), 7.00 (s, 1H, H-1), 7.00–7.30 (m, 10H, arom.), 7.46 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$+C_6D_6) δ: 47.9 (C-5) 69.9 (C-6), 70.3 ($O\underline{C}H_2Ph$), 71.2 ($O\underline{C}H_2Ph$), 76.4 (C-7), 95.8 (C-8), 127.5–129.0 (m, arom.), 131.0 (C-3), 137.7, 139.4 (s-arom.), 138.0 (C-9a), 140.0 (C-1), 147.8 (C-9); FAB MS: 363 ($[M+H]^+$).