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Short Synthesis of Piperidine Based Hexopyranose Mimics. A Remarkable Example of *Syn* Hydrogenation.

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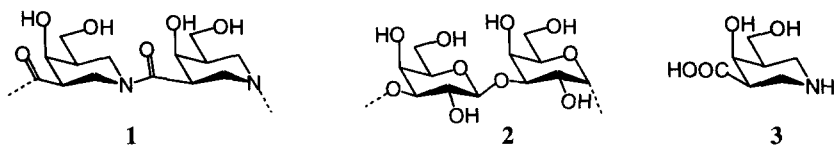
Abstract: A short synthesis of several diastereomeric dihydroxylated piperidinecarboxylic acids were devised with the key step being regioselective alkylation of a dianion.

Glycomimetics (structural analogues of oligosaccharides) is an important new area of carbohydrate chemistry.[1] These molecules may be used to influence many biological events such as the interactions of cells with antibodies, vira and bacteria. Glycomimetics possesing a peptide backbone, carbopeptoids,[1a] are particularly interesting, because they allow exploitation of the powerful techniques of solid-phase peptide synthesis and combinatorial chemistry in their synthesis.[1a-d,1h] In a project targeting a bioisosteric carbopeptoid we aimed at creating structures of type **1** (Fig 1), which have a high degree of resemblance to oligosaccharide **2**. Some other carbopeptoids have been reported,[1a-d] but none of these are bioisosteric with an oligosaccharide.



1 **2** **3**

Fig 1. Structure of both the monomer and oligomer of an oligosaccharide analogue.

The limiting factor in this approach has been the efficient synthesis, in adequate amounts, of the monomers, such as **3**, particularly those imitating biologically important monosaccharides.[2] We now wish to report the discovery of a short and efficient synthesis of several stereoisomers of these dihydroxy piperidinecarboxylic acids including both the galactose analogue (±)-**3** and the glucose analogue, and some surprising chemistry encountered during the synthesis of these compounds.

Our synthesis starts with the commercially available Dieckmann adduct **4** (Scheme 1). We have found that direct alkylation[3-4] of the dianion **5** allows selective introduction of a hydromethyl group in the 5-position. Thus, **4** was protected as the BOC derivative ((^{t}BuOCO)$_2$O, THF/aq. Na_2CO_3 (1:1), 25 °C, 1 h, 95 %), and then converted into the dianion **5** by treatment with NaH (1.15 eq.) and then BuLi (1.1 eq.). The solution of **5** was then treated with various alkylating agents. Addition of 1.15 eq. of chloromethyl methyl ether gave 95% of the 5-alkylated product (±)-**6a**,[5-6] treatment with 1.0 eq. of chloromethyl trimethylsilylethyl ether gave 57% of the corresponding product (±)-**6b**, while reaction with 1.15 eq chloromethyl benzyl ether gave 96% of crude (±)-**6c**.

Reduction of the enolic C=C in **6a-b** gave surprising results and was therefore investigated in detail (Table 1). Catalytic hydrogenation, which was expected to give stereoselective addition of hydrogen from the less hindered face to give *ribo*-isomer (±)-**8**, gave mainly *lyxo*-isomer (±)-**7**. The hydrogenation of **6b**, catalysed by Pd/C, gave **7b** as the exclusive product in 90% yield. The *ribo*-isomer **8** was (with most catalysts)

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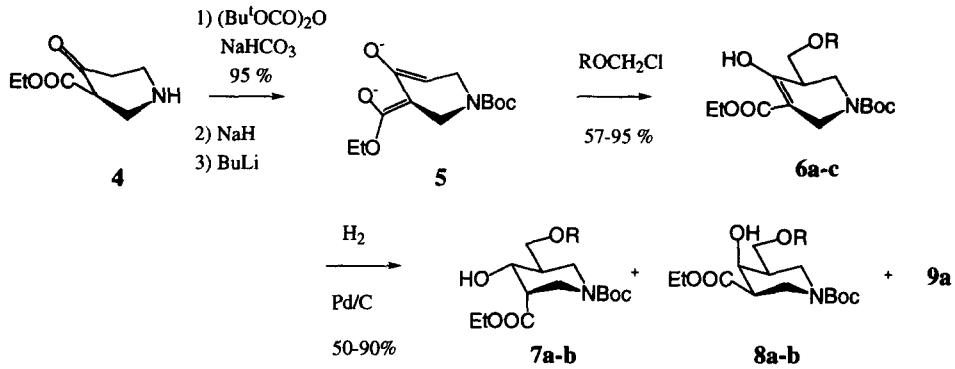
formed as a minor product, and in some cases a third compound (±)-**9**, which presumably was the *arabino*-isomer, was formed. The reason for the predominant formation of **7** was surprising.



Scheme 1. Synthesis of **7-9** (**a**: R= Me, **b**: R= CH_2CH_2TMS, **c**: R= Bn)

Though the literature is rather unclear regarding the stereoselectivity of hydrogenation, it is nevertheless general that addition of hydrogen occur from the less hindered face of alkenes. However there are in the literature examples of a so called haptophilic effect which causes H_2 to be added from the same side as a polar substituent such as hydroxymethyl.[7]

Table 1. Reduction conditions for reduction of **6**.

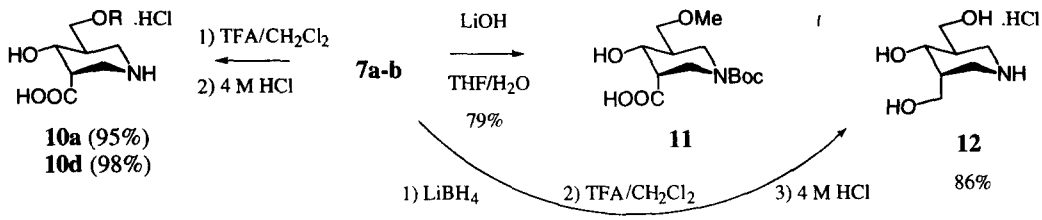
Reagent	Solvent	Starting material	Pressure (bar)	Temp. (°C)	Yield (total)	Ratio **7/8/9a**
H_2/Rh	EtOH	**6a**	35	50	74%	1:1:1
H_2/Pd	EtOH	**6a**	40	50	94%	6:3:1
H_2/Pd + Et_3N	EtOH	**6a**	40	50	95%	7:3:0
H_2/Ni	MeOH	**6a**	33	50	96%	4:1:2
H_2/Pt	EtOH	**6a**	30	50	60%	1:1:1
H_2/Pt + KOH	EtOH	**6a**	30	50	90%	3:2:1
H_2/Pt	^{t}BuOH	**6a**	30	50	66%	1:1:1
$NaBH_4$	EtOH	**6a**	1	25	78%	1:1:0
Bakers yeast (sugar/O_2)	H_2O	**6a**	1	25	35%	3:4:0
H_2/Pd + EtN(iPr)$_2$	EtOH[#]	**6b**	42	50	90%	1:0:0
H_2/Pd + EtN(iPr)$_2$	EtOH[¤]	**6b**	42	50	89%	3:1:0

[**6b**] = 0.01 M. ¤ [**6b**] = 0.02 M.

Matters are further complicated for β-ketoesters, because these compounds switch between the enol- and keto-form depending on polarity of the solvent, and some product may arise from reduction of keto tautomer. Little help is gained from the literature because in all previously reported cases of catalytic hydrogenation of γ-substituted 6-ring β-ketoesters the stereochemical outcome was not elucidated or reported.[8] Based on the available information it seems reasonable to suggest that in this case the high selectivity for the *lyxo* isomer is caused by hydrogenation of the enol form with a haptophilic effect of the CH_2OR group. The formation of **9a** with some catalysts may be explained by some reduction of the keto-form.

A number of other reducing agents were also investigated: Sodium borohydride gave a mixture of stereoisomers consisting of **7a** and **8a** (Table 1). Interestingly the bakers yeast reduction gave mainly *ribo*

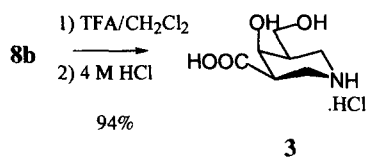
isomer **8a** but in low yield. In summary the best way to prepare **7a-b** was Pd-catalysed hydrogenation in the presence of a tertiary amine which gave 50% **7a** or 90% **7b** after chromatographic separation/purification. Similarly **8b** was best prepared by Pd-catalysed hydrogenation in which cases **8b** could be isolated in 19% yield.



Scheme 2. Synthesis of **10-12** (**a**: R= Me, **b**: R= CH_2CH_2TMS, **c**: R= Bn, **d**: R=H)

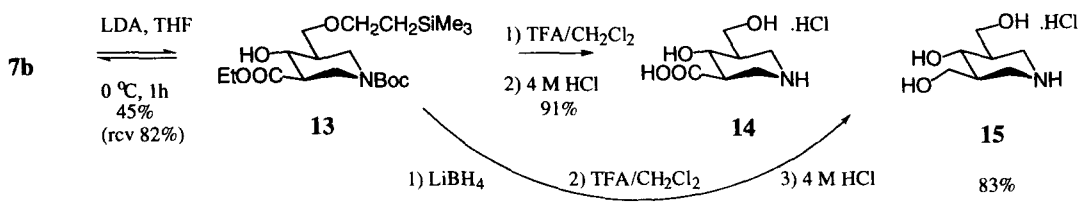
To confirm the stereochemistry of **7** and **8**, **7b** was reduced with $LiBH_4$ and deprotected with TFA/HCl to give the di(hydroxymethyl)piperidine (±)-**12** (Schemes 2 and 3). The fact that the former compound was asymmetric strongly suggested the indicated stereochemistry and gave, together with NMR,[6] conclusive evidence for the proposed structure. NMR by itself was not clear as compound **7a** (and **10a**) apparently was a mixture of conformers giving atypical couplings.

Both **7a**, **7b** and **8 b** were deprotected by acidic hydrolysis to give the aminoacids (±)-**10** and (±)-**3** resembling allose and galactose, respectively (Scheme 4). Selective hydrolysis of the ester with LiOH gave a N-Boc protected derivative that can be used directly in solid phase synthesis as demonstrated by conversion of **7a** to **11** in 79% yield.



Scheme 3. Synthesis of **3**

To obtain the important aminoacid resembling glucose, the *lyxo*-isomer **7b** was isomerised with LDA into a 1:1 mixture of **7b** and **13** (Scheme 4). These two compounds could be separated to give (±)-**13** in 45% isolated yield (recovered yield: 82%). Deprotection of **13** with TFA followed by HCl/H_2O gave amino acid (±)-**14** in 91% yield. The stereochemistry of **13** was confirmed by reduction with $LiBH_4$ followed by deprotection with TFA and HCl/H_2O to give symmetrical piperidine **15**.



Scheme 4. Synthesis of **13-15**

Compounds (±)-**3**, (±)-**10d**, (±)-**12**, (±)-**14** and **15** are all members of the family of compounds called 1-azasugars which are often glycosidase inhibitors,[9] and therefore these 5 compounds were tested for inhibtion of yeast α-glucosidase and almond β-glucosidase. Negligable inhibition (Ki > 1 mM) was observed except for **12** which inhibited β-glucosidase with a Ki of 200 μM. The lack of inhibtion by **14** and **15** showed that substitution of the 3-OH of isofagomine ((*3R,4R,5R*)-4,5-dihydroxy-3-hydroxymethylpiperidine) with a

carboxylate (**14**) or hydroxymethyl group (**15**) decreased inhibition of β-glucosidase with more than a factor 10^4.

In this communication, we have reported an effective synthesis of some important sugar mimetics. It may be argued that the separation of stereoisomers decreases the efficiency; however because of the shortness of the synthesis the overall yields of **3**, **10d** and **14** are high (10%, 48% and 20%, respectively). Future work will focus on incorporating these in solid phase synthesis and combinatorial chemistry.

ACKNOWLEDGEMENTS

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5. ^{13}C NMR-data (d6-DMSO, 100°C): **6a**, δ 171.2 (C-3'), 169.8 (br, C-4), 155.2 (Boc), 97.8 (br, C-3), 80.4 (Boc), 71.1 (C-5'), 61.1 (Et), 59.4 (OMe), 40-44 (C-2, C-5, C-6), 28.8 (Boc), 14.6 ppm (Et). **7a**, δ 171.4 (C-3'), 154.3 (Boc), 78.9 (Boc), 71.9 (C-5'), 66.8 (C-4), 59.8 (Et), 58.5 (OMe), 43.9, 41.9, 40.9 (C-2, C-3, C-5, C-6), 28.4 (Boc), 14.2 ppm (Et). ($CDCl_3$): **6c**, δ 171.0 (C-3'), 169.8 (br, C-4), 155.0 (Boc), 138.3, 128.6, 128.2 (Ph), 97.8 (br, C-3), 80.3 (Boc), 73.8 (Bn), 68.8 (C-5'), 60.5 (Et); 43.0-40.5 (all br, C-2, C-5, C-6), 28.7 (Boc), 14.7 ppm (Et). **11**, δ 176.3 (C-3'), 155.3 (Boc), 80.6 (Boc), 73 (br, C-5'), 59.6 (OMe), 46.2, 44.0, 42.9, 40.4 (C-2, C-3, C-5, C-6), 28.8 ppm (Boc). (D_2O): **3**, δ 172.1 (C-3'), 62.2, 59.0 (C-4, C-5'), 42.7, 38.8(2C), 37.6 ppm (C-2, C-3, C-5, C-6). **10a**, δ 173.2 (C-3'), 70.3 (C-5'), 64.7(C-4), 57.4 (OMe), 41.6, 40.6, 39.6, 36.0 ppm (C-2, C-3, C-5, C-6). **10d**, δ 173.4 (C-3'), 64.2, 58.7 (C-4, C-5'), 41.7, 40.7, 40.5, 37.6 ppm (C-2, C-3, C-5, C-6). **12**, δ 63.9, 58.9, 58.3 (C-4, C-3', C-5'), 40.9 (2C), 38.3, 35.9 ppm (C-2, C-3, C-5, C-6). **14**, δ 171.6 (C-3'), 65.3, 56.9 (C4, C-5'), 45.3, 42.8, 41.8, 39.8 ppm (C-2, C-3, C-5, C-6). **15**, δ 65.1 (C-4), 58.2 (2C, C-3', C-5), 43.9 (2C), 41.2 ppm (2C, C-2, C-3, C-5, C-6).
6. ^{1}H NMR-data (d6-DMSO, 100°C): **6a**, δ 12.02 (w s, enol OH), 4.08 (q, 2H, Et), 4.0-3.1 (m, 7H), 3.16 (s, 3H, OMe), 1.50 (s, 9H, Boc), 1.12 (t, 3H, Et). **7a**, δ 4.55 (t, 2H, Et), 3.99 (dd, 1H, $J_{3,4}$ 4.0 Hz, $J_{4,5}$ 5.3 Hz, H-4), 3.65 (dd, 1H, $J_{2eq,2ax}$ 13.6 Hz, $J_{2eq,3}$ 4.65 Hz, H-2eq), 3.42 (dd, 1H, $J_{6eq,6ax}$ 13 Hz, $J_{5,6eq}$ 4.0 Hz, H-6eq), 3.4-3.28 (3H, H-6ax, 2 x H-5'), 3.29 (s, 3H, OMe), 2.60 (m, 1H, H-3), 2.11 (m, 1H, H-5), 1.43 (s, 9H, *t*-butyl), 1.25 (t, 3H, Et). ($CDCl_3$): **6b**, δ 12.1 (s, 1H, OH), 4.2 (q, 2H, CH_2O), 3.2-4.0 (m, 8H, CH_2O, H-2's, H-6's, H-5''s), 2.6 (m, 1H, H-5), 1.45 (s, 9H, tBu), 1,25 (t, 3H, Me), 0.9 (t, 2H, CH_2), 0.0 (s, 9H, TMS). **7b**, δ 4.15 (q, 2H, CH_2O), 4.0 (dd, 1H, *J* 6.5 Hz, *J* 3.5 Hz, H-4), 3.0-3.8 (m, 8H, CH_2O, H-2's, H-6's, H-5''s), 2.7 (m, 1H, H-3), 2.2 (m, 1H, H-5), 1.45 (s, 9H, tBu), 1.25 (t, 3H, Me), 0.9 (t, 2H, CH_2), 0.0 (s, 9H, TMS). **8b**, δ 4.48 (bs, 1H, H-4), 4.2 (bq, 3H, CH_2O, H-5'a), 3.9 (dd, 1H, $J_{5'a,5'b}$ 12.5 Hz, $J_{5,5'b}$ 3 Hz, H-5'b), 3.5 (m, 4H, CH_2O, H-2eq, H-6eq), 3.2 (t, 1H,$J_{2eq,2ax}$, $J_{2ax,3}$ 12.5 Hz, H-2ax), 3.0 (t, 1H, $J_{6eq,6ax}$, $J_{5,6ax}$ 12.5 Hz, H-6ax), 2.5 (bd, 1H, H-3), 1.8 (m, 1H, H-5), 1.45 (s, 9H, tBu), 1,25 (t, 3H, Me), 0.9 (t, 2H, CH_2), 0.0 (s, 9H, TMS). **13**, δ 4.2 (m, 4H, CH_2O, H-5'a, H-5'b), 3.85 (t, 1H, $J_{3,4}$, $J_{4,5}$ 9.5 Hz, H-4), 3.5 (m, 4H, CH_2O, H-2eq, H-6eq) 2.7 (bt, 1H, $J_{2eq,2ax}$, $J_{2ax,3}$ 12 Hz, H-2ax), 2.5 (m, 2H, H-3, H-6ax), 1.8 (m, 1H, H-5), 1.45 (s, 9H, tBu), 1.25 (t, 3H, Me), 0.9 (t, 2H, CH_2), 0.0 (s, 9H, TMS). (D_2O): **10a**, δ 4.20 (dd, 1H, $J_{3,4}$ 3.8 Hz, $J_{4,5}$ 5.6 Hz, H-4), 3.64 (dd, 1H, $J_{5'a,5'b}$ 10.5 Hz, $J_{5,5'a}$ 5.2 Hz, H-5'a), 3.57 (dd, $J_{5'a,5'b}$ 10.5 Hz, $J_{5'b,5}$ 6.0 Hz, H-5'b), 3.42 (dd, 1H,$J_{2eq,2ax}$ 10 Hz, $J_{2eq,3}$ 3.7 Hz, H-2eq), 3.39 (dd, 1H, $J_{6eq,6ax}$ 13.4 Hz, $J_{6eq,5}$ 4.1 Hz, H-6eq), 3.31 (s, 3H, OMe), 3.29 (dd, 1H, $J_{2ax,2eq}$ 10 Hz, $J_{2ax,3}$ 9.8 Hz, H-2ax), 3.23 (dt, 1H, $J_{3,2ax}$ 9.8 Hz, $J_{3,2eq}$ 3.7 Hz, $J_{3,4}$ 3.8 Hz, H-3), 3.15 (dd, 1H, $J_{6ax,6eq}$ 13.4 Hz, $J_{6ax,5}$ 6.4 Hz, H-6ax), 2.25 (sxt, 1H, *J* ~5 Hz, H-5).
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