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Total synthesis of new C-6 homologues of 1-deoxynojirimycin and 1-deoxy-L-idonojirimycin†

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Novel piperidine lactones 1 and 2, which represent direct precursors to the new C-6 homologues of 1-deoxynojirimycin (3) and 1-deoxy-L-idonojirimycin 4, were prepared by key Pd^{II}-catalysed aminocarbonylation of protected aminoalkene 10.

The inhibitors of glycosidases, enzymes involved in many crucial biochemical pathways,[1] could be very valuable in the treatment of serious human diseases such as diabetes,[2] cancer[3] and viral infections including AIDS.[4] The prominent members of this class of compounds are polyhydroxylated piperidines (often referred to as 'azasugars'). There has been an enormous effort put toward their efficient syntheses as well as toward the preparation of their various derivatives over the last decade. However, only a few of the already published synthetic strategies deal with the preparation of C-6 homologues of azasugars.[5–8] Here we report on the synthesis of new homologues of 1-deoxynojirimycin (**3**) and 1-deoxy-L-idonojirimycin (**4**), (Fig. 1).

Our synthetic plan relies on the successful $PdCl_2$-catalysed aminocarbonylation of the benzyl protected aminoalkene **10** yielding the desired lactones **1** and **2**. Generally, aminocarbonylation of 3-hydroxypent-4-enylamines giving pyrrolidine lactones proceeds easily,[9,10] which is in contrast to 4-hydroxy-hex-5-enylamines producing the corresponding piperidine lactones (Scheme 1).

To the best of our knowledge, there are only a few papers in the literature which deal with such a transformation on similar but simpler substrates.[10,11] However, reported yields are fairly low and no further synthetic elaboration of the prepared piperidine lactones has been reported. The common feature of almost all published amino-/amido-carbonylations (either producing pyrrolidine or piperidine lactones) is the use of electron-withdrawing protecting groups (tosyl, CO_2Me, CO_2Bn, CONHMe, CONHPh, CONHBn) on the NH function of the aminoalkenes. However, properties of such protecting groups (introduction, deprotection, chemical inertness and stability) were not suitable for our proposed plan for the total synthesis. Therefore, we decided to explore the applicability of the benzyl protecting group in the aminocarbonylation producing the piperidine lactones. We report here the above-mentioned strategy in the total synthesis of new C-6 homologues of 1-deoxynojirimycin (**3**) and 1-deoxy-L-idonojirimycin (**4**).

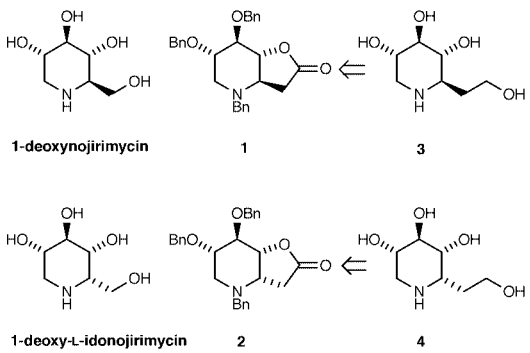

Fig. 1 Homologues of 1-deoxynojirimycin and 1-deoxy-L-idonojirimycin.

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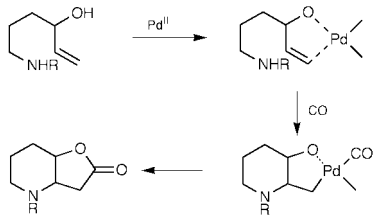

Scheme 1

Thus, the key substrate **10** was prepared by analogy with the known procedure according to the literature:[12] benzylidenation of the starting methyl-α-D-glucoside **5** afforded the diol **6**, which was subsequently benzylated to a fully-protected compound **7**. Acidic hydrolysis of **7** and nucleophilic displacement of the primary hydroxy function of **8** yielded bromide **9**, the latter being finally converted to the desired (2*S*,3*S*,4*R*)-*N*-benzyl-2,3-di-*O*-benzyl-2,3,4-trihydroxyhex-5-enylamine **10**.

First attempts to cyclise **10** under standard carbonylation conditions[11a] (1 atm CO, 0.1 equiv. $PdCl_2$, 3 equiv. $CuCl_2$, 3 equiv. AcONa, AcOH, conditions A) at room temperature failed and always the starting material was isolated. Gratifyingly, simply raising of temperature to 50 °C led to the complete consumption of aminoalkene **10** while the colour of the reaction mixture changed from dark green to ochre. However, aminocarbonylation of **10** yielded a complex mixture of compounds from which desired lactones **1** and **2** were isolated in the ratio 1 : 4.8 as main products. The major by-product of the reaction turned out to be *N*-benzyl-2,3-di-*O*-benzyl-6-chloro-1,6-dideoxy-L-idonojirimycin **11**‡ (Scheme 2).

We then searched for reaction conditions that would produce more of lactone **1** than **2** and suppress the formation of the side product **11**. We were pleased to find that a catalytic system consisting of 0.1 equiv. $PdCl_2$, 1 equiv. *p*-benzoquinone, 2 equiv. LiCl, 2 equiv. AcONa in THF under 1 atm CO at room temperature (conditions B) afforded a mixture of lactones **1** and **2** in the ratio 3.7 : 1 with no formation of **11**. Our suspicion that $CuCl_2$ (used in excess as reoxidant) might be responsible for the formation of undesired **11** was thus proved. The definitive confirmation came from the experiment in which aminoalkene **10** was subjected to conditions A but with exclusion of CO atmosphere. The only product we were able to isolate was the chloroderivate **11**§ (Scheme 3).

The separation and purification of **1** and **2** by FLC and subsequent reduction of both lactone rings gave the piperidine

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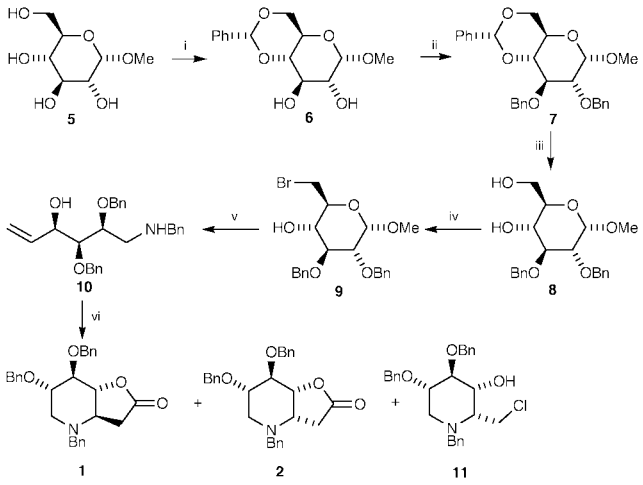
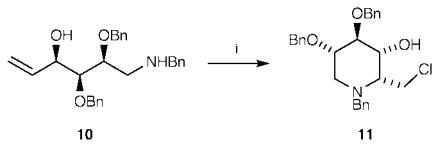
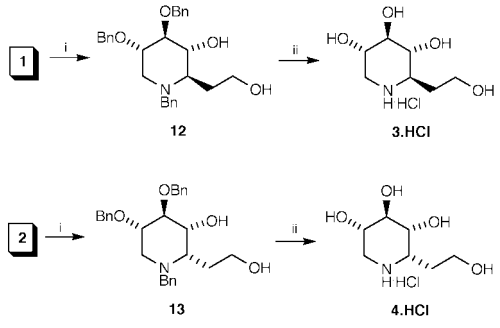


Scheme 2 *Reagents and conditions*: i, $PhCH(OEt)_2$, cat. CSA, $CHCl_3$, 81%; ii, BnBr, NaH, DMF, 75%; iii, H_2SO_4, MeOH, 97%; iv, Ph_3P, CBr_4, pyridine, 79%; v, Zn dust, $BnNH_2$, $NaBH_3CN$, PrOH–H_2O (19:1), 64%; vi, conditions A, 50 °C, 4–7 h, FLC, 46% of **1** + **2** (dr = 1:4.8), 9% of **11** or conditions B, room temp., 17 h, FLC, 66% of **1** + **2** (dr = 3.7:1).



Scheme 3 *Reagents and conditions*: i, conditions A without CO, room temp., 48 h, FLC, 70%.

diols **12** [mp = 97–98 °C; $[\alpha]_D^{31}$ −19.4 (*c* 0.29, CH_2Cl_2); *m/z* 417 (M − $CH_2OH)^+$] and **13** [$[\alpha]_D^{31}$ −1.32 (*c* 0.34, CH_2Cl_2); *m/z* 447 (M − $1)^+$]. Final catalytic debenzylation of both tetraols afforded the desired (2*R*,3*R*,4*R*,5*S*)-2-(2-hydroxyethyl)-3,4,5-trihydroxypiperidine **3** [mp 177–179 °C; $[\alpha]_D^{26}$ +30 (*c* 0.55, MeOH); *m/z* 177 (M − $HCl)^+$] and (2*S*,3*R*,4*R*,5*S*)-2-(2-hydroxyethyl)-3,4,5-trihydroxypiperidine **4** (mp 202–203 °C; $[\alpha]_D^{32}$ +20.2 (*c* 0.42, MeOH); *m/z* 177 (M − $HCl)^+$] as hydrochlorides (Scheme 4).¶



Scheme 4 *Reagents and conditions*: i, $LiBH_4$, THF, room temp., 64–65% ii, H_2, 10% Pd/C, MeOH, HCl, room temp., DOWEX (H^+), 82–90%.

In conclusion, we have performed the first successful Pd^{II}-catalysed aminocarbonylation of highly substituted 4-hydroxyhex-5-enylamine that contains a Bn-protected amine group.‖ In contrast to the literature precedents,[10,11] we observed the formation of both diastereoisomeric *cis*- and *trans*-fused piperidine lactones. Their ratio depended on the reaction conditions and these compounds represent direct precursors for the synthesis of new derivatives of polyhydroxylated piperidines. The applicability of this methodology has been demonstrated in the total synthesis of new C-6 homologues of 1-deoxynojirimycin (**3**) and 1-deoxy-L-idonojirimycin (**4**).

In addition, we have observed an interesting type of $PdCl_2$/$CuCl_2$ catalysed chloroaminocyclisation of substituted 4-hydroxyhex-5-enylamine producing the corresponding piperidine derivative **11** which could be useful in the synthesis of various piperidine and azepine alkaloids.[13] Investigation of the scope and limitations of the presented methodology is under progress and will be reported in due course.

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Notes and references

‡ The ratio of diastereoisomeric lactones **1** and **2** was determined by quantitative ^{13}C NMR spectroscopy with suppressed NOE effect. *Selected data* for **1**: $[\alpha]_D^{24}$ −64.9 (*c* 1.23, CH_2Cl_2); *m/z* 443 (M − $1)^+$. For **2**: $[\alpha]_D^{30}$ −6.05 (*c* 0.74, CH_2Cl_2); *m/z* 444 $(M)^+$. For **11**: $[\alpha]_D^{25}$ +35.1 (*c* 0.7, CH_2Cl_2); *m/z* 451 (M − $1)^+$. The relative configurations of **1**, **2** and **11** were established on the basis of NOESY and DIFNOE NMR experiments.

§ An analogous transformation using $PdCl_2(PhCN)_2$ and $CuCl_2$ in PrCN has been reported. However, neither the configuration of the product(s) nor the diastereoisomeric excess were given: M. Wada, H. Aiura and K. Akiba, *Heterocycles*, 1987, **26**, 929.

¶ All new compounds exhibit satisfactory elemental analyses and spectroscopic data. The absolute configuration of **3**·**HCl** was determined by single X-ray analysis (ref. 14).

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