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 PdCl2-catalysed aminocarbonylation of protected aminoalkene 10.

The inhibitors of glycosidas, enzymes involved in many crucial biochemical pathways,1 could be very valuable in the treatment of serious human diseases such as diabetes,2 cancer3 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 PdCl2-catalysed aminocarbonylation of the benzyl protected aminoalkene 10 yielding the desired lactones 1 and 2. Generally, aminocarbonylation of 3-hydroxy-4-enylamines giving pyrrolidine lactones proceeds easily,9,10 which is in contrast to the literature which deal with such a transformation on similar 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, CO2Me, CO2Bn, CONHMe, CONHPn, CONHBn) on the NH function of the aminooalkenes. 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).

Thus, the key substrate 10 was prepared by analogy with the known procedure according to the literature:12 benzyldenation of the starting methyl-α-D-glucose 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 (2S,3S,4R)-N-benzyl-2,3-diol-3-0-benzyl-2,3,4-trihydroxyhex-5-enylamine 10.

First attempts to cyclise 10 under standard carbonylation conditions11a (1 atm CO, 0.1 equiv. PdCl2, 3 equiv. CuCl2, 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-diol-3-0-benzyl-6-chloro-1,6-di-deoxy-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. PdCl2, 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 CuCl2 (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 1

Fig. 1 Homologues of 1-deoxynojirimycin and 1-deoxy-L-idonojirimycin.
diols 12 [mp = 97–98 °C; [α]D19° +19.4 (c 0.29, CH2Cl2); m/z 417 (M – CH2OH)+] and 13 ([α]D19° −1.32 (c 0.34, CH2Cl2); m/z 447 (M – 1)+]. Final catalytic debenzylation of both tetraols afforded the desired (2R,3R,4R,5S)-2-(2-hydroxyethyl)-3,4,5-trihydroxyxypiperidine 3 [mp 177–179 °C; [α]D22° +30 (c 0.55, MeOH); m/z 177 (M − HCl)+] and (2S,3R,4R,5S)-2-(2-hydroxyethyl)-3,4,5-trihydroxyxypiperidine 4 (mp 202–203 °C; [α]D22° +20.2 (c 0.42, MeOH); m/z 177 (M − HCl)+) as hydrochlorides (Scheme 4)‡.

In conclusion, we have performed the first successful PdII-catalysed aminocarbonylation of highly substituted 4-hydroxyxypiperidines 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-deoxyjolimycin (3) and 1-deoxy-l-idojolimycin (4).

In addition, we have observed an interesting type of PdCl2/CuCl2 catalysed chloroaminocyclisation of substituted 4-hydroxyxypiperidine 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 13C NMR spectroscopy with suppressed NOE effect. Selected data for 1: [α]D0°C −64.9 (c 1.23, CH2Cl2); m/z 443 (M − 1)+. For 2: [α]D0°C +6.05 (c 0.34, CH2Cl2); m/z 444 (M)+. For 11: [α]D19°C +35.1 (c 0.7, CH2Cl2); 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 PdCl2(PhCN)2 and CuCl2 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 3HCl was determined by single X-ray analysis (ref. 14).


14 M. Koman, P. Szolcsányi and T. Gracza, submitted for publication.