Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2579–2597

TETRAHEDRON: *ASYMMETRY*

Pd(II)-catalysed aminocarbonylation as a key step in the total synthesis of C-6 homologues of 1-deoxynojirimycin and 1-deoxy-L-idonojirimycin†

Peter Szolcsányi,[a] Tibor Gracza,[a,*] Marian Koman,[b] Nad'a Prónayová and Tibor Liptaj[c]

[a]*Department of Organic Chemistry, Faculty of Chemical Technology, Slovak University of Technology, Radlinského 9, 812 37 Bratislava, Slovakia*
[b]*Department of Inorganic Chemistry, Faculty of Chemical Technology, Slovak University of Technology, Radlinského 9, 812 37 Bratislava, Slovakia*
[c]*Central NMR Laboratories, Faculty of Chemical Technology, Slovak University of Technology, Radlinského 9, 812 37 Bratislava, Slovakia*

Received 4 May 2000; accepted 5 June 2000

Abstract

The first successful Pd(II)-catalysed aminocarbonylation of the highly substituted benzylaminoalkene **5** allows the direct preparation of fused piperidine lactones **3** and **4**, which are subsequently converted to the novel C-6 homologue of 1-deoxynojirimycin **1** and 1-deoxy-L-idonojirimycin **2**. The study of the influence of various catalytic conditions on the diastereoselectivity and product distribution of the key aminocarbonylation is presented.

1. Introduction

Azasugar glycosidase inhibitors[1] are analogues of monosaccharides in which the ring oxygen is replaced by nitrogen. This substitution renders the compounds metabolically inert, but does not prevent their recognition by glycosidases and other carbohydrate-recognising proteins.[2] As a consequence, an in vivo competitive inhibition of glycosidases results in significant alteration of many crucial biochemical pathways and other important biological functions of living organisms.

* Corresponding author. E-mail: gracza@chelin.chtf.stuba.sk
† Part of a PhD Thesis by P.S., Slovak University of Technology, Bratislava, 1998.

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00226-3

Therefore, glycosidase inhibitors have a great potential in the diagnostics and treatment of obesity and diabetes mellitus,[3] cancer,[4] viral infections[5] including AIDS,[6] and hereditary lysosomal storage diseases.[7]

In that context there is continued interest in the synthesis and biological evaluation of chiral non-racemic polyhydroxylated piperidines and their various derivatives as potent glycosidase inhibitors. Numerous successful synthetic approaches to this class of compounds have appeared over the last decade. Homoazasugars with CH_2-homologation in the side chain may be interesting compounds for testing structure–activity relationships. Indeed, there is a strong synthetic effort put toward the efficient preparation of different homologues of polyhydroxylated piperidines.[8] However, only a few of the already published synthetic strategies deal with the preparation of C-6 homologues of azasugars, iminoheptitols[9] and iminooctitols.[10] Here we report on the first stereoselective synthesis of such new homologues of 1-deoxynojirimycin **1** and 1-deoxy-L-idonojirimycin[9f] **2** as their hydrochloride salts[11] (Fig. 1).

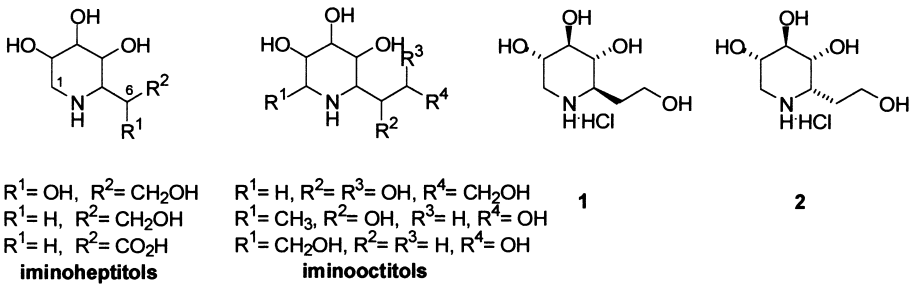
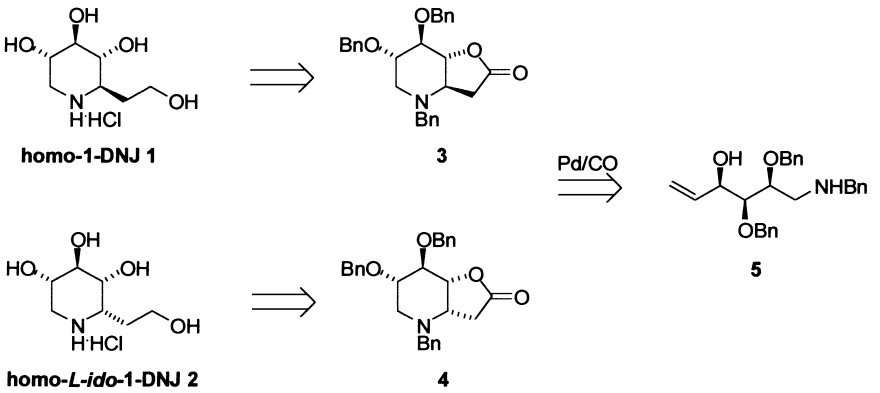


Figure 1.

Our retrosynthetic plan relied on the key Pd(II)-catalysed aminocarbonylation of highly oxygenated and *N*-benzyl protected aminoalkene **5**, which could, in principle, provide both desired diastereoisomeric lactones with *L-gulo* **3**, and *L-ido* **4** configurations, respectively. We envisaged that in the case of their successful preparation, our targets **1** and **2** would be in hand by final routine transformations of lactones **3** and **4** (Scheme 1).



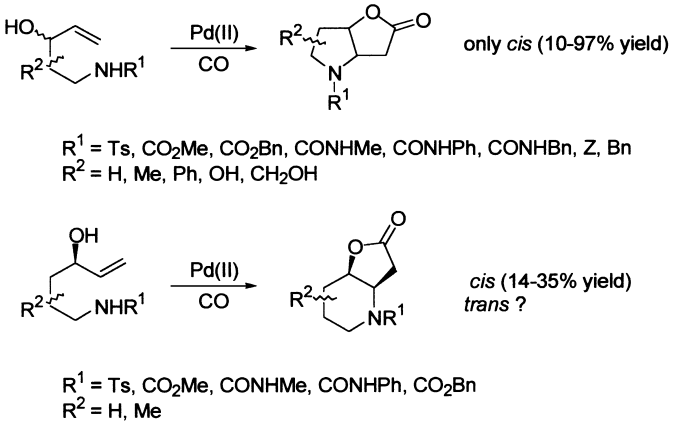
Scheme 1.

2. Results and discussion

2.1. Methodology

Generally, Pd(II)-catalysed amino-/amidocarbonylation of *N*-protected 1-amino-pent-4-ene-3-ols proceeds well,[12] and selectively provides *cis*-fused pyrrolidine-γ-lactones,[13] which have since been utilised in efficient total syntheses of valuable natural products[14] and related compounds.[15] Compared to 1-amino-pent-4-ene-3-ols, the homologous 6-amino-hex-2-ene-3-ols are much less reactive towards intramolecular Pd(II)-catalysed amino-/amidocarbonylation. It should be noted at this point that reactions leading to the formation of five-membered rings are not necessarily applicable to the synthesis of six-membered rings. Moreover, the additional issue of the diastereoselectivity of the formation of corresponding piperidine lactones must be taken into account.

To the best of our knowledge, there are only three papers in the literature, which deal with such a transformation on similar but less functionalised substrates.[12c,13c,16] However, reported yields of aminocarbonylations have not as yet reached the range of preparative usefulness and no further synthetic elaboration of the prepared piperidine lactones has been reported. The important common feature of almost all published amino-/amidocarbonylations (either producing pyrrolidine or piperidine lactones) until now is the use of electron withdrawing protecting groups (tosyl, carbamate, amide) of the *N*H-function of aminoalkenes (Scheme 2).



Scheme 2.

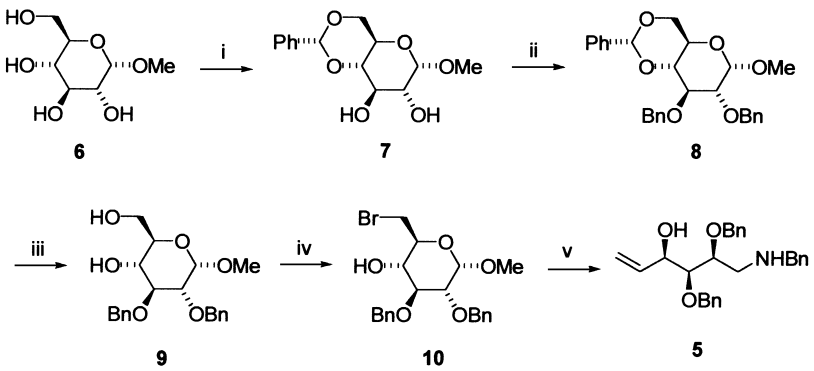
This was claimed to be essential for optimal adjustment of the *N*-nucleophilicity in order to favour the cyclisation step over the competing *N*–Pd complexation.[15] However, the properties of such protecting groups (introduction, deprotection, chemical inertness and stability) were not suitable for our proposed plan of the total synthesis. Therefore, we decided to explore the applicability of the benzyl-protecting group in the Pd(II)-catalysed aminocarbonylation to produce the piperidine lactones. We have formulated two basic aims:

(i) to attempt the Pd(II)-catalysed aminocarbonylation of highly functionalised and *N*-benzyl-protected aminoalkene **5** producing the corresponding fused piperidine-lactones **3** and **4**; to explore the influence of different catalytic conditions of the key reaction (i.e. catalyst, reoxidant, additive, solvent, temperature) on the product composition;

(ii) to find and select the best reaction conditions for the highest possible stereoselective preparation of both desired lactones **3** and **4**; to utilise the prepared compounds in the total synthesis and to prepare two C-6 homologues of 1-DNJ **1** and L-*ido*-1-DNJ **2** as perspective glycosidase inhibitors.

2.2. Synthesis of the key aminoalkenetriol **5**

Our preparation of the key substrate for the Pd(II)-catalysed aminocarbonylation, the benzyl-protected aminoalkenetriol **5**, commences from cheap and commercially available methyl-α-D-glucoside **6** and is analogous to known literature procedures. Thus, benzylidenation of the starting material **6** with benzaldehyde diethylacetal[17] afforded the protected diol **7**,[18] which was subsequently benzylated under standard conditions[19] to give fully protected **8** in 61% yield in two steps. An acid-mediated deprotection of acetal **8** using 2% sulfuric acid in MeOH gave the diol **9** in almost quantitative yield and a subsequent nucleophilic displacement[20] of the primary OH function under Mukaiyama conditions furnished pure bromoalcohol **10** in 79% yield. The last transformation of **10** involved a one-pot three-step sequence[21] (reductive elimination, ring opening and reductive amination) giving the desired (2*S*,3*S*,4*R*)-1-benzylamino-2,3-di-*O*-benzyl-hex-5-ene-2,3,4-triol **5** in 64% yield (Scheme 3). With the key aminoalkenetriol **5** in our hands (30% overall yield in five steps) the stage was set for the key Pd(II)-catalysed aminocarbonylation.



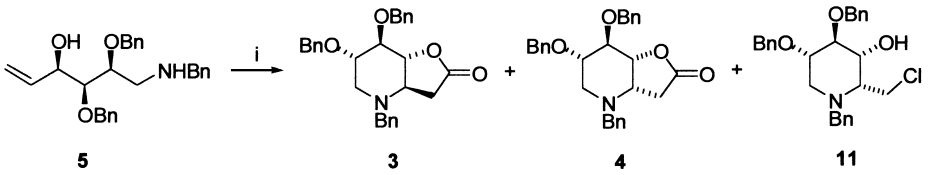
Scheme 3. Reactions and conditions: (i) $PhCH(OEt)_2$, cat. CSA, $CHCl_3$, reflux, 3 h, 81%; (ii) BnBr, NaH, DMF, 0°C, 3 h, 75%; (iii) 2% H_2SO_4/MeOH, rt, 3 h, 97%; (iv) Ph_3P, CBr_4, pyridine, 0°C, 3 h→60°C, 30 min, 79%; (v) Zn dust, $BnNH_2$, $NaBH_3CN$, *n*-PrOH:H_2O (19:1), reflux, 2 h, 64%

2.3. Palladium(II)-catalysed aminocarbonylation of alkene **5**

First attempts to cyclise aminoalkenetriol **5** under standard carbonylation conditions[12c] (1 atm. CO, cat. $PdCl_2$, 3 equiv. $CuCl_2$, 3 equiv. AcONa, AcOH) at room temperature failed and the starting material was always reisolated. However, elevation of the temperature up to 50°C led to the complete consumption of aminoalkenetriol **5** while the colour of the reaction mixture changed from dark green to ochre.‡ However, aminocarbonylation of **5** furnished a crude brown oil as a

‡ This significant colour change allows a convenient monitoring of the reaction course and actually reflects a reduction of $CuCl_2$, used in excess as reoxidant, to its Cu^+ form.

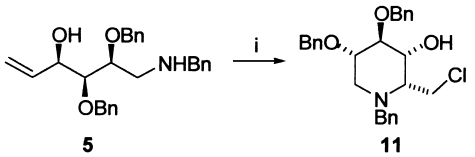
complex mixture of compounds from which desired lactones with L-*gulo* **3** and L-*ido* **4** configuration were isolated in the ratio of 1:4.8 (65% *d.e.* by quantitative ^{13}C NMR) and in 46% yield. Much to our surprise, the major by-product of the reaction turned out to be *N*-benzyl-2,3-di-*O*-benzyl-6-chloro-1,6-dideoxy-L-idonojirimycin **11** in 9% yield (Scheme 4).



5 **3** **4** **11**

Scheme 4. Reactions and conditions: (i) CO (balloon), 0.1 equiv. $PdCl_2$, 3 equiv. $CuCl_2$, 3 equiv. AcONa, glacial AcOH, 50°C, 6.5 h, FLC, chloride **11** (9%)+mixture of L-*gulo* lactone **3**/L-*ido* lactone **4** (1/4.8, 46%)

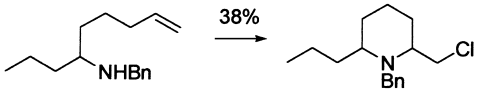
The course of the aminocarbonylation of alkene **5**, as well as the product distribution, was surprising and requires further comment. First of all, this reaction is the first known example of a Pd(II)-catalysed aminocarbonylation of a highly functionalised and *N*-benzyl-protected aminoalkene producing the corresponding fused piperidine lactones. In contrast to the known literature precedents, our result with the alkene **5** shows that aliphatic amines are also capable of undergoing the intramolecular Pd(II)-catalysed aminocarbonylation giving bicyclic [4.3.0] piperidine lactones. Secondly, this is the first known precedent of a Pd(II)-catalysed aminocarbonylation of a protected aminoalkenetriol producing both possible diastereoisomers of piperidine lactones. It is obvious that in contrast to pyrrolidines, piperidines can by fused to five-membered lactones either in the *cis*- or *trans*-fashion. However, known literature examples report either the formation of *cis*-fused lactones[12c,16] exclusively (but without any explanation of such an impressive stereodiscrimination) or this issue was not addressed at all.[13c] Thirdly, there are no reports detailing the formation of cyclic chloro derivative by-products such as **11** during aminocarbonylations in previous papers; however, Tamaru and Yoshida[12c,16] observed the formation of acyclic 6-chlorohex-4-enylamines as side products. The literature search revealed papers describing the use of $Pd(II)/CuCl_2$ systems for chlorohydroxylation[22] of alkenes. Our suspicion that the formation of undesired **11** might be a result of abuse of $CuCl_2$ (used in excess as reoxidant) for such $PdCl_2$-mediated side reactions was proved by applying non-chlorinating[23] aminocarbonylation conditions to alkene **5**. We were pleased to find that a catalytic system consisting of $PdCl_2$, *p*-benzoquinone (BQ), LiCl, AcONa and THF afforded the mixture of L-*gulo* **3** and L-*ido* **4** lactones in the ratio of 3.7:1 (58% *d.e.* by quantitative ^{13}C NMR) and in 66% yield with no formation of **11**. The definitive confirmation of our hypothesis came from a simple experiment in which aminoalkenetriol **5** was subjected to the standard aminocarbonylation conditions but with exclusion of carbon monoxide. The only product we were able to isolate was the chloroderivative **11** (Scheme 5).



5 **11**

Scheme 5. Reactions and conditions: (i) 0.1 equiv. $PdCl_2$, 3 equiv. $CuCl_2$, 3 equiv. AcONa, glacial AcOH, rt, 48 h, FLC, chloride **11** (70%)

Thus, we coincidentally found an interesting type of $PdCl_2/CuCl_2$-mediated chloroaminocyclisation of alkene **5**. To the best of our knowledge, there is only one literature precedent[24] describing an analogous transformation. However, the authors employed a much simpler substrate [$PdCl_2(MeCN)_2$, $CuCl_2$, PrCN] and neither the configuration of the product(s) nor the diastereoisomeric excess were given (Scheme 6).



Scheme 6.

The result of the aminocarbonylation of **5** that employed BQ as an alternative reoxidant brought our attention to another interesting issue.[§] It was apparent that a change in the nature of the reoxidant ($CuCl_2 \leftrightarrow$BQ), solvent (AcOH↔THF) and additive (AcONa↔LiCl) has a tremendous influence on the diastereoselectivity and product distribution in the aminocarbonylation of alkene **5**. This was a very important and yet unprecedented observation and therefore it was decided to explore this phenomenon in a more detailed and systematic fashion. Our screening strategy was based on the variations of all reaction components (catalyst, reoxidant, additive, solvent) and temperature. The following reagents and conditions were chosen: *catalyst*: three Pd(II)-salts with different ligand spheres and 'secondary' structures—$PdCl_2$ (oligomer), $PdCl_2(MeCN)_2$ (monomer) and $Pd(OAc)_2$ (dimer); *reoxidant*: two 'complementary' Cu(II)-salts and one organic oxidant—$CuCl_2$ (chlorinating), $Cu(OAc)_2$ and BQ (both non-chlorinating); *additive*: AcONa as a weak base eliminating 2 equiv. of HCl evolved during the aminocarbonylation (also acts as a buffer in the case of AcOH as solvent) and LiCl as the promotor of the redox process; *solvent*: four solvents commonly used in Pd-catalysed reactions, which differ in polarity parameters and proton-donating properties—AcOH, MeOH, THF and MeCN; *temperature*: two different temperatures: rt and 50°C. From all of these selected options we set up three suitable combinations of differing catalytic systems for the aminocarbonylation of **5** as follows:

A: 0.1 equiv. $PdCl_2$, 3 equiv. $CuCl_2$, 3 equiv. AcONa;
B: 0.1 equiv. $PdCl_2$, 1 equiv. BQ, 2 equiv. LiCl, 2 equiv. AcONa;
C: 0.1 equiv. $Pd(OAc)_2$, 3 equiv. $Cu(OAc)_2$, 3 equiv. AcONa.

These were applied under an atmospheric pressure of carbon monoxide in all four different solvents and at indicated temperatures. Our results are summarised in Tables 1–3 (Schemes 7–9).

Our search for optimal reaction conditions for the aminocarbonylation of **5** gave a number of encouraging results. First of all, we gathered further proof of our hypothesis that $CuCl_2$ might be responsible for the formation of chloro derivative by-product **11**. We were able to isolate compound **11** in all cases (except that of MeOH) when employing conditions *A* (Table 1) but in no case without the presence of $CuCl_2$ (conditions *B* and *C*, Tables 2 and 3). In addition, we did not observe the formation of **11** in the stoichiometric aminocarbonylation of **5** (1 equiv. $PdCl_2$) with exclusion of $CuCl_2$ (Table 1, entry 7). However, the ratio of lactones **3**:**4** in this case (1:1.9) was different to that obtained under the same but catalytic conditions (1:4.8, Table 1, entry 2).

§ Note that the ratio of lactones **3**/**4** formed by using BQ (3.7:1) is reversed to that obtained by using $CuCl_2$ (1:4.8).

Table 1

Solvent	Temperature	Reaction time	Ratio of *L-gulo* 3 vs. *L-ido* 4 (*d.e.*)	Isol. yield of 3+4	Isolated yield of 11
AcOH	r.t.	48 hrs	no reaction		
AcOH	50°C	4-7 hrs	1 : 4.8 (65 %)	46 %	9 %
THF	r.t.	7 hrs	1 : 1.1 (5 %)	28 %	14 %
MeOH	r.t.	10 hrs	1 : 2.2 (37 %)	36 %	0 %
MeCN	r.t.	8 hrs	1 : 2.0 (34 %)	24 %	5 %
AcOH[a]	r.t.	24 hrs	no reaction		
AcOH[a]	50°C	7 hrs	1 : 1.9 (32 %)	32 %	0 %

[a] The stoichiometric experiment (1 eq. $PdCl_2$) with exclusion of reoxidant $CuCl_2$.

Table 2

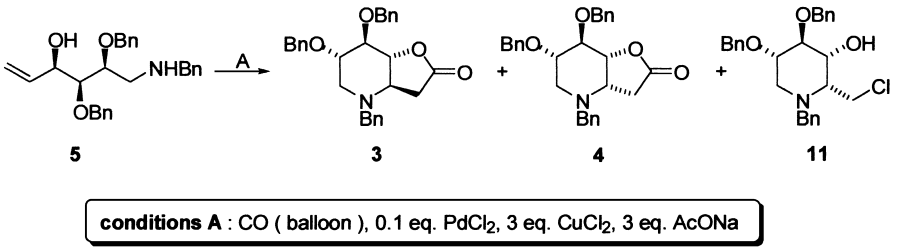
Solvent	Temperature	Reaction time	Ratio of *L-gulo* 3 vs. *L-ido* 4 (*d.e.*)	Isol. yield of 3+4
AcOH	r.t.	24 hrs	no reaction	
AcOH	50°C	47 hrs	1 : 5.6 (70 %)	32 %
THF	r.t.	17 hrs	3.7 : 1 (58 %)	66 %
MeOH	r.t.	72 hrs	<1 : >19 (≥90 %)	9 %[a]
MeOH	50°C	48 hrs	<1 : >19 (≥90 %)	21 %[a]
MeCN	r.t.	48 hrs	no reaction	
MeCN	50°C	24 hrs	1.9 : 1 (31 %)	43 %

[a] Incomplete conversion.

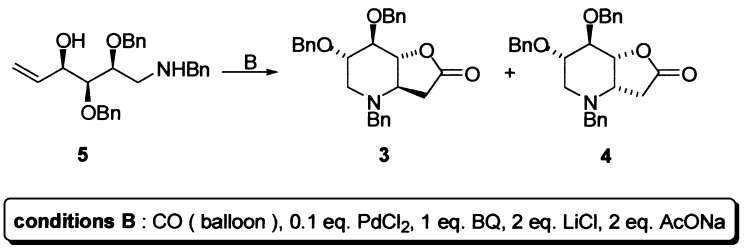
Table 3

Solvent	Temperature	Reaction time	Ratio of *L-gulo* 3 vs. *L-ido* 4 (*d.e.*)	Isol. yield of 3+4
AcOH	r.t.	24 hrs	no reaction	
AcOH	50°C	23 hrs	5.4 : 1 (69 %)	19 %
THF	r.t.	22 hrs	very low conversion	
THF	50°C	48 hrs	1 : 1.4 (17 %)	29 %[a]
MeOH	r.t.	47 hrs	unidentified products	
MeCN	r.t.	48 hrs	1. : 1.3 (13 %)	26 %[a]

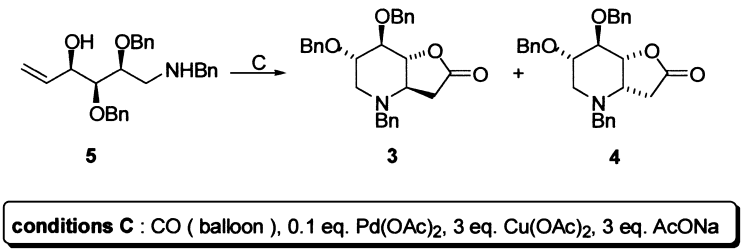
[a] Incomplete conversion.



Scheme 7.



Scheme 8.

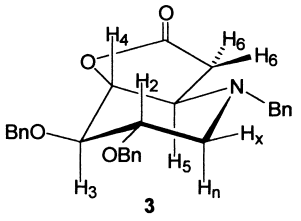


Scheme 9.

This could suggest the existence of two different catalytic species involved: in the case of $PdCl_2$/$CuCl_2$, the formation of certain types of Pd–Cu heterobimetallic species is reasonable[25] in contrast to the oligomeric monometallic structure of $[PdCl_2]_n$ itself in the case of stoichiometric aminocarbonylation. Secondly, we discovered that other catalytic systems are employable in the aminocarbonylation of the alkene **5** and produce desired lactones **3** and **4** (Tables 2 and 3). However, we could not find any reasonable correlation, which would explain the influence of certain reaction parameters on the diastereoselectivity of aminocarbonylation of **5**. Thirdly, we were delighted to find that we are able to govern the course of the reaction and product distribution by simple variation of reaction components. Thus, the best *d.e.* (69%) in favour of *L-gulo* lactone **3** was obtained under conditions *C* in AcOH (entry 2, Table 3); however, due to the low yield (19%) of the reaction it is much more practical to employ conditions *B* in THF (58% *d.e.*, 66% yield, Table 2, entry 3) for the preparation of this product. On the other hand, the best *d.e.* (≥90%, the other diastereoisomer was not observable in the 300 MHz NMR spectrum) in favour of *L-ido* lactone **4** was obtained under conditions *B* in MeOH (entries 4 and 5, Table 2); however, due to the slow reaction, incomplete conversion and therefore low yields (9 and 21%) it

is much more practical to employ either the same conditions but in AcOH (70% *d.e.*, 32% yield, entry 2, Table 2) or conditions *A* in AcOH (65% *d.e.*, 46% yield, entry 2, Table 1) for the preparation of L-*ido* lactone **4**. Thus, at this stage we were able to prepare either desired lactones **3** or **4** in a more or less stereoselective manner by a simple variation of reaction components.

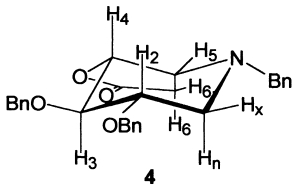
The last issue that should be discussed is the determination of *d.e.*'s in the previous study as well as the determination of relative configurations of both lactones **3**, **4** and chloro derivative **11**. Diastereoisomeric excesses have been determined by integration of corresponding OCH_2Ph signals in quantitative ^{13}C NMR spectra (75.43 MHz, $CDCl_3$, TMS: 73.5 and 73.8 ppm for L-*gulo* **3**; 72.3 and 74.1 ppm for L-*ido* **4**) with suppressed NOE effect of the crude reaction mixtures (just filtered through short plug of silica gel to remove the inorganic salts). The relative configuration of L-*gulo* lactone **3** was established on the basis of ^1H NMR as follows: H-4 proton appeared to be a triplet (instead of dd) with two coupling constants: $J_{3,4}=9.0$ and $J_{4,5}=9.2$ Hz indicating the *trans*-position of H-4 and H-5 protons of **3**. Additionally, the NOESY spectrum of L-*gulo* lactone **3** shows the following space relationships, which also confirm the proposed configuration (Fig. 2).



Proton	Space relationship
$H\text{-}1_n$	$H\text{-}1_x$, H-3, H-5
$H\text{-}1_x$	$H\text{-}1_n$, H-2
H-4	H-2
H-5	H-3

Figure 2.

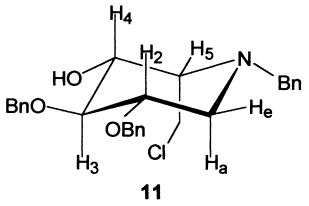
The relative configuration of L-*ido* lactone **4** was established on the basis of DIFNOE and NOESY ^1H NMR experiments, which revealed the *cis*-relationship of H-4 and H-5 protons (Fig. 3). Also, a lower value of their coupling constant ($J_{4,5}=7.3$ Hz) in comparison to **3** supports this observation. However, such a value of the coupling constant of two *cis*-related protons is rather high and would suggest a significant distortion of the chair conformation of the piperidine ring as a result of the lactone fusion in a *cis*-fashion.



Irradiated H	Response
H-4	H-5 (1%), H-2 (2%)
H-5	H-4 (2%)
Proton	**Space relationship**
H-4	H-5
H-5	H-4, H-6, H-6′

Figure 3.

Finally, the relative configuration of chloro derivative **11** was established as in the previous two cases using ^1H NMR. The coupling constant $J_{4,5}=3.0$ Hz suggested the *cis*-relationship and this statement was supported by DIFNOE ^1H NMR experiment, which confirmed a *cis*-relationship of H-4 and H-5 protons and thus established the configuration of **11** as L-*ido* (Fig. 4).

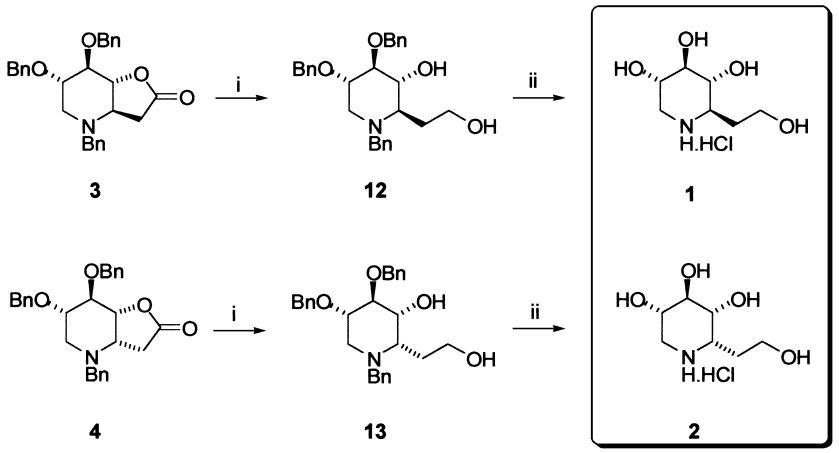


Irradiated H	Response
H-2	H-4 (5%)
H-4	H-2 (5%), H-5 (9%)
H-5	H-4 (3%)

Figure 4.

2.4. Completion of the total synthesis of *1* and *2*

With pure lactones L-*gulo* **3** and L-*ido* **4** in our hands the total synthesis was set up for the last two steps. Reductive opening[15] of both lactone rings with $LiBH_4$ led to the diols **12** and **13** in good yields. Final catalytic debenzylation followed by ion-exchange chromatography purification afforded the desired targets 1,5,6-trideoxy-1,5-imino-D-*gluco*-heptitol **1** and 1,5,6-trideoxy-1,5-imino-L-*ido*-heptitol **2** as hydrochlorides (Scheme 10).



Scheme 10. Reactions and conditions: (i) $LiBH_4$, dry THF, 0°C→rt, 3 h, FLC, **12** (64%), **13** (65%); (ii) H_2 (balloon), 10% Pd/C, HCl, MeOH, rt, overnight, Dowex® (H^+ form), **1** (90%), **2** (82%)

The values of ^1H NMR coupling constants of D-*gluco* **12** ($J_{4,5}=9.0$ Hz) and L-*ido* **13** ($J_{4,5}=4.7$ Hz) diols were in perfect agreement with their 4,5-*trans* and 4,5-*cis* proton relationships, respectively. The *trans*-relationship of H-4 and H-5 protons of the D-*gluco* iminoheptitol **1** was confirmed by their coupling constant ($J_{4,5}=8.2$–8.5 Hz), which indicates the desired relative configuration. Finally, the absolute configuration of **1** was determined by single crystal X-ray analysis[26] (Fig. 5).

3. Conclusion

We have performed the first successful Pd(II)-catalysed aminocarbonylation of highly functionalised and *N*-benzyl-protected aminoalkene **5** affording the corresponding piperidine lactones **3**

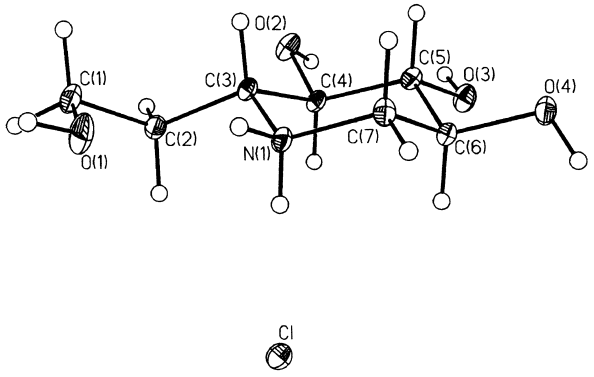


Figure 5.

and **4**. This is an unprecedented case of the employment of an aliphatic amine in such an aminocarbonylation reaction. In contrast to the known literature precedents we observed the formation of both possible diastereoisomers depending on the catalytic conditions used. We also observed the formation of chloro derivative by-product **11** when employing $CuCl_2$ in excess as a reoxidant. The reason for this was the abuse of $CuCl_2$ for Pd-mediated side reactions as confirmed by the experiment with exclusion of CO; the only isolated product was the diastereomerically pure **11**. Thus, we coincidentally found the highly stereoselective chloroaminocyclisation of substituted aminoalkene **5** leading to a piperidine derivative that could be very useful as a building block in the synthesis of naturally occurring piperidines and azepines.[27]

Finally, we conducted a screening study in order to find the optimal conditions for the aminocarbonylation of **5** in terms of diastereoselectivity and suppression of the formation of side products. By simple variation of different components (catalyst, reoxidant, additive, solvent, temperature) we were able to govern the course of the aminocarbonylation as well as the product distribution in a desirable way and thus prepare both lactones **3** and **4** in a more or less stereoselective manner. The final synthetic manipulations led to the first total synthesis of iminoheptitol **1**, a new homologue of naturally occurring 1-deoxynojirimycin. The potential glycosidase inhibitory properties of the iminoheptitols **1** and **2** will be tested in the very near future.

4. Experimental

4.1. General methods

All reagents were used as received without further purification unless otherwise specified. All solvents were distilled before use: THF and Et_2O from Na/benzophenone; toluene from Na; MeCN from P_2O_5; DMF from KOH; MeOH from MeONa; CH_2Cl_2 and $CHCl_3$ from activated 4 Å molecular sieves. Petrol ether refers to the fraction of light petroleum ether boiling in the range 40–60°C and hexanes refer to the fraction 60–65°C. Flash column liquid chromatography (FLC) was performed on silica gel Kieselgel 60 (40–63 μm, 230–400 mesh) and analytical thin-layer chromatography (TLC) was performed on aluminum plates pre-coated with either 0.2 mm (DC-Alufolien, Merck) or 0.25 mm silica gel 60 F_{254} (ALUGRAM® SIL G/UV_{254}, Macherey–Nagel). The compounds were visualised by UV fluorescence and by dipping the plates in an aqueous

H_2SO_4 solution of cerium sulfate/ammonium molybdate followed by charring with a heat-gun. Melting points were obtained using a Büchi 510 capillary melting point apparatus and a Kofler hot plate and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter and a POLAR L-μP polarimeter (IBZ Messtechnik) with a water-jacketed 10 000 cm cell at a wavelength of sodium line D ($\lambda = 589$ nm). Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1} and concentrations are given in g/100 ml. Elemental analyses were performed by the Microanalytical Service of University of Stuttgart and by Microanalytical Service of Slovak University of Technology. Infrared spectra were recorded either on a Philips Analytical PU9800 FTIR spectrometer or a Perkin–Elmer 1750 FTIR spectrophotometer as KBr discs (KBr) or as thin films on KBr plates (film). ^{1}H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) and a Varian VXR-300 (299.94 MHz) spectrometer. Chemical shifts (δ) are quoted in ppm and are either referenced to the tetramethylsilane (TMS) as internal standard ($\delta_{Me} = 0.00$ ppm for 299.94 MHz) or the residual protic solvent ($CHCl_3$, $\delta_H = 7.26$ ppm for 200 MHz; CH_3OH, $\delta_H = 3.34$ ppm for 299.94 MHz) was used as the internal reference. Coupling constants (J) are recorded in hertz. The following abbreviations were used to characterise signal multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet), b (broad). Abbreviations with quotation marks mean that the appearance of the signal is different to that theoretically predicted. The COSY, NOESY and DIFNOE techniques were used in assignment of proton–proton relationships and the determination of relative configuration. ^{13}C NMR spectra were recorded on a Varian Gemini 200 (50.32 MHz) and a Varian VXR-300 (75.43 MHz) spectrometer. The multiplicities of carbons were assigned from a broadband decoupled analysis used in conjunction with either an APT or a DEPT program. Chemical shifts are quoted in ppm and are either referenced to the tetramethylsilane (TMS) as internal standard ($\delta = 0.00$ ppm for 75.43 MHz) or the central resonance of $CDCl_3$ ($\delta = 77.0$ ppm for 50.32 MHz) and CD_3OD ($\delta = 49.0$ ppm for 75.43 MHz) was used as the internal reference. The following abbreviations were used to characterise signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet). The mark '↔' means that corresponding signals can be interchanged. The numbering of lactones **3** and **4** for characterisation of NMR signals as depicted in Figs. 2 and 3 is in accord with the numbering of piperidines **1**, **2**, **12** and **13** for better comparison of all spectral data. The HETCOR and HMQC techniques were used throughout for the assignment of the proton–carbon relationships. Low-resolution mass spectra were recorded on a V.B. Masslab 20-250 (EI), a V.G. Platform II (APCI), and a MS 902 S (EI) mass spectrometer, respectively, with only molecular ions being reported.

4.2. (2S,3S,4R)-1-Benzylamino-2,3-di-O-benzyl-hex-5-ene-2,3,4-triol **5**

Acid treated zinc dust [(102.3 g, 1.565 mol, 60 equiv.) prepared by gradual washing with 3% HCl (600 ml), H_2O (3×500 ml), EtOH (200 ml), acetone (200 ml), dry Et_2O (200 ml) and finally dried in vacuo] was added to the solution of bromoalcohol **10** (11.4 g, 0.26 mol) in ^{n}PrOH:H_2O (19:1, 460 ml) mixture with vigorous stirring. Then $BnNH_2$ (42 g, 42.7 ml, 0.392 mol, 15 equiv.) and $NaBH_3CN$ (3.28 g, 0.052 mol, 2 equiv.) were added and the resulting mixture was stirred at reflux for 2 h. After cooling to rt the suspension was filtered through Celite® pad and washed with EtOH (100 ml). The filtrate was evaporated in vacuo and the residue was dissolved in Et_2O (500 ml) and treated with 20% aq. HCl (90 ml). After 1 h the mixture was basified with 15% aq. sol. NaOH and diluted with H_2O (100 ml), the organic phase was separated and the water layer was extracted with CH_2Cl_2 (3×200 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo giving the crude product as an oil, which was purified by FLC (silica gel, 50% AcOEt/

petrol ether) affording pure aminoalkenetriol **5** (R_f 0.25) as a pale yellow oil (6.9 g, 64%); $[\alpha]_D^{23} = +27.8$ (*c* 1 in $CHCl_3$); δ_H (200 MHz; $CDCl_3$) 2.86 (1H, dd, $J_{1a,2} = 4.0$, $J_{1a,1b} = 12.3$, H-1_a), 3.00 (1H, dd, $J_{1b,2} = 1.5$, $J_{1a,1b} = 12.0$, H-1_b), 3.60–3.69 (2H, m, H-2, H-3), 3.66 (1H, d, $J = 13.4$, NCH_2Ph), 3.86 (1H, d, $J = 12.9$, NCH_2Ph), 4.43–4.45 (1H, m, H-4), 4.47 (1H, d, $J = 12.2$, OCH_2Ph), 4.54 (1H, d, $J = 12.2$, OCH_2Ph), 4.58 (1H, d, $J = 11.9$, OCH_2Ph), 4.68 (1H, d, $J = 11.8$, OCH_2Ph), 5.20 (1H, d, $J_{5,6E} = 10.4$, H-6_E), 5.43 (1H, d, $J_{5,6Z} = 17.2$, H-6_Z), 6.05 (1H, ddd, $J_{4,5} = 5.0$, $J_{5,6E} = 10.5$, $J_{5,6Z} = 17.1$, H-5); δ_C (50.32 MHz, $CDCl_3$) 46.3 (t, C-1), 53.7 (t, NCH_2Ph), 69.3 (d, C-4), 72.3, 74.0 (2d, 2OCH_2Ph), 77.4, 81.1 (2d, C-2↔C-3), 115.0 (t, C-6), 127.6, 127.9, 128.1, 128.5, 128.6, 128.7, 128.8 (all d, all CH of Ph), 138.4, 138.5, 139.0 (3s, $3C_{ipso}$ of Ph), 139.4 (d, C-5); ν_{max} (film)/cm^{-1} 3312 (w, OH); *m*/*z* (APCI$^+$) 418 (M^+); found: C, 78.08; H, 7.58; N, 3.68; $C_{27}H_{31}O_3N$ requires: C, 77.67; H, 7.48; N, 3.35%.

4.3. General procedure for the aminocarbonylation of an alkene **5**

To a dry, one-necked round-bottomed flask equipped with a side-arm stopcock and containing a magnetic stirring bar, a mixture of reagents depending on the catalytic conditions used [i.e. (*A*) $PdCl_2$ (0.1 equiv.), $CuCl_2$ (3 equiv.) and AcONa (3 equiv.); (*B*) $PdCl_2$ (0.1 equiv.), BQ (1 equiv.), LiCl (2 equiv.) and AcONa (2 equiv.); (*C*) $Pd(OAc)_2$ (0.1 equiv.), $Cu(OAc)_2$ (3 equiv.) and AcONa (3 equiv.)] and fitted with a CO balloon was added the aminoalkenetriol **5** (1 equiv.) dissolved in the appropriate solvent (AcOH, THF, MeOH). [The setup for reactions running in MeCN was different: $PdCl_2$ was placed in a flask and stirred in dry acetonitrile overnight while the brown suspension turned into yellow slurry of $PdCl_2(MeCN)_2$. Then $CuCl_2$, AcONa and the substrate in dry MeCN were added.] The apparatus was then purged with CO and the resulting mixture was stirred at the indicated temperature (rt or 50°C) and for the indicated period of time while the colour of the reaction changed. The complex reaction mixture was filtered on a Celite® pad, washed several times with the appropriate solvent and the filtrate was evaporated in vacuo. [In the case of AcOH last traces of the residual solvent were removed by co-evaporation with toluene.] The oily residue was subjected to purification by FLC on silica gel (10% AcOEt/hexanes) yielding chloro derivative **11** as a pale yellow oil and/or mixture of two diastereoisomeric lactones **3** and **4** (*L-gulo*+*L-ido*) as a pale yellow oil.

4.3.1. *Conditions* A

AcOH: $PdCl_2$ (43 mg, 0.2397 mmol), $CuCl_2$ (967 mg, 7.19 mmol), AcONa (590 mg, 7.19 mmol), substrate **5** (1 g, 2.397 mmol) in glacial AcOH (30 ml); 50°C, 6.5 h; colour of the reaction mixture changed from green to ochre; chloride **11** 100 mg (9%)+mixture of *L-gulo* **3** and *L-ido* **4** lactones 488 mg (46%) in a ratio 1:4.8 (65% *d.e.*).

THF: $PdCl_2$ (5 mg, 0.03 mmol), $CuCl_2$ (97 mg, 0.721 mmol), AcONa (59 mg, 0.719 mmol), substrate **5** (100 mg, 0.24 mmol) in dry THF (4 ml); rt, 7 h; colour of the reaction mixture changed from dark green to light green; chloride **11** 15 mg (14%)+mixture of *L-gulo* **3** and *L-ido* **4** lactones 30 mg (28%) in a ratio 1:1.1 (5% *d.e.*).

MeOH: $PdCl_2$ (4 mg, 0.024 mmol), $CuCl_2$ (97 mg, 0.721 mmol), AcONa (59 mg, 0.719 mmol), substrate **5** (100 mg, 0.24 mmol) in dry MeOH (4 ml); rt, 10 h; colour of the reaction mixture remained green; mixture of *L-gulo* **3** and *L-ido* **4** lactones 38 mg (36%) in a ratio 1:2.2 (37% *d.e.*).

MeCN: $PdCl_2$ (4 mg, 0.024 mmol) in dry MeCN (0.5 ml) (brown→yellow); $CuCl_2$ (97 mg, 0.721 mmol), AcONa (59 mg, 0.719 mmol) (yellow→gray green); substrate **5** (100 mg, 0.24 mmol) in dry MeCN (2.5 ml); rt, 8 h; colour of the reaction mixture changed from dark green to

light green; chloride **11** 5 mg (5%)+mixture of *L-gulo* **3** and *L-ido* **4** lactones 25 mg (24%) in a ratio 1:2.0 (34% *d.e.*).

4.3.2. Conditions B

AcOH: $PdCl_2$ (5 mg, 0.028 mmol), *p*-benzoquinone (26 mg, 0.24 mmol), LiCl (21 mg, 0.495 mmol), AcONa (40 mg, 0.488 mmol), substrate **5** (100 mg, 0.24 mmol) in glacial AcOH (3 ml); 50°C, 47 h; colour of the reaction mixture changed from brown to black; mixture of *L-gulo* **3** and *L-ido* **4** lactones 34 mg (32%) in a ratio 1:5.6 (70% *d.e.*).

THF: $PdCl_2$ (5 mg, 0.028 mmol), *p*-benzoquinone (26 mg, 0.24 mmol), LiCl (21 mg, 0.495 mmol), AcONa (40 mg, 0.488 mmol), substrate **5** (100 mg, 0.24 mmol) in dry THF (5 ml); rt, 17 h; colour of the reaction mixture changed from red–brown to brown–black; mixture of *L-gulo* **3** and *L-ido* **4** lactones 70 mg (66%) in a ratio 3.7:1 (58% *d.e.*).

MeOH: $PdCl_2$ (5 mg, 0.028 mmol), *p*-benzoquinone (26 mg, 0.24 mmol), LiCl (21 mg, 0.495 mmol), AcONa (40 mg, 0.488 mmol), substrate **5** (100 mg, 0.24 mmol) in dry MeOH (4 ml); rt, 3 days; colour of the reaction mixture changed from red–brown to black; incomplete conversion; mixture of *L-gulo* **3** and *L-ido* **4** lactones 10 mg (9%) in a ratio $<1:>19$ ($\geq$90% *d.e.*).

MeCN: $PdCl_2$ (5 mg, 0.028 mmol) in dry MeCN (0.5 ml) (brown$\rightarrow$yellow); *p*-benzoquinone (26 mg, 0.24 mmol), LiCl (21 mg, 0.495 mmol), AcONa (40 mg, 0.488 mmol), substrate **5** (100 mg, 0.24 mmol) in dry MeCN (2.5 ml); 50°C, 24 h; colour of the reaction mixture changed from brown to black; mixture of *L-gulo* **3** and *L-ido* **4** lactones 46 mg (43%) in a ratio 1.9:1 (31% *d.e.*).

4.3.3. Conditions C

AcOH: $Pd(OAc)_2$ (9 mg, 38 μmol), $Cu(OAc)_2$ (206 mg, 1.136 mmol), AcONa (93 mg, 1.136 mmol), substrate **5** (158 mg, 0.3787 mmol) in glacial AcOH (5 ml); 50°C, 23 h; colour of the reaction mixture changed from blue–green to black; mixture of *L-gulo* **3** and *L-ido* **4** lactones 21 mg (19%) in a ratio 5.4:1 (69% *d.e.*).

THF: $Pd(OAc)_2$ (6 mg, 24 μmol), $Cu(OAc)_2$ (131 mg, 0.719 mmol), AcONa (59 mg, 0.719 mmol), substrate **5** (100 mg, 0.24 mmol) in dry THF (5 ml); 50°C, 48 h; mixture of *L-gulo* **3** and *L-ido* **4** lactones 31 mg (29%) in a ratio 1:1.4 (17% *d.e.*).

MeCN: $Pd(OAc)_2$ (6 mg, 24 μmol), $Cu(OAc)_2$ (131 mg, 0.719 mmol), AcONa (59 mg, 0.719 mmol), substrate **5** (100 mg, 0.24 mmol) in dry MeCN (5 ml); rt, 48 h; mixture of *L-gulo* **3** and *L-ido* **4** lactones 28 mg (26%) in a ratio 1:1.3 (13% *d.e.*).

4.4. Stoichiometric aminocarbonylation of an alkene **5** *using* $PdCl_2$

A dry, 25 ml one-necked round-bottomed flask equipped with a side-arm stopcock, containing a magnetic stirring bar, $PdCl_2$ (43 mg, 0.24 mmol, 1 equiv.) and AcONa (59 mg, 0.719 mmol, 3 equiv.) was fitted with a CO balloon and aminoalkenetriol **5** (100 mg, 0.24 mmol, 1 equiv.) dissolved in glacial AcOH (3 ml) was added. The apparatus was purged with CO and the resulting green mixture was stirred at 50°C for 7 h while the colour of the reaction turned black. The mixture was filtered on a Celite® pad, washed several times with AcOH and the filtrate was evaporated in vacuo. The last traces of the solvent were removed by co-evaporation with toluene and the residue was filtered through short plug of silica gel yielding the crude mixture of two diastereoisomeric lactones **3** and **4** (*L-gulo*+*L-ido*) as an oil (34 mg, 32%) in a ratio 1:1.9 (32% *d.e.*).

All crude mixtures of lactones from aminocarbonylations were combined and *L-gulo* **3** and *L-ido* **4** lactones were separated by FLC on silica gel (gradient elution with hexanes:AcOEt = 100:0→95:1→9:1→4:1) yielding pure compounds.

4.5. *3,7-Anhydro-2,7-dideoxy*-N-*benzyl-5,6-di*-O-*benzyl-3,7-imino*-L-gulo-*1,4-heptonolactone* **3**

Pale yellow oil; R_f (0.28, 25% AcOEt/hexanes); $[\alpha]_D^{24} = -64.9$ (*c* 1.23 in CH_2Cl_2); δ_H (299.94 MHz, $CDCl_3$) 2.07 (1H, 't', $J_{1n,2} = 10.6$, $J_{1n,1x} = 11.1$, H-1_n), 2.41 (1H,'t', $J_{5,6n} = 2.4$, $J_{6x,6n} = 14.2$, H-6_n), 2.59 (1H, dd, $J_{5,6x} = 6.2$, $J_{6x,6n} = 14.4$, H-6_x), 2.56–2.63 (1H, m, H-5), 3.11 (1H, dd, $J_{1x,2} = 4.3$, $J_{1n,1x} = 11.1$, H-1_e), 3.35 (1H, d, $J = 13.5$, NCH_2Ph), 3.60–3.68 (2H, m, $J_{1x,2} = 4.7$, $J_{3,4} = 8.8$, H-2, H-3), 3.70 (1H, d, $J = 13.1$, NCH_2Ph), 3.97 (1H,'t', $J_{3,4} = 9.0$, $J_{4,5} = 9.2$, H-4), 4.57 (1H, d, $J = 11.5$, OCH_2Ph), 4.73 (1H, d, $J = 11.4$, OCH_2Ph), 4.74 (1H, d, $J = 11.4$, OCH_2Ph), 4.91 (1H, d, $J = 11.5$, OCH_2Ph), 7.25–7.39 (15H, m, 15 CH of Ph); δ_C (75.43 MHz, $CDCl_3$) 35.5 (t, C-6), 57.2 (t, C-1), 60.0 (t, NCH_2Ph), 64.6 (d, C-5), 73.5 (t, OCH_2Ph), 73.8 (t, OCH_2Ph), 77.9 (d, C-2), 82.2 (d, C-3), 84.3 (d, C-4), 127.6, 127.7, 127.8, 127.9, 128.4, 128.5, 128.8 (all d, all CH of Ph), 136.8, 138.0, 138.1 (all s, all C_{ipso} of Ph), 173.9 (s, C-7); ν_{max} (film)/cm^{-1} 1794 (s, C=O); *m*/*z* (EI) 443 (M^+–1); found: C, 75.64; H, 6.69; N, 3.10; $C_{28}H_{29}O_4N$ requires: C, 75.82; H, 6.59; N, 3.16%.

4.6. *3,7-Anhydro-2,7-dideoxy*-N-*benzyl-5,6-di*-O-*benzyl-3,7-imino*-L-ido-*1,4-heptonolactone* **4**

Pale yellow oil; R_f (0.34, 25% AcOEt/hexanes); $[\alpha]_D^{30} = -6.05$ (*c* 0.74 in CH_2Cl_2); δ_H (299.94 MHz, $CDCl_3$) 2.34 (1H, dd, $J_{5,6x} = 7.4$, $J_{6n,6x} = 17.0$, H-6_x), 2.53 (1H, dd, $J_{1n,2} = 7.8$, $J_{1n,1x} = 12.5$, H-1_n), 2.61 (1H, dd, $J_{5,6n} = 10.1$, $J_{6n,6x} = 17.1$, H-6_n), 2.81 (1H, dd, $J_{1x,2} = 3.5$, $J_{1n,1x} = 12.8$, H-1_x), 3.51 (1H, d, $J = 13.5$, NCH_2Ph), 3.56–3.62 (2H, m, H-2, H-3), 3.63–3.73 (1H, m, H-5), 3.68 (1H, d, $J = 13.7$, NCH_2Ph), 4.52 (1H, 't', $J_{3,4} \cong J_{4,5} = 7.3$, H-4), 4.54 [1H, d, $J = 12.0$, (C-2)OCH_2Ph], 4.60 [1H, d, $J = 11.7$, (C-2)OCH_2Ph], 4.74 [1H, d, $J = 11.3$, (C-3)OCH_2Ph], 4.82 [1H, d, $J = 11.3$, (C-3)OCH_2Ph], 7.20–7.34 (15H, m, 15 CH of Ph); δ_C (75.43 MHz, $CDCl_3$) 27.7 (t, C-6), 48.6 (t, C-1), 58.1 (d, C-5), 59.2 (t, NCH_2), 72.3 [t, (C-2)OCH_2], 74.1 [t, (C-3)OCH_2], 76.4 (d, C-3), 81.2 (d, C-4), 81.3 (d, C-2), 126.7, 127.7, 127.9, 128.4, 128.5, 128.6 (all d, all CH of Ph), 137.1, 138.0, 138.1 (3s, 3C_{ipso} of Ph), 174.7 (s, C-7); ν_{max} (film)/cm^{-1} 1779 (s, C=O); *m*/*z* (EI) 444 (M^+); found: C, 75.64; H, 6.69; N, 3.10; $C_{28}H_{29}O_4N$ requires: C, 75.82; H, 6.59; N, 3.16%.

4.7. N-*Benzyl-2,3-di*-O-*benzyl-6-chloro-1,5,6-trideoxy-1,5-imino-L-iditol* **11**

Pale yellow oil; R_f (0.7, 25% AcOEt/hexanes); $[\alpha]_D^{25} = +35.1$ (*c* 0.7 in CH_2Cl_2); δ_H (299.94 MHz, $CDCl_3$) 2.63 (1H, dd, $J_{1e,2} = 2.6$, $J_{1a,1e} = 12.8$, H-1_e), 2.83 (1H, dd, $J_{1a,2} = 5.1$, $J_{1a,1e} = 12.8$, H-1_a), 3.12 (1H, 'dt', $J_{4,5} = 3.0$, $J_{5,6a} = 6.1$, $J_{5,6b} = 6.2$, H-5), 3.35 (1H, d, $J_{4,OH} = 9.0$, OH), 3.53 (1H, d, $J = 14.2$, NCH_2Ph), 3.56 (1H, m, H-2), 3.66 (1H, 't', $J_{2,3} \cong J_{3,4}$ 4.8, H-3), 3.85 (2H, 'd', $J = 6.7$, H-6), 3.99 (1H, m, H-4), 4.08 (1H, d, $J = 13.8$, NCH_2Ph), 4.31 (1H, d, $J = 11.8$, OCH_2Ph), 4.41 (1H, d, $J = 11.8$, OCH_2Ph), 4.60 (1H, d, $J = 11.8$, OCH_2Ph), 4.67 (1H, d, $J = 11.8$, OCH_2Ph), 7.17–7.34 (15H, m, 15 CH of Ph); δ_C (75.43 MHz; $CDCl_3$) 42.2 (t, C-6), 49.5 (t, C-1), 58.0 (t, NCH_2Ph), 63.7 (d, C-5), 69.4 (d, C-4), 71.0 (t, OCH_2Ph), 72.9 (t, OCH_2Ph), 75.6 (d, C-2), 76.9 (d, C-3), 127.2, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.4, 128.5, 128.6 (all d, all CH of Ph), 137.6, 138.1, 139.2 (all s, all C_{ipso} of Ph); ν_{max} (film)/cm^{-1} 1102 (s); *m*/*z* (EI) 451 (M^+–1); found: C, 71.74; H, 6.73; N, 3.14, Cl, 7.83; $C_{27}H_{30}O_3NCl$ requires: C, 71.75; H, 6.69; N, 3.10, Cl, 7.84%.

4.8. Chloroaminocyclisation of an alkene **5** using $PdCl_2/CuCl_2$

The aminoalkenetriol **5** (50 mg, 0.12 mmol) dissolved in glacial AcOH (1.5 ml) was added to a mixture of $PdCl_2$ (4 mg, 0.24 mmol, 0.2 equiv.), $CuCl_2$ (48 mg, 0.36 mmol, 3 equiv.) and AcONa (29 mg, 0.36 mg, 3 equiv.) and stirred at rt for 48 h. The green suspension was filtered on a Celite® pad, washed with AcOH and evaporated in vacuo. The last traces of the residual solvent were removed by co-evaporation with toluene and the crude residue was purified by FLC (10% AcOEt/hexanes) yielding chloro derivative **11** as a pale yellow oil (37 mg, 70%). The physical and spectroscopical data were identical to those of chloro derivative **11** previously obtained from aminocarbonylation of **5**.

4.9. N-*Benzyl-2,3-di*-O-*benzyl-1,5,6-trideoxy-1,5-imino-D*-gluco-*heptitol* **12**

The *L-gulo* lactone **3** (77 mg, 0.174 mol) was dissolved in dry THF (5 ml), cooled to 0°C and $LiBH_4$ (23 mg, 1.044 mmol, 6 equiv.) was added under Ar with vigorous stirring. After 3 h at rt, the mixture was carefully neutralised with aq. HCl (pH≈7) and diluted with water (30 ml). The mixture was then extracted with AcOEt (3×30 ml) and dried over $MgSO_4$. Evaporation in vacuo furnished the crude solid, which was purified by FLC (silica gel, 50% AcOEt/hexanes) yielding *D-gluco* diol **12** (R_f 0.15) as a white solid (50 mg, 64%); m.p. 97–98°C; $[\alpha]_D^{31} = -19.4$ (*c* 0.29 in CH_2Cl_2); δ_H (299.94 MHz, $CDCl_3$) 1.99–2.08 (2H, m, $J_{1a,1b} = 11.9$, H-1_a, H-6_a), 2.13–2.28 (1H, m, H-6_b), 2.51–2.63 (1H, m, $J_{5,6a} \cong J_{5,6b} = 4.5$, $J_{4,5} = 9.0$, H-5), 3.03 (1H, dd, $J_{1b,2} = 4.4$, $J_{1a,1b} = 12.1$, H-1_b), 3.10–3.40 (2H, b, 2OH), 3.36 (1H, 't', $J_{2,3} \cong J_{3,4} = 8.5$, H-3), 3.35 (1H, d, $J = 13.7$, NCH_2Ph), 3.60 (1H, 'dt', $J_{1b,2} = 4.3$, $J_{2,3} = 8.6$, H-2), 3.66 (1H, 't', $J_{3,4} = 8.6$, $J_{4,5} = 9.0$, H-4), 3.74–3.93 (2H, m, H-7), 4.13 (1H, d, $J = 13.3$, NCH_2Ph), 4.45 (1H, d, $J = 11.5$, OCH_2Ph), 4.52 (1H, d, $J = 11.5$, OCH_2Ph), 4.70 (1H, d, $J = 11.5$, OCH_2Ph), 4.98 (1H, d, $J = 11.4$, OCH_2Ph), 7.18–7.40 (15H, m, 15 CH of Ph); δ_C (75.43 MHz; $CDCl_3$) 29.4 (t, C-6), 53.1 (t, C-1), 56.6 (t, NCH_2Ph), 60.2 (t, C-7), 64.1 (d, C-5), 71.2 (d, C-4), 72.2 (t, OCH_2Ph), 74.8 (t, OCH_2Ph), 77.2 (d, C-2), 85.2 (d, C-3), 127.4, 127.7, 127.8, 127.9, 128.4, 128.5, 128.6, 128.9 (all d, all CH of Ph), 138.0, 138.6 (2s, $2C_{ipso}$ of Ph); ν_{max} (KBr)/cm^{-1} 3403 (bs, OH); *m/z* (EI) 417 (M^+–CH_2OH); found: C, 74.86; H, 7.48; N, 3.02; $C_{28}H_{33}O_4N$ requires: C, 75.12; H, 7.44; N, 3.13%.

4.10. N-*Benzyl-2,3-di*-O-*benzyl-1,5,6-trideoxy-1,5-imino*-L-ido-*heptitol* **13**

The *L-ido* lactone **4** (510 mg, 1.151 mmol) was dissolved in dry THF (15 ml), cooled to 0°C and $LiBH_4$ (100 mg, 4.602 mmol, 4 equiv.) was added under Ar with vigorous stirring. After 3 h at rt, the mixture was carefully neutralised with aq. HCl (pH≈7) and diluted with water (30 ml). The mixture was then extracted with AcOEt (3×30 ml) and dried over $MgSO_4$. Evaporation in vacuo furnished a crude oil, which was purified by FLC (silica gel, 50% AcOEt/hexanes) yielding *L-ido* diol **13** (R_f 0.22) as a colourless oil (331 mg, 65%); $[\alpha]_D^{31} = -1.32$ (*c* 0.34 in CH_2Cl_2); δ_H (299.94 MHz; $CDCl_3$) 1.82–1.95 (2H, m, H-6), 2.74 (2H, 'd', $J = 6.8$, H-1), 3.05–3.15 (1H, m, $J_{4,5} = 4.7$, H-5), 3.12–3.78 (6H, m, H-2, H-3, H-7, 2 OH), 3.60 (1H, d, $J = 13.3$, NCH_2Ph), 3.82 (1H, d, $J = 13.2$, NCH_2Ph), 3.86 (1H, dd, $J_{4,5} = 4.7$, $J_{3,4} = 8.4$, H-4), 4.50 (2H, 's', OCH_2Ph), 4.67 (1H, d, $J = 11.5$, OCH_2Ph), 4.92 (1H, d, $J = 11.3$, OCH_2Ph), 7.23–7.40 (15H, m, 15 CH of Ph); δ_C (75.43 MHz, $CDCl_3$) 29.7 (t, C-6), 48.0 (t, C-1), 58.1 (t, NCH_2Ph), 61.2 (d, C-5), 62.1 (t, C-7), 69.7 (d, C-4), 71.9 (t, OCH_2Ph), 74.5 (t, OCH_2Ph), 76.6, 81.2 (2 d, C-2↔C-3), 127.4, 127.7, 127.8, 127.9, 128.4, 128.5, 128.7 (all d, all CH of Ph), 137.9, 138.3, 138.4 (all s, all C_{ipso} of Ph); ν_{max} (film)/cm^{-1}

3370 (bs, OH); *m*/*z* (EI) 447 (M^+–1); found: C, 74.92; H, 7.42; N, 3.13; $C_{28}H_{33}O_4N$ requires: C, 75.12; H, 7.44; N, 3.13%.

Alternatively, the $LiBH_4$ reduction was carried out with a mixture of lactones **3** and **4**. Thus, the mixture of *L-gulo* **3** and *L-ido* **4** lactones (172 mg, 0.388 mmol) was dissolved in dry THF (10 ml), cooled to 0°C and $LiBH_4$ (34 mg, 1.552 mmol, 4 equiv.) was added under Ar with vigorous stirring. After 3 h at rt, the mixture was carefully neutralised with aq. HCl (pH ≈7), diluted with AcOEt (50 ml), washed with water (30 ml) and dried over $MgSO_4$. Evaporation in vacuo furnished a semicrystalline oil (164 mg), which was purified by FLC (silica gel, gradient elution with hexanes: AcOEt: 9:1→4:1→3:1→2:1) yielding two fractions: (1) fraction: *L-ido* diol **13** as a colourless oil (75 mg, 43%); and (2) fraction: *D-gluco* diol **12** as a white solid (25 mg, 14%). The physical and spectroscopic data were identical to those of previously obtained.

4.11. 1,5,6-Trideoxy-1,5-imino-D-gluco-heptitol hydrochloride **1**

The *D-gluco* diol **12** (70 mg, 0.157 mmol) was dissolved in EtOH (8 ml) containing 35% HCl (seven drops) and 10% Pd/C (44 mg) was added. The flask was purged with hydrogen by repeated pumping-filling and the mixture was stirred under the H_2 atmosphere overnight. The catalyst was filtered off, washed with EtOH and the filtrate was evaporated in vacuo. The residue was dissolved in deionised H_2O (2 ml) and put on the top of a column of Dowex® 50WX8-400 ion-exchange resin [1.5 g, H_2O (3 ml), washed sequentially with H_2O (15 ml)→MeOH (15 ml)→H_2O (15 ml) prior to use]. The column was washed with water to the neutrality (ca. 10 ml) and the product was eluted with 2.5% NH_4OH solution. Removal of volatiles in vacuo and redissolving the residue in MeOH, addition of two drops of 35% HCl, filtration and evaporation afforded the hydrochloride salt of *D-gluco* homologue **1** as a colourless semicrystalline oil (30 mg, 90%), which can be crystallised from MeOH/^{t}BuOMe; m.p. 177–179°C; $[\alpha]_D^{26}=+30$ (*c* 0.55 in MeOH); δ_H (299.94 MHz, CD_3OD) 1.86 (1H, 'ddt', $J_{6a,7b}=4.6$, $J_{6a,7a}=8.1$, $J_{6a,6b}=12.8$, H-6_a), 2.27 (1H, 'ddt', $J_{6b,7a}=4.1$, $J_{6b,7b}=5.9$, $J_{6a,6b}=12.4$, H-6_b), 2.89 (1H, 't', $J_{1a,1e}\cong J_{1a,2}=12.0$, H-$1_a$), 3.20 (1H, 'dt', $J_{4,5}=8.5$, $J_{5,6a}=9.5$, H-5), 3.39 (1H, dd, $J_{1e,2}=4.7$, $J_{1a,1e}=12.9$, H-1_e), 3.40 (1H, 't', $J_{4,5}=8.2$, $J_{3,4}=10.2$, H-4), 3.44 (1H, 't', $J_{2,3}=8.9$, $J_{3,4}=10.2$, H-3), 3.73 (1H, ddd, $J_{1e,2}=5.0$, $J_{2,3}=8.8$, $J_{1a,2}=11.5$, H-2), 3.81 (1H, ddd, $J_{6b,7a}=4.4$, $J_{6a,7a}=8.0$, $J_{7a,7b}=12.3$, H-7_a), 3.91 (1H, 'dt', $J_{6a,7b}=4.7$, $J_{6b,7b}=6.1$, H-7_b); δ_C (75.43 MHz, CD_3OD) 32.2 (t, C-6), 48.1 (t, C-1), 60.2 (t, C-7), 60.8 (d, C-5), 68.5 (d, C-2), 72.5 (d, C-3), 78.3 (d, C-4); ν_{max} (film)/cm^{-1} 3353 (bs, OH); *m*/*z* (EI) 177 (M^+–HCl); found: C, 39.21; H, 7.58; N, 6.38, Cl, 16.50, $C_7H_{16}O_4NCl$ requires: C, 39.35; H, 7.55; N, 6.56, Cl, 16.59%.

4.12. 1,5,6-Trideoxy-1,5-imino-L-ido-heptitol hydrochloride **2**

The *L-ido* diol **13** (112 mg, 0.25 mmol) was dissolved in EtOH (10 ml) containing 35% HCl (10 drops) and 10% Pd/C (70 mg) was added. The flask was purged with hydrogen by repeated pumping-filling and the mixture was stirred under an H_2 atmosphere overnight. The catalyst was filtered off, washed with EtOH and filtrate evaporated in vacuo. The residue (58 mg) was dissolved in deionised H_2O (2 ml) and put on the top of a column of Dowex® 50WX8-400 ion-exchange resin [4.6 g, H_2O (5 ml), washed sequentially with H_2O (20 ml)→MeOH (30 ml)→H_2O (20 ml) prior to use]. The column was washed with water to the neutrality (ca. 20 ml) and the product was eluted with 2% NH_4OH solution. Removal of volatiles in vacuo and redissolving the residue in MeOH, addition of two drops of 35% HCl, filtration and evaporation afforded a the

hydrochloride salt of *L-ido* homologue **2** as a colourless oil (44 mg, 82%); $[\alpha]_D^{32} = +20.2$ (*c* 0.42 in MeOH); {lit.:[9f] $[\alpha] = +13.85$ (*c* 0.8 in H_2O) for free base}; δ_H (299.94 MHz, CD_3OD) 1.95–2.05 (2H, m, $J_{6,7} = 5.3$, $J_{5,6} = 6.7$, H-6), 3.25 (1H, d, $J_{1a,1b} = 12.8$, H-1_a), 3.46 (1H, d, $J_{1a,1b} = 13.1$, H-1_b), 3.60-3.71 (1H, 't', $J_{5,6} = 6.4$, H-5), 3.72–3.87 (2H, m, $J_{6,7} = 5.2$, H-7), 3.87–3.92 (1H, 's', H-4), 3.93–4.20 (2H, m, H-2, H-3); δ_C (75.43 MHz, CD_3OD) 32.2 (t, C-6), 47.3 (t, C-1), 55.0 (d, C-5), 59.0 (t, C-7), 67.9, 68.1 (2 d, C-2↔C-3), 70.4 (d, C-4); ν_{max} (film)/cm^{-1} 3800–3000 (bs, OH); *m*/*z* (EI) 177 (M^+–HCl); found: C, 39.56; H, 7.57; N, 6.52, Cl, 16.23, $C_7H_{16}O_4NCl$ requires: C, 39.35; H, 7.55; N, 6.56, Cl, 16.59%.

Acknowledgements

We are grateful to Professor V. Jäger (Stuttgart) for helpful ideas, discussions and support. This research was supported by VW Stiftung (Hannover) and The Slovak Grant Agency. We thank TauChem Ltd (Bratislava) for providing us with carbon monoxide and Dr. Darren J. Dixon (Cambridge) for proof reading and comments.

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