Access to Homoglyconojirimycins via Ring Isomerisation of Pentahydroxylated Azepanes

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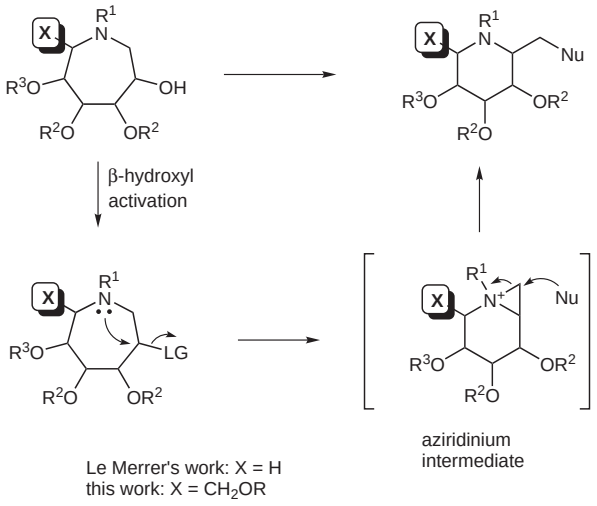
Abstract: *N*-Benzyl pentahydroxyazepanes undergo ring isomerization during mesylation of the hydroxyl group β to the nitrogen via a neighboring nitrogen participation involving a transient aziridinium species which is trapped by chlorine. The resulting chloromethyl tetrahydroxypiperidines have been converted into the corresponding homoglyconojirimycins.

Key words: azasugars, aziridinium, glycosidases, piperidines, ring contractions

Over the years, polyhydroxylated piperidines have attracted a lot of attention from the synthetic community[1] because of their interesting structures and potent biological activities including glycosidase inhibition.[2] More recently, iminosugars have found new therapeutic applications including a nonhormonal approach to male contraception[3] and potential immunosuppressive activity.[4]

Nojirimycin was the first natural piperidine azasugar isolated[5] but its hemiaminal function makes this compound quite unstable. Nature has solved this problem by producing a vast number of chemically stable 1-deoxy derivatives such as deoxynojirimycin[6] and 1-C-derivatives including homoglyconojirimycins,[7] both families displaying strong inhibition on glycosidases. Homoglyconojirimycins are of interest since the presence of an extra methylene group at C-1 improves the selectivities of these piperidines towards glycosidases. Considering the high potential of iminosugars as drug candidates,[8] new routes to homoglyconojirimycins and iminosugar-*C*-glycosides are still needed.[9] Ring expansion of substituted hydroxymethyl pyrrolidines towards piperidines is well documented[10] as is the similar transformation of hydroxymethyl piperidines to azepane and azepine scaffolds.[11] These heterocyclizations involve activation of the hydroxyl group β to the nitrogen, formation of a transient aziridinium species which is subsequently attacked by a nucleophile at the methine carbon to furnish the expanded ring. Ring contraction of activated β-hydroxyazepanes through a similar aziridinium intermediate has only been reported by Le Merrer[12] and Lohray[13] who have used this strategy to generate tetrasubstituted piperidines. These structures lack the important hydroxymethyl group at C-5 and do not closely mimic the parent pyranoside. We report herein a similar approach applied to pentahydroxylated azepanes, which affords six-membered iminosugar *C*-glycosides bearing a hydroxymethyl group at C-5 and a chloromethyl functionality at C-1 ready for further transformation (Scheme 1).



Scheme 1

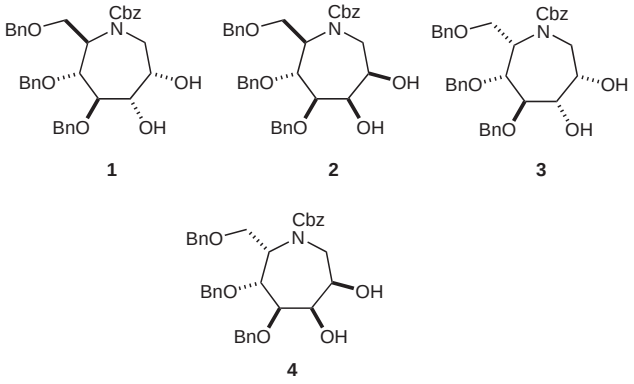


Figure 1

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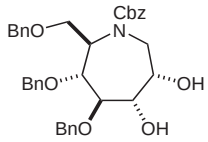
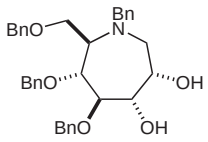
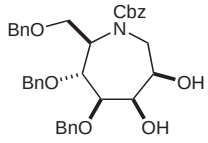
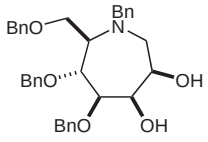
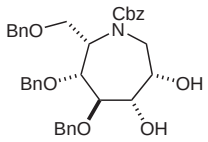
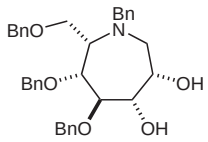
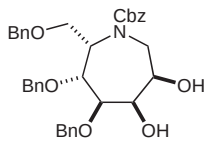
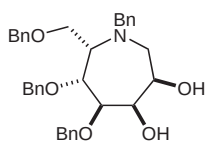
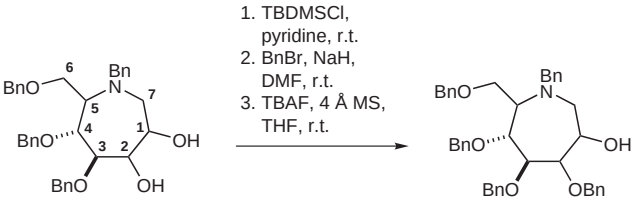
Our group[14] and Dhavale[15] have recently reported the synthesis and the biological evaluation of pentahydroxylated azepanes. During our route, *cis*-dihydroxyazepanes **1**–**4** have been obtained (Figure 1) that constitute useful precursors to generate iminosugar *C*-glycoside derivatives via the ring-contraction strategy described above.

Ring expansion of piperidines towards azepanes has been shown to work well with *N*-benzyl derivatives but not with *N*-tosyl analogues[11e] emphasizing the requirement for a rather nucleophilic endocyclic nitrogen. Conversion of the *Z*-protected azepanes **1**–**4** to the more nucleophilic *N*-benzyl derivatives **5**–**8** was thus needed and we found that hydrogenolysis with Lindlar's catalyst in methanol in the presence of catalytic triethylamine followed by chemoselective N-benzylation of the crude dihydroxyamine with benzyl bromide and potassium carbonate afforded the desired *N*-benzyl *cis*-diols **5**–**8** in good yield (Table 1).

Ring isomerisation of diols **5**–**8** avoiding protection steps was attempted but regioselective activation of the β-hydroxyl group did not take place and only a small amount of the 2-hydroxy chloromethyl piperidines were isolated after tedious column chromatography. Compulsory selective protection of the 2-hydroxyl group in compounds **5**–**8** was achieved as follows. Silylation of the less hindered β-hydroxyl group in azepanes **5**–**8** and benzylation of the remaining free 2-hydroxyl group followed by desilylation with TBAF afforded the desired β-hydroxyazepanes **9**–**12** in satisfactory yield (Scheme 2).

Table 1 Synthesis of *N*-Benzyl *cis*-Diols **5**–**8**

Entry	*N*-Cbz derivative	*N*-Benzyl derivative	Yield (%)
1	 **1**	 **5**	90
2	 **2**	 **6**	89
3	 **3**	 **7**	82
4	 **4**	 **8**	78



5 (1*S*,2*S*,5*R*)
6 (1*R*,2*R*,5*R*)
7 (1*S*,2*S*,5*S*)
8 (1*R*,2*R*,5*S*)

9 (56%)
10 (47%)
11 (37%)
12 (45%)

Scheme 2

The key ring-contraction step was then investigated. When treated with MsCl in dichloromethane in the presence of triethylamine, β-hydroxyazepanes **9**–**12** yielded the desired chloromethyl piperidines **13**–**16** in high yields (Table 2).[16] To confirm that the reaction proceeds with overall retention of configuration as previously observed[12] and to take advantage of these new chloromethyl piperidines, compounds **13**–**16** were converted into the corresponding homoglyconojirimycins. A two-step literature procedure[17] including chlorine displacement by an acetate followed by deacetylation furnished the primary alcohols **17**–**20** in moderate yield (unoptimized). Final hydrogenolysis under acidic conditions quantitatively afforded the chlorohydrates of known α-homonojirimycin (α-HNJ, **21**),[18] β-homomannojirimycin (β-HMJ, **22**),[19] and very recently reported β-L-homoidonojirimycin (**23**) and α-L-homogulonojirimycin (**24**,[20] Table 2). L-homoazasugar **23** was assayed towards a range of commercially available glycosidases and was found to be a poor α-L-fucosidase (15% of inhibition at 1 mM concentration) and β-glucosidase (19% of inhibition at 1 mM concentration) inhibitor.

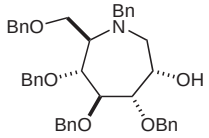
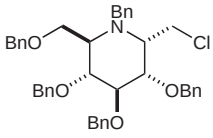
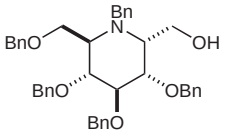
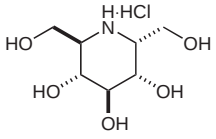
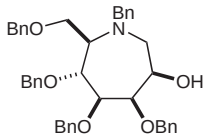
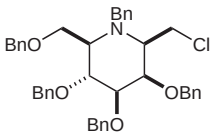
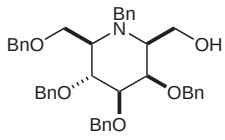
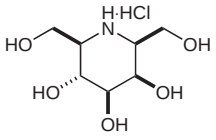
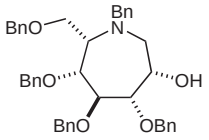
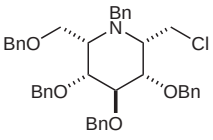
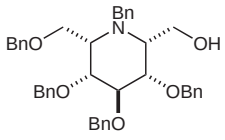
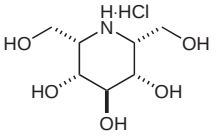
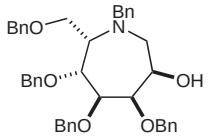
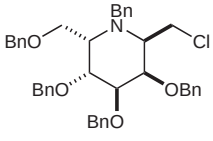
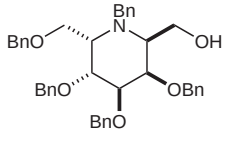
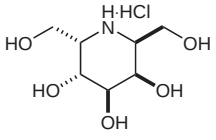
In summary, a general strategy involving activation of the hydroxyl group β to the nitrogen has been applied to a series of *N*-benzyl pentahydroxyazepanes to afford a new set of ring-contracted chloromethyl tetrahydroxypiperidines which are useful 1-*C*-iminosugar precursors. Further manipulation of the chloromethyl moiety furnished the corresponding homoglyconojirimycins. Work is now in progress to explore this strategy with other available azepanes.[21]

Representative Experimental Procedures

Typical Procedure for N-Benzylation of Azepanes

Dihydroxyazepane **1** (218 mg, 0.36 mmol) was dissolved in EtOH (18 mL) and a catalytic amount of Et_3N (24 μL) was added followed by Lindlar's catalyst (218 mg). The reaction vessel was purged from

Table 2 Synthesis of Chloromethyl Piperidines **13**–**16**

Entry	β-Hydroxyazepane	Chloromethyl piperidine	Yield (%)	Hydroxymethyl piperidine	Yield (%)	Homoglyconojirimycin
1	 **9**	 **13**	79	 **17**	51	 **21**
2	 **10**	 **14**	54	 **18**	38	 **22**
3	 **11**	 **15**	86	 **19**	26	 **23**
4	 **12**	 **16**	75	 **20**	39	 **24**

air and filled with H_2. The suspension was stirred under an H_2 atmosphere for 4 h by which time TLC (cyclohexane–EtOAc–HCOOH, 3:2:0.1) showed a complete reaction. The reaction mixture was filtered through a Celite® plug, eluted with MeOH and concentrated to afford the N-deprotected azepane as an oil. This oil was dissolved in a mixture of EtOH–H_2O (7:1, 1 mL) and K_2CO_3 (153 mg, 1.1 mmol) followed by addition of benzyl bromide (55 μL, 0.46 mmol). The reaction mixture was refluxed for 2 h, extracted with CH_2Cl_2, dried with $MgSO_4$ and concentrated. Purification by flash column chromatography (cyclohexane–EtOAc, 5:2) afforded the *N*-benzylazepane **5** (183 mg, 90% yield) as an oil.

Typical Procedure for Ring Contraction of Azepanes

β-Hydroxyazepane **9** (82 mg, 0.128 mmol) was dissolved in dry CH_2Cl_2 (1.2 mL) under argon and the solution was cooled at 0 °C. Then, Et_3N (36 μL, 0.258 mmol) followed by MsCl (15 μL, 0.194 mmol, of a 0.1% v/v solution of MsCl in CH_2Cl_2) were added. The reaction mixture was stirred at 0 °C for 2 h and the solution was concentrated. Purification by flash column chromatography (cyclohexane–EtOAc, 25:1) afforded the corresponding chloromethyl piperidine **13** (67 mg, 0.101 mmol, 79% yield) as an oil.

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