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Polyhydroxylated Piperidines and Azepanes from *D*-Mannitol
Synthesis of 1-Deoxynojirimycin and Analogues

Lydie Poitout, Yves Le Merrer, Jean-Claude Depezay

Université René Descartes. Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, associé au CNRS, 45, rue des Saints-Pères, 75270 Paris cedex 06. France.

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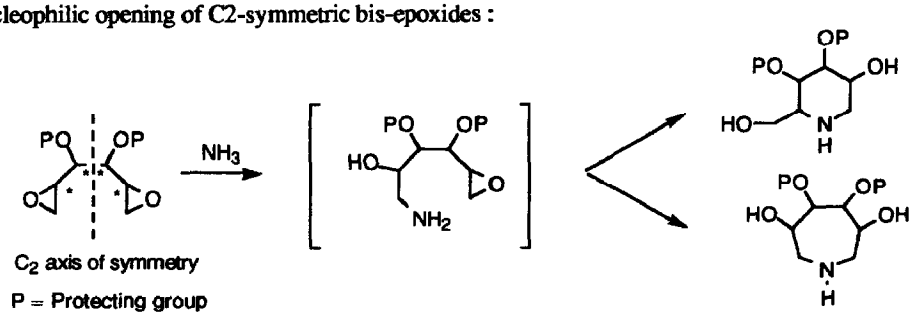
Abstract. *D*-mannitol and *L*-iditol bis-epoxides, easily obtained from *D*-mannitol, are convenient substrates for the synthesis of polyhydroxylated piperidines and azepanes, *via* a nucleophilic opening of one epoxy function followed by a spontaneous intramolecular ring closure. Using this strategy 1-deoxynojirimycin and analogues were prepared.

Many inhibitors of glycosidases[1] are natural or synthetic analogues of pyranoses in which the ring oxygen is replaced by a nitrogen atom and the anomeric hydroxyl group is removed. These azasugars have also potential therapeutic utility in the treatment of various diseases, such as diabetes, cancer and viral infections (especially anti HIV activity).[2] It is thus not surprising that the synthesis of azasugars, such as 1-deoxynojirimycin (1,5-dideoxy-1,5-imino-*D*-glucitol)[3] and its structural analogues have been the subject of extensive synthetic efforts.

Synthetic routes to azasugars, independently of semisynthetic methods employing enzymatic reaction, have commonly entailed azide displacement/reduction and *N*-alkylative cyclization with protecting group manipulations.[3]

We wish to describe here a new approach to the synthesis of enantiopure azasugars that hinges on a double nucleophilic opening of C2-symmetric bis-epoxides :



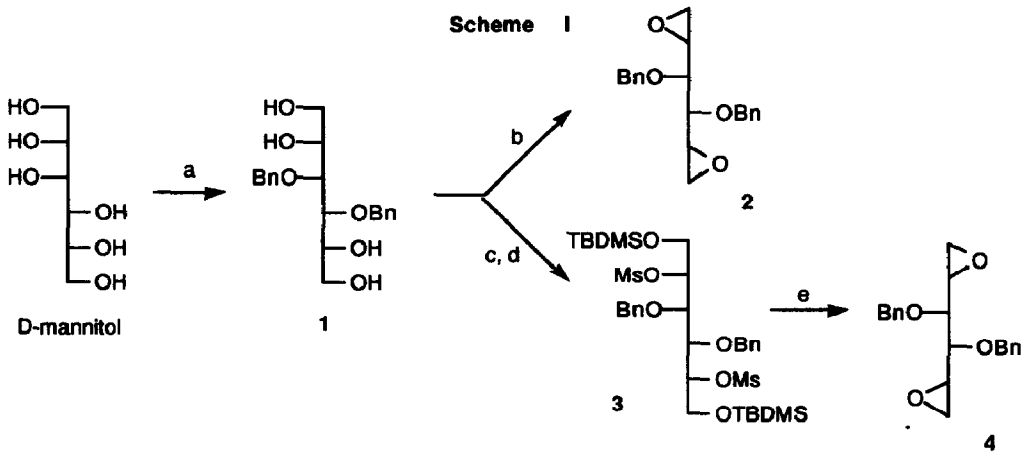
C_2 axis of symmetry

P = Protecting group

Formally this approach involves a regiospecific opening of one epoxy function by ammonia followed by a spontaneous intramolecular ring closure to give piperidine with inversion of configuration at C2 (6-Exo-Tet cyclization)[4] and/or azepane (7-Endo-Tet cyclization).

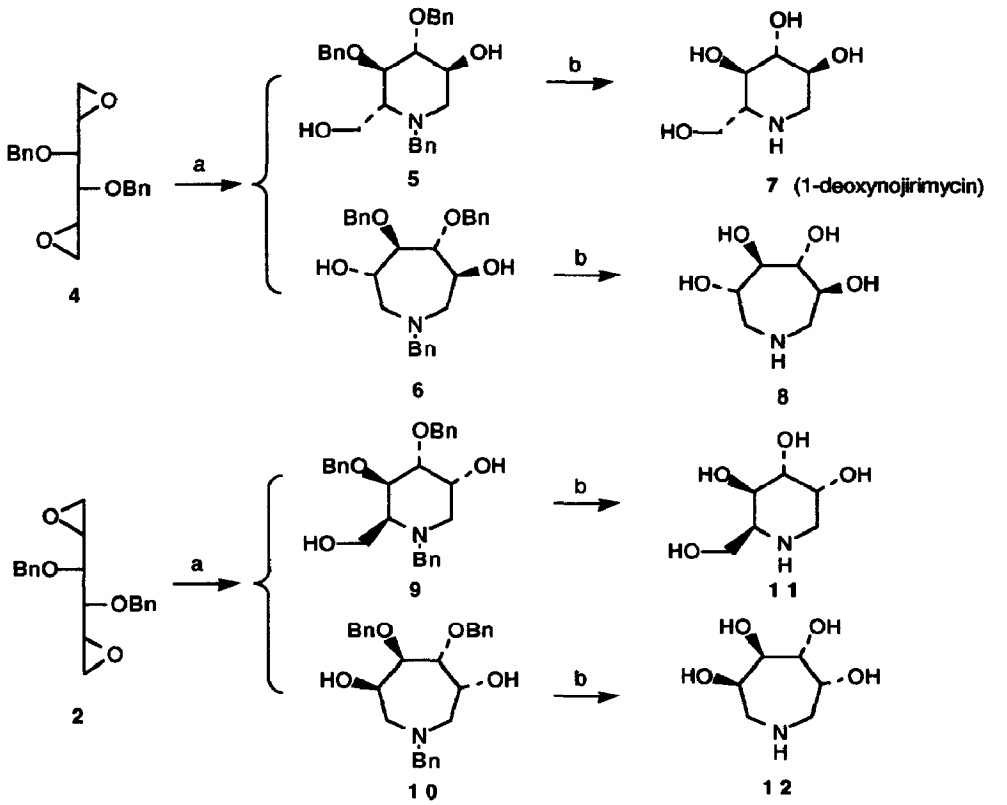
Flexible optically active bis-epoxides with a C2-axis of symmetry were easily obtained from *D*-mannitol according to the reaction sequence depicted in Scheme I. Both bis-epoxides, 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-*D*-mannitol **2** and *L*-iditol **4** were prepared in one and three steps respectively, using 3,4-di-*O*-benzyl-*D*-mannitol **1** as a single common chiral synthon. The preparation, on a multigram scale of the tetrol **1** had already been described[5] in three steps from *D*-mannitol. We transformed the tetrol **1** into bis-epoxide **2** with retention of

Scheme I



(a) i : $Me_2C(OMe)_2$, $SnCl_2$, $(CH_2OMe)_2$, 50%; ii : NaH, BnBr, nBu_4NI, THF; iii : CH_3CO_2H, H_2O, 40°C, 87%, Ref (5). (b) Ph_3P, DIAD, 130°C, 86%. (c) TBDMSCl, imidazole, DMF, 0°C, 80%. (d) MsCl, NEt_3, CH_2Cl_2, 0°C, 98%. (e) HCl, CH_3OH, 20°C then NaOH, H_2O, 20°C, 75%.

Scheme II



(a) $BnNH_2$, see conditions in Table I. (b) H_2, Pd Black, CH_3CO_2H, 15 h, 100%.

configuration at C2 and C5 *via* the Mitsunobu reaction[6] (Ph_3P, DIAD *in vacuo* [α : 0.01 mm] at 130°C for 3 h, followed by flash column chromatography) in 86% yield.

On the other hand, the tetrol **1** afforded the bis-epoxide **4** with inversion of configuration at C2 and C5 in 59% overall yield by the following reactions : selective silylation of the primary alcohol functions (TBDMSCl, imidazole, DMF, 0°C, 80%), mesylation (MsCl, Et_3N, CH_2Cl_2, 0°C, 98%) then removal of the silyl groups of **3** by acid and alkaline treatment of the resultant diol according to a methodology used for a related system.[7]

No epimerization occured during these sequences as confirmed by the absence of diastereoisomer signals in ^1H (250 MHz) or ^{13}C NMR spectra of the compounds **2** and **4**.[8]

In an effort to develop new synthesis of enantiomerically pure azasugars, we have examined the opening of these bis-epoxides by benzylamine under different experimental conditions (Scheme II, Table I). The regiospecific opening of one epoxy function followed by spontaneous 6-exo ring closure was expected to be favored kinetically, according to Baldwin's rules,[4] over the competiting reaction 7-endo ring closure and, be favored also over the substitution at both C1 and C6 by two equivalents of amine.

We have observed that the reaction of bis-epoxide **4** with benzylamine in aprotic medium (entries 1,2) gives mainly the 6-exo adduct, whereas in protic medium (entries 3,4) or in aprotic medium but with Lewis acid (entry 5) gives mainly the 7-endo adduct. Similar results were also observed when these conditions were applied to the bis-epoxide diastereoisomer **2** (compare entries 7 and 8 with entries 1 and 4, respectively). It should be noted that with these conformationally flexible bis-epoxides no significant double terminal addition (C1,C6) was observed, even with a large excess of nucleophile (as solvent, entry 6). A mixture of piperidine and azepane has also been obtained by cyclisation of an aminoepoxide derived from *D*-glucose.[9]

So, the aminocyclization can be directed towards piperidines (**5** and **9** which can be isolated with 45 and 50% yield, respectively) or azepanes (**6** and **10** which can be isolated with 66 and 67% yield, respectively) by selecting the appropriate conditions ($CHCl_3$ reflux or in aqueous solution in presence of buffer benzylammonium-benzylamine).

Table I : Reaction of bis-epoxides **2** and **4** with benzylamine.

Entry	Epoxide	Reaction conditions	Ratio 6-exo/7-endo	Yield (%)[a]
1	**4**	$BnNH_2$ 5eq[b] / $CHCl_3$ / reflux / 48 h	55 / 45	**5** : 45, **6** : 33
2	**4**	$BnNH_2$ 5eq[b] / $PhCH_3$ / reflux / 11 days	55 / 45	**5** : 49, **6** : 39
3	**4**	$BnNH_2$ 3eq[b] / H_2O / 25°C / 48 h	25 / 75	**5** : 19, **6** : 58
4	**4**	$BnNH_2$ 10eq[b] / H_2O / $HClO_4$ 5eq / 25°C / 4 h	12 / 88[c]	**5** : 9, **6** : 66
5	**4**	$BnNH_2$ 2.1eq[b] / CH_3CN / $LiClO_4$ / 25°C / 15 h[d]	20 / 80	**5** : 14, **6** : 54
6	**4**	$BnNH_2$ as solvent / 60°C / 15 h	14 / 86[c]	
7	**2**	$BnNH_2$ 5eq[b] / $CHCl_3$ / reflux / 48 h	55 / 45	**9** : 50, **10** : 45
8	**2**	$BnNH_2$ 10eq[b] / H_2O / $HClO_4$ 5eq / 25°C / 4 h	30 / 70	**9** : 28, **10** : 67

(a) Yield of each isolated compound after flash chromatography separation. (b) Equivalent of benzylamine for one molecule of bis-epoxide. (c) Determined by ^1H NMR (250 MHz). (d) Ref (10).

Hydrogenolytic removal of both *N,O*-benzyl protecting groups using Pd black in acetic acid, gave after purification by ion exchange chromatography the corresponding azasugars (**7-12**) in quantitative yield. ^{13}C NMR spectra of **8** and **12**, as those of **6** and **10**, exhibit only three carbon resonances (regardless of carbon

atoms of benzyl groups in the latter case), thus confirming that it pocesses a C2 axis of symmetry,[11] these compounds have a potential utility as inhibitors of HIV protease.[12] The 1-deoxynojirimycin **7** and azepane analogue **8** were characterized[11] by comparison of their physical properties with those reported in literature.

In summary, this paper indicates a new route to the construction of the nitrogen ring of chiral polyhydroxylated piperidines and azepanes by intramolecular ring closure of bis-epoxides issued from *D*-mannitol. The synthesis of 1-deoxynojirimycin **7** and its azepane analogue **8**, but also those of 1,5-dideoxy-1,5-imino-*L*-gulitol **11** and its azepane analogue **12**, are reported.

Our current efforts involve the utilization of intermediates **5-12** for the preparation of potential AIDS drugs, and the study of the bis-epoxides ring closure by other nucleophiles. The results of that work will be reported in due course.

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7. Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1991**, 56, 1386. Compound **4** has been previously prepared by Portal, M. in our laboratory : thesis, Université Pierre et Marie Curie, Paris, **1993**.
8. Selected physical data of bis-epoxides **2** and **4** :

   2 : $[\alpha]_D$ +5 (c 1.4, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) : 2.60(ABX, J=-5.5, 2.5Hz, H_1), 2.73(ABX, J=-5.5, 4Hz, $H_{1'}$), 3.11(m, H_2), 3.38(m, H_3), 4.66-4.55(AB, OCH_2Ph), 7.26(Ph); ^{13}C NMR ($CDCl_3$) : 46.0(C1), 50.5(C2), 73.4(OCH_2Ph), 78.4(C3), 127.8, 127.9, 128.3, 137.9(Ph).

   4 : $[\alpha]_D$ -43 (c 1.1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) : 2.51(ABX, J=-5, 2.5Hz, H_1), 2.71(ABX, J=-5, 4Hz, $H_{1'}$), 3.19(m, H_2), 3.25(m, H_3), 4.82-4.59(AB, OCH_2Ph), 7,30(Ph); ^{13}C NMR($CDCl_3$) : 43.1(C1), 52.4(C2), 72.3(OCH_2Ph), 80.7(C3), 127.7, 127.9, 128.3, 137.9(Ph).
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11. Selected physical data of azasugars **7**, **8**, **11** and **12** :

    7 : $[\alpha]_D$ +46 (c 0.86, H_2O), Lit[3f] +47 (H_2O); M.p; 194-196°, Lit[3f] 196°; ^1H and ^{13}C NMR are in accord with literature data[3].

    8 : $[\alpha]_D$ +20 (c 0.8, H_2O), Lit[13] +19.9(c 2, H_2O); ^1H NMR (250 MHz, D_2O) : 2.77(dd, J=-14, 7.5Hz, $H_{1'}$), 3.04(dd, J=-14, 3.5Hz, $H_{1'}$), 3.49(dd, J=1.5, 5.5Hz, H_3), 3.7(m, H_2); ^{13}C NMR(D_2O) : 53.6(C1), 74.8, 77.9(C2,3).

    11 : $[\alpha]_D$ +9 (c 0.58, H_2O); ^1H NMR (250 MHz, D_2O) : 2.87(dd, J=-12.5, 11Hz, H_{1a}), 3.05(dd, J= -12.5, 4.5, H_{1e}), 3.20(*br.* t, J=6Hz, H_5), 3.70(t, J=6Hz, $H_{6,6'}$), 3.96(s, $H_{3,4}$), 4.05(ddd, J=11, 4.5, 2Hz, H_2); ^{13}C NMR(D_2O) : 45.7(C1), 57.1(C5), 62.4(C6), 66.6, 70.7, 71.8(C2-4).

    12 : $[\alpha]_D$ -38 (c 0.52, H_2O); M.p.183-185°; ^1H NMR (250 MHz, D_2O) : 2.84(dd, J=-14, 6Hz, H_1), 2.93(dd, J=-14, 3.5Hz, $H_{1'}$), 3.90(s, H_3), 4.05(m, H_2); ^{13}C NMR(D_2O) : 51.1(C1), 73.1, 75.1(C2,3).
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