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Synthesis of Azasugars.[1] Part 2[2]
Isomerization of Polyhydroxylated Azepanes

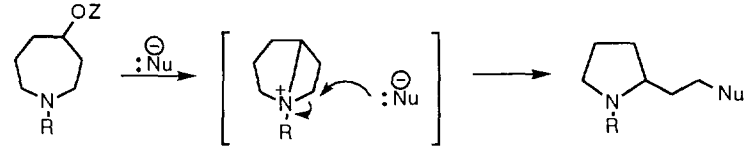
Lydie Poitout, Yves Le Merrer,* Jean-Claude Depezay

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

Key words : Azasugar, azepane, aziridinium, isomerization, (1R-(6*endo*, 7*exo*)-8-oxa-3-azabicyclo [3.2.1]octane-6,7-diol).

Abstract : Isomerization of enantiopure C_2-symmetric 3,5-dihydroxyazepane derivatives has been studied. The neighboring nitrogen participation occurs during mesylation to give a chloromethyl-piperidine, whereas from the L-*ido*-azepane a chiral bridged morpholine structure (1R-(6*endo*, 7*exo*)-8-oxa-3-azabicyclo[3.2.1]octane-6,7-diol) is obtained under Mitsunobu conditions.

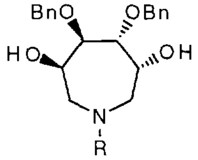
During the course of our ongoing project concerning the sugar-like alkaloids,[2,3] we have been interested in defining conditions which could lead to isomerize the skeleton of C_2-symmetric polyhydroxylated azepanes. To our knowledge, only two reports[4] concerning the skeleton rearrangement of 4-*O*-activated azepanes to 2-substituted pyrrolidines, *via* an azetidinium salt, are described :



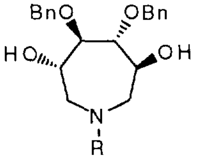
ZO⁻ = good leaving group

It is surprising to note that the corresponding rearrangement of 3-*O*-activated azepanes, *via* an aziridinium salt, has never been studied.

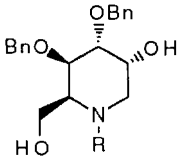
Recently we developped a straightforward synthesis of enantiomerically pure 3,4-di-*O*-benzyl-1,6-dideoxy-1,6-imino-D-mannitol and L-iditol **1** and **2**, and 3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-L-gulitol and D-glucitol **3** and **4**,[3] respectively :



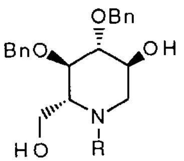
1
(*D*-*manno*-azepane)



2
(*L*-*ido*-azepane)

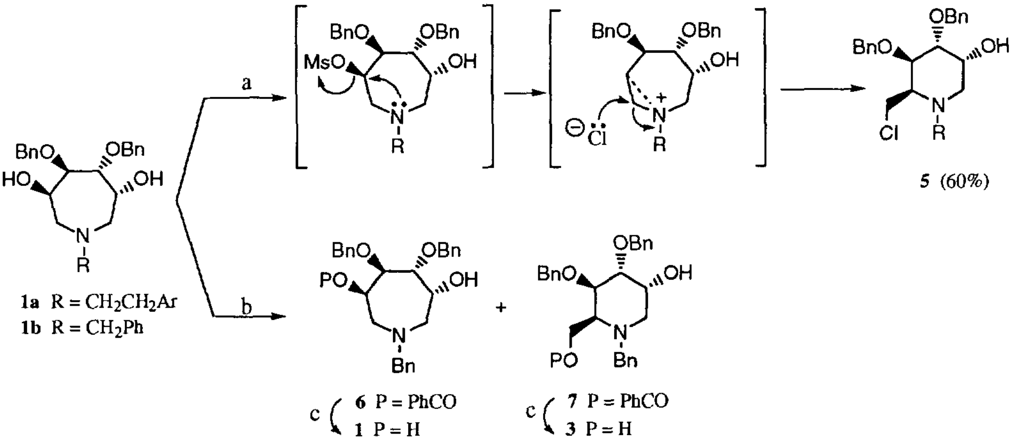


3
(*L*-*gulo*-piperidine)



4
(*D*-*gluco*-piperidine)

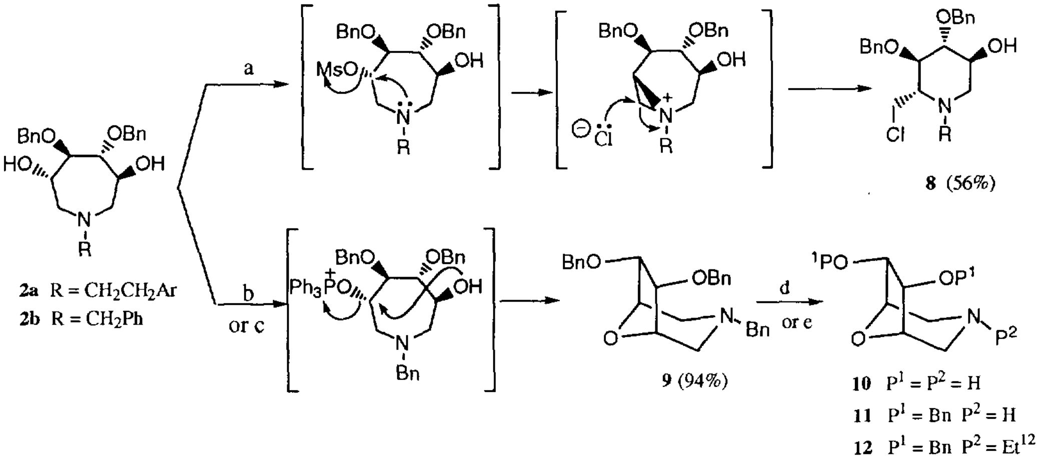
Scheme I[7]



(Ar = 1-*N*-*tert*butyloxycarbonyl-indol-3-yl)[5]

(a) 1.4 eq MsCl, Et_3N, CH_2Cl_2, 0°C, 60%. (b) 1.2 eq. [Ph_3P-DEAD-$PhCO_2H$], THF, 0°C, 64%. (c) MeOH, K_2CO_3

Scheme II[7]



(a) 1.4 eq MsCl, Et_3N, CH_2Cl_2, 0°C, 56%. (b) 1.2 eq. [Ph_3P-DEAD-$PhCO_2H$], THF, 0°C, 80%. (c) 1.2 eq. [Ph_3P-DEAD], THF, 0°C, 94%. (d) H_2, Pd black, then ion exchange chromatography on DOWEX®, 100% of **10**. (e) H_2, 10% Pd/C, EtOH, **11** and **12**, 43 and 55%, respectively.[12]

In the purpose to study an eventual isomerization of the skeleton of C_2-symmetric polyhydroxylated azepanes **1** and **2** (for which R is an alkyl substituted group such as CH_2CH_2Ar,[5] or CH_2Ph), we have performed the hydroxyl-activation either by mesylation, or by transformation into an alkoxyphosphonium salt under Mitsunobu conditions using benzoic acid.[6] In the latter case methanolysis of the resulting benzoate would gave back an alcohol function.

From the D-*manno*-azepane **1** : Treatment of **1a**[5] with mesylchloride (1.4 equiv) in triethylamine at 0°C affords directly the chloromethyl-piperidine **5** which was isolated in 60% yield after flash chromatography. This result shows that the 3-*O*-mesyl-azepane was unstable in these experimental conditions and that proceeds *via* an aziridinium chloride, followed by its nucleophilic opening by chloride ion to give the unique chloromethyl-piperidine. Furthermore reaction of **1b** with 1.2 equiv. of triphenylphosphine-diethylazodicarboxylate-benzoic acid in THF at 0°C (Scheme I)[7] yielded a mixture of two monobenzoyl derivatives **6** and **7** (65%).[8] By methanolysis in presence of K_2CO_3, **6** gave back alcohol **1** (36% after flash chromatography separation), and **7** afforded the piperidine **3** in 24% yield. As above, this result shows that the reaction undergoes *via* an aziridinium intermediate, the nucleophilic opening of which giving rise to the formation of the two isomers **6** and **7**.[9] It is possible that in the latter case the formation of the two products results from a kinetic control; whereas in the former case, two products (chloroazepane and chloromethyl-piperidine) could be initially formed, and the 3-chloroazepane was further converted, *via* the aziridinium ion, to the more stable rearranged product (Cl^- better leaving group than $PhCOO^-$).

From the L-*ido*-azepane **2** : Similar treatment of **2a**[5] with mesylchloride gave the chloromethyl-piperidine **8** in 56% yield. The previous Mitsunobu conditions applied to the azepane **2b** (Scheme II)[7] gave only one product **9**, isolated in 80% yield after flash chromatography. Yield of **9** could be improved up to 94% without benzoic acid.

The chiral bridged morpholine structure of **9** is in agreement with its spectral data (^1H NMR, ^{13}C NMR, MS).[10] Nevertheless, to confirm this structure, we have fully deprotected **9** by hydrogenolysis (H_2, Pd black, AcOH, followed by ion exchange chromatography, quantitative yield) into the known **10**.[11] Due to the unsatisfactory correlation of the optical rotation, and ^1H and ^{13}C NMR data with literature,[12] the compound **9** has been partly hydrogenolyzed to **11** by using 10% Pd/C (43%, unoptimized yield).[13] The structure and the enantiomeric purity of **11** were confirmed by its optical rotation, ^1H and ^{13}C NMR which showed a close analogy with the reported values.[14]

The formation of the bridged compound **9** can be interpreted as an intramolecular displacement of the alkoxyphosphonium intermediate by the other free hydroxyl group of the azepane, concurrently to the evolution towards the aziridinium.

The chiral bridged morpholine [1R-(6*endo*, 7*exo*)-8-oxa-3-azabicyclo[3.2.1]octane-6,7-diol] **10** is an interesting structure, because the *N*-substituted derivatives of 8-oxa-3-azabicyclo[3.2.1]octane possess various biological activities.[15]

In conclusion, the ring contraction of enantiopure C_2-symmetric polyhydroxylated azepanes with mesylchloride gives chloromethyl-piperidines which can be used directly in a chain extension reaction by nucleophilic substitution of the halogen. Further utilization of this methodology in the synthesis of non-peptide mimetics of somatostatin, as well as relevant biological data of the new bicyclic compound with several glycosidases, will be reported in due course.

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References and notes :

1. Part of this work was presented at Journées de Chimie Organique 1995, Palaiseau.
2. Part I : see previous paper in this issue.
3. Poitout, L.; Le Merrer, Y.; Depezay, J-C. *Tetrahedron Lett.* **1994**, *35*, 3293-3296
4. (a) Johnson, P.Y.; Lisak, J. *Tetrahedron Lett.* **1975**, 3801-3802 (b) Sakanow, S.; Haruswa, S.; Yamazaki, N.; Yoneda, R.; Kurhara, T. *Chem. Phar. Bull.* **1990**, *38*, 2981-2985.
5. Compounds **1a** and **2a**, for which R is CH_2CH_2Ar with Ar =1-*N*-*tert*butyloxycarbonyl-indol-3-yl, have been obtained by aminoheterocyclization of 1,2:5,6-dianhydro-3,4-*O*-dibenzyl-D-mannitol and L-iditol with tryptamine, followed by action of di-*tert*butyldicarbonate, according to ref 3. Further utilization of these compounds in the synthesis of non-peptide mimetics of somatostatin will be described elsewhere.
6. (a) Mitsunobu, O. *Synthesis* **1981**, 1-28. (b) Hughes, D.L. *Org. React.* **1992**, *42*, 335-395.
7. All new compounds gave spectral data (^1H NMR, ^{13}C NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.
8. Benzoic acid can be replaced by hydrazoic acid to give a mixture of 3-azidoazepane and azidomethyl-piperidine.
9. For analogous thiepanes rearrangement, see : Fuzier, M.; Le Merrer, Y.; Depezay, J-C. *Tetrahedron Lett.* **1995**, *36*, 6443-6446.
10. Selected physical data of **9** : $[\alpha]_D$ -32 (c 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 7.35-7.10(m, 15H, Ph), 4.63-4.48(m, 4H, OCH_2Ph), 4.32(d, 1H, H_7, $J_{6,7}$ 2.4), 4.23(*br* d, 1H, H_5), 4.16(dd, 1H, H_6, $J_{6,5}$ 6), 4.10(s, 1H, H_1), 3.53-3.44(AB, 2H, NCH_2Ph, J 13), 2.86(d, 1H, H_{4endo}, $J_{4,4'}$ 11.6), 2.65(d, 1H, H_{2endo}, $J_{2,2'}$ 11.2), 2.44(dd, 1H, H_{2exo}), 2.26(dd, 1H, H_{4exo}). ^{13}C NMR (63 MHz, $CDCl_3$) 138.2, 138.1, 138.0, 128.5, 128.3, 128.1, 127.8, 127.7, 127.6, 126.7(Ph), 87.0, 86.3($C_{6,7}$), 79.1, 75.6($C_{1,5}$), 72.6, 71.4(OCH_2Ph), 62.1(NCH_2Ph), 56.0, 51.6($C_{2,4}$).
11. Kilonda, A.; Dequeker, E.; Compernolle, F.; Delbeke, P.; Toppet, S.; Babady-Bila; Hoornaert, G.J. *Tetrahedron* **1995**, *51*, 849-858.
12. $[\alpha]_D$ -30 (c 0.8, MeOH), Lit.[11] $[\alpha]_D$ -4.4 (c 2.3, MeOH). This unsatisfactory correlation was probably due to a different acido-basic species of the product (amine, ammonium). ^1H NMR (250 MHz, CD_3OD) 4.24(d, 1H, H_6, $J_{6,5}$ 6.4), 4.16(*br.* s, 1H, H_7), 4.12(*br.* d, 1H, H_5), 3.79(*br.* s, 1H, H_1), 2.95(*br.* d, 1H, H_4), 2.89(*br.* s, 2H, $H_{2,2'}$), 2.78(d, 1H, $H_{4'}$, $J_{4,4'}$ 13.2). ^{13}C NMR (63 MHz, CD_3OD) 83.6, 82.8, 82.0, 79.2($C_{1,5-7}$), 48.4, 45.6($C_{2,4}$).
13. The *N*-ethyl derivative **12**, which results from alkylation of **11** by the solvent, was also isolated (55% yield).
14. $[\alpha]_D$ -8 (c 0.7, $CHCl_3$), Lit.[11] $[\alpha]_D$ -6.4 (c 0.6, $CHCl_3$). ^1H NMR (250 MHz, C_6D_6) 7.20(m, 10H, Ph), 4.30(m, 4H, OCH_2Ph),4.21(*br* d, 1H, H_6, $J_{6,5}$ 6), 401(*br* s, 2H, $H_{7,5}$), 392(*br* s, 1H, H_1), 2.98(d, 1H, H_{4endo}, $J_{4,4'}$ 13), 2.93(d, 1H, H_{2endo}, $J_{2,2'}$ 13), 2.76(d, 1H, H_{2exo}), 2.32(d, 1H, H_{4exo}). ^{13}C NMR (63 MHz, $CDCl_3$) 137.7, 137.6, 128.4, 127.9(Ph), 86.7, 86.0($C_{6,7}$), 79.2, 76.7($C_{1,5}$), 72.9, 71.4 (OCH_2Ph), 48.3, 45.1($C_{2,4}$).
15. (a) Cope, A.C.; Baxter, W.N. *J. Am. Chem. Soc.* **1955**, *77*, 393. (b) Miller, A.D. *U.S. 3,856,783*, 1974. *Chem. Abstr.* **1975**, *82*, 98010u. (c) Miller, A.D. *U.S. 3,953,596*, 1976. *Chem. Abstr.* **1977**, *7*, 135351g. (d) Hiltemann, R.; Wallweber, H. Hoffmeister, F.H.; Kroneberg, H.G. *Ger. 1,795,848,* 1977. *Chem. Abstr.* **1978**, *88*, 105183g.

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