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A new highly diastereoselective synthesis of *epi*-inositol from D-galactose[1]

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Abstract

The inososе derivative **3** was obtained with high stereoselectivity by intramolecular aldol condensation of the aldohexos-5-ulose derivative **2**, and it was selectively reduced and debenzylated to give *epi*-inositol in high yield. The stereochemistry and the preferred conformations of compounds **3**–**7** were determined through 1D and 2D NMR experiments.

Keywords: intramolecular aldol condensations; carbohydrates; inositols; reduction.

Inositols (hexahydroxycyclohexanes) are an interesting group of carbocyclic sugar analogues which continue to attract a great deal of attention from synthetic chemists[2] because of their various biological activities.[3] Of the nine possible stereoisomers (seven achiral forms and one enantiomeric couple) *myo*-inositol is present in all living organisms and readily available; D- and L-*chiro*-inositols are prepared from the naturally occurring methyl ethers (+)-pinitol and (−)-quebrachitol, respectively.[4] The remaining six inositols are unnatural and many synthetic routes to them have been developed.[5]

Having recently developed a general approach to at least one enantiomer of the four diastereoisomeric aldohexos-5-uloses,[6] we have started a project for their transformation into inositols through an intramolecular aldol cyclization followed by reduction of the intermediate inosose. Although several synthetic approaches to inositols from carbohydrates are based on an aldol-type cyclization step,[2] for instance in the case of the mercury(II)-promoted rearrangement of hex-5-enopyranosides, the so called Ferrier(II) reaction,[2,7] few examples of a direct aldol condensation of a 1,5-dicarbonyl hexose are reported, the most relevant being Kiely's biomimetic synthesis of *myo*-inositol from D-*xylo*-hexos-5-ulose,[8] leading, without isolation and characterization of the intermediate inosose, to a mixture of inositols. This paper reports the results obtained starting from 2,6-di-*O*-benzyl-L-*arabino*-aldohexos-5-ulose (**2**) which leads to a highly stereoselective route (Scheme 1) to *epi*-inositol (**6**), an unnatural and expensive isomer,

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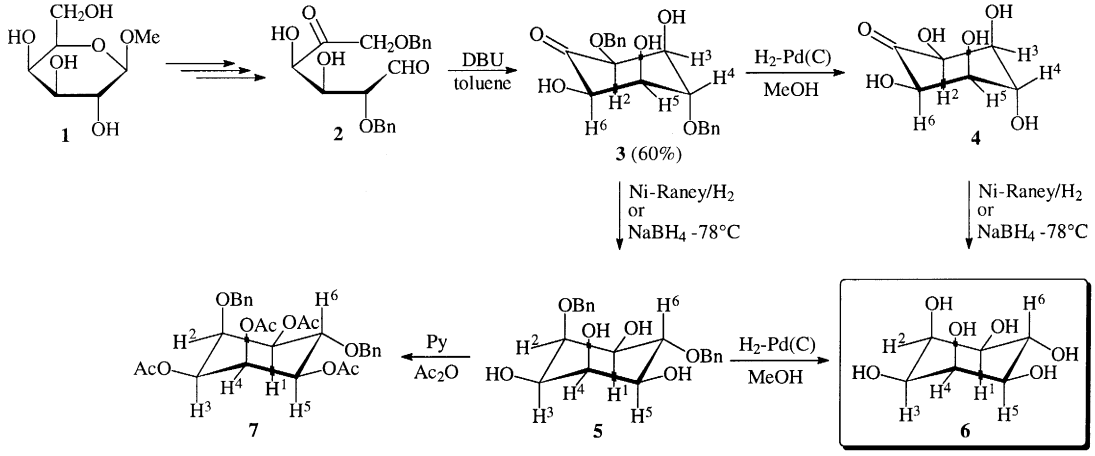
which was previously prepared[5f] in very limited yield starting from *myo*-inositol by inversion of the configuration of one –CHOH group through an oxidation with nitric acid, followed by reduction with sodium amalgam or by catalytic (Pt) hydrogenation.



Scheme 1.

Compound **2** (1.18 mmol), easily obtained from the commercially available methyl β-D-galactopyranoside **1** through a previously described[6a] synthetic route, was treated with DBU (0.16 mmol) in toluene (20 ml) at room temperature; a smooth reaction took place leading, after 6 h, to the complete disappearance of **2** and the formation of a major product (TLC), accompanied only by unidentified products with R_f=0. After neutralization with Amberlyst® 15, flash chromatography of the residue gave 2L-2,4-di-*O*-benzyl-(2,3,5,6/4)-pentahydroxycyclohexanone **3**[9] in 60% yield. The catalytic debenzylation (10% Pd/C in EtOH) of **3** produced quantitatively the previously unreported *meso* inosose **4**.[10] The stereochemistry and the preferred conformer of these two inososes was determined by 1D and 2D (NOE, COSY and HETCOR) NMR experiments; in particular, inosose **4** having a symmetry plane through C-1 and C-4, shows in its ^{1}H NMR spectrum only three signals,[10] likewise its ^{13}C NMR spectrum shows signals at 68.97, 74.13 and 79.20 ppm together with the signal for the carbonyl group (208.84 ppm). Furthermore, the *J* values (3.4 and 4 Hz) of H-2(6), H-3(5) and H-4 establish that the preferred conformer has three axial hydroxyl groups. The inosose **3** had the same conformational situation as evidenced by the analogous values of the vicinal protonic coupling constants and by the presence of long-range couplings between H-2 and H-6 (*J*=1.3 Hz) and H-3 and H-5 (*J*=2.3 Hz).

The *cis*-axial/equatorial disposition of the oxygenated substituents of the two new chiral centres of **3**, point to a kinetically controlled aldol condensation, that could be ascribed to the preferred conformation of the intermediate chiral enolate and of the following ring closure transition state. When the aldol condensation was carried out with 0.005 M NaOH in aqueous methanol the formation of **3** was not stereospecific, a second inosose being formed as minor product (ratio of about 2:1, overall yield of 70%), thus indicating that the solvent and/or the base promoter play a specific role in the stereochemical outcome of the reaction. The structure of the second inosose is under investigation.

Inosose **3** was then selectively reduced both by catalytic hydrogenation (Ni–Raney/H_2 40 psi, EtOH, rt 12 h; 92% yield) and with hydride ($NaBH_4$, MeOH, −78°C 1 h; 90% yield) to give, exclusively, the *epi*-inositol derivative **5**[11] deriving from the attack of hydrogen or hydride on the less hindered side of the ketone. The structure of **5** was unequivocally proven by the NMR data of its 1,2,3,5-tetraacetate **7**[12] where the H-6 proton appears as a double doublet (4.46 ppm) with a large $J_{ax/ax}$ (9.61 Hz) coupling with the adjacent H-1 and H-5 protons; the H-5 proton (5.17 ppm) shows a small $J_{ax/eq}$ because it couples with

the H-4 proton (3.30 Hz) as in the case of the H-3 proton (5.04 ppm), which has a small $J_{ax/eq}$ coupling with the H-2 (3.23 Hz) and H-4 (3.10 Hz) protons.

Finally, *epi*-inositol **6**[13] was obtained in nearly quantitative yields by catalytic debenzylation of inositol derivative **5**, or by reduction of inosose **4**. The structure of *epi*-inositol **6** was confirmed by a comparison of its analytical and spectroscopic data with those reported in the literature.[14]

In conclusion, our synthetic strategy offers a simple method to synthesize *epi*-inositol in a highly stereoselective way and with a good chemical yield, by means of a process which leads to a single stereoisomer, although it involves the formation of three new chiral centres. We are now engaged in a program aimed at extending this synthetic scheme to other diastereoisomeric aldohexos-5-uloses, with various kinds of functionalities, with the scope of establishing a general route to the biologically interesting cyclitols, starting from readily available D-galactose derivatives.

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9. 2L-2,4-Di-*O*-benzyl-(2,3,5,6/4)-pentahydroxycyclohexanone **3**: yield 60%, m.p. 110–112°C, white crystals from ethyl acetate (found: C, 67.22; H, 6.44. $C_{20}H_{22}O_6$ requires: C, 67.03; H, 6.29%); $[\alpha]_D^{25}$ −69.23 (*c* 0.26, $CHCl_3$); ν_{max} (KBr) 3473, 3452, 3380, 1724, 1625 cm^{-1}; δ_H (CD_3CN, 500 MHz) 4.06 (dd, 1H, $J_{3,4}$=3.1, $J_{4,5}$=3.2 Hz, H-4), 4.46 (ddd, 1H, $J_{5,6}$=4.3, $J_{3,5}$=2.3 Hz, H-5), 4.53 (1H, dd, $J_{2,3}$=3.4, $J_{2,6}$=1.3 Hz, H-2), 4.55 (ddd, 1H, H-3), 4.58 (dd, 1H, H-6), 4.56 and 4.83 (AB system, 2H, J_{AB}=12 Hz, benzylic CH_2), 4.68 and 4.77 (AB system, 2H, J_{AB}=11.5 Hz, benzylic CH_2), 7.37–7,46 (m, 10H, phenyl H); δ_C (CD_3CN, 125 MHz) 72.58 (CH_2), 73.25 (CH_2), 75.96 (C-6), 76.75 (C-3), 76.85 (C-4), 77.46 (C-5), 81.63 (C-2), 126.65–139.07 (phenyl C), 207.52 (C=O).

10. 2,3,5,6/4-Pentahydroxycyclohexanone **4**: yield 96%, m.p. 118–120°C, white crystals from ethanol (found: C, 40.47; H, 5.71. $C_6H_{10}O_6$ requires: C, 40.43; H, 5.66%); ν_{max} (KBr) 3351, 2924, 1728, 1629 cm^{-1}; δ_H (DMSO-d_6/D_2O 200 MHz) 3.96 (dd, 1H, spl. ≅3.4 and 4.0 Hz), 4.09 (dd, 2H, spl. ≅3.4 and 4.0 Hz), 4.43 (d, 2H, spl. ≅4.0 Hz); δ_C (DMSO-d_6 50 MHz) 68.97, 74.13 (2×), 79.20 (2×) and 208.84 (C=O).
11. 1D-2,6-Di-*O*-benzyl-*epi*-inositol **5**: yield 92%, m.p. 178–180°C, white crystals from ethyl acetate (found: C, 66.73; H, 6.66. $C_{20}H_{24}O_6$ requires: C, 66.65; H, 6.71%); $[\alpha]_D^{25}$ −271.85 (*c* 0.94, $CHCl_3$); ν_{max} (KBr) 3390, 2922, 1642, 1451 cm^{-1}.
12. 1D-1,3,4,5-Tetraacetyl-2,6-di-*O*-benzyl-*epi*-inositol **7**: yield 98%, syrup (found: C, 63.70; H, 6.18. $C_{28}H_{32}O_{10}$ requires: C, 63.63; H, 6.10%); $[\alpha]_D^{25}$ −6.23 (*c* 0.96, $CHCl_3$); ν_{max} (NaCl) 3478, 2924, 2890, 1739 cm^{-1}; δ_H (C_6D_6, 200 MHz) 1.83 (s, 3H, CH_3), 1.70 (s, 6H, CH_3), 1.67 (s, 3H, CH_3), 4.16 (ddd, 1H, $J_{1,2}$=3.23, $J_{2,3}$=3.1, $J_{2,4}$=1.2 Hz, H-2), 4.46 (dd, 1H, $J_{1,6}$=9.6, $J_{5,6}$=9.6 Hz, H-6), 4.54 (s, 2H, CH_2), 4.61 (s, 2H, CH_2), 5.04 (dd, 1H, $J_{3,4}$=3.3, Hz, H-3), 5.17 (dd, 1H, H-1) 5.33 (dd, 1H, $J_{4,5}$=3.5 Hz, H-5), 5.92 (ddd, 1H, H-4), 7.05–7.40 (m, 10H, phenyl H); δ_C (C_6D_6, 50 MHz) 20.62 (CH_3), 20.51 (CH_3), 20.34 (CH_3 ×2), 68.97 (C-3), 69.52 (C-4), 70.82 (C-5), 73.02 (C-1), 74.89 (CH_2), 75.12 (CH_2), 75.72 (C-6), 77.08 (C-2), 139.16–139.28 (phenyl C), 169.13, 169.24, 169.57, 170.10 (C=O).
13. *epi*-Inositol **6**: yield 95%, m.p. 280–282°C, white crystals from ethanol (lit.[5f] 285°C); ν_{max} (KBr) 3410, 3220, 2950, 1638 cm^{-1}. ^{13}C NMR data identical to those previously reported.[14]
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