Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 3313–3315

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Intramolecular Aldol Cyclization of L-*lyxo*-Hexos-5-ulose Derivatives: A New Diastereoselective Synthesis of D-*chiro*-Inositol†

Giorgio Catelani,[a,*] Antonino Corsaro,[b] Felicia D'Andrea,[a] Manuela Mariani[a] and Venerando Pistarà[b]

[a]*Dipartimento di Chimica Bioorganica e Biofarmacia, Università degli Studi di Pisa, Via Bonanno, 33, I-56126 Pisa, Italy*
[b]*Dipartimento di Scienze Chimiche, Università degli Studi di Catania, Viale A. Doria, I-95125 Catania, Italy*

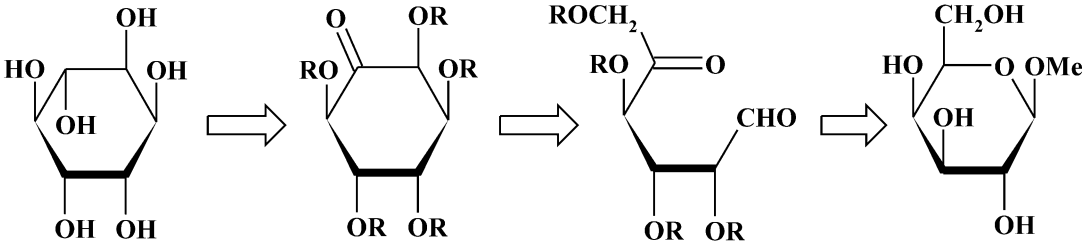
Received 10 May 2002; revised 6 August 2002; accepted 14 August 2002

Dedicated to the memory of Professor Serena Catalano

Abstract—The DBU-promoted intramolecular aldol condensation of two partially protected L-*lyxo*-hexos-5-ulose derivatives (**8** and **9**), in turn obtained starting from methyl β-D-galactopyranoside, takes place with fairly good yield and complete diastereoselectivity to give 2L-(2,3,6/4,5)-pentahydroxycyclohexanone derivatives, **10** and **11**. The stereoselective reduction of inosose **10** with sodium triacetoxyborohydride leads, after catalytic debenzylation, to D-*chiro*-inositol (**1**), while the sodium borohydride reduction furnishes, with opposite stereoselectivity, a derivative of *allo*-inositol.

D-*chiro*- (**1**) and L-*chiro*-inositol, the sole couple of optically active members of the inositol family, have attracted a great deal of attention because of their biological interest.[1] The potentiality of D-*chiro*-inositol (**1**) in the treatment of polycystic ovary syndrome[2] has been recognized. 1L-*chiro*-Inositol 2,3,5-triphosphate was postulated to act as an inhibitor of the enzymes involved on the 1D-*myo*-inositol 1,4,5-triphosphate metabolism.[3]

Although D-*chiro*-inositol (**1**) is available from natural sources as the antibiotic kasugamycin[4] or the 4-*O*-methyl ether, (+)-pinitol, a component of the sugar pine extracts,[5] several chemical or chemo-enzymatic synthetic efforts have been made, using, with different efficiency, a broad range of starting materials. The most exploited synthetic ways include: (a) the stereoselective epimerization of readily available *myo*-inositol,[6] (b) the Ferrier-II reaction of hex-5-enopyranosides,[7] (c) the



1 **2** **3** **4**

Scheme 1.

†Part 16 of the series: Chemical Valorization of Milk-Derived Sugars. This series title replaces the previous one: Rare and Complex Saccharides from D-Galactose and Other Milk-Derived Sugars. For part 15, see ref 21.

*Corresponding author. Tel.: +39-050-44074; fax: +39-050-43321; e-mail: giocate@farm.unipi.it

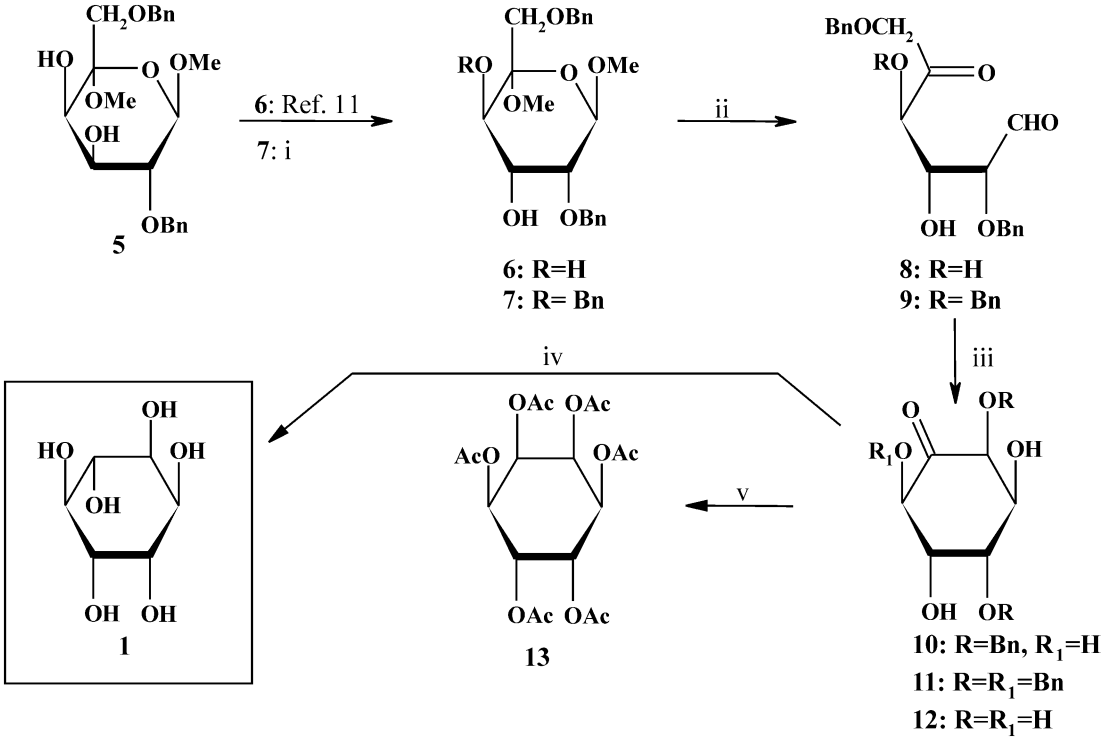
0960-894X/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(02)00692-3

enantio- and regioselective functionalization of cyclohexene[8] or halobenzenes.[9] In this context, we have been attracted by the routes involving as the final step a diastereoselective hydride reduction of an appropriately protected β-hydroxyinososse,[7a,9] owing to our recent findings on the highly diastereoselective preparation of such types of intermediates through a base-promoted intramolecular aldol cyclization of hexos-5-ulose derivatives.[10] We have, thus, developed the idea retrosynthetically depicted in Scheme 1, that, starting from methyl β-D-galactopyranoside (**4**) provides the preparation of L-*lyxo*-hexos-5-ulose derivatives **3**,[11] their intramolecular aldol condensation to inososes **2** and, finally, their stereoselective reduction followed by deprotection to **1**.

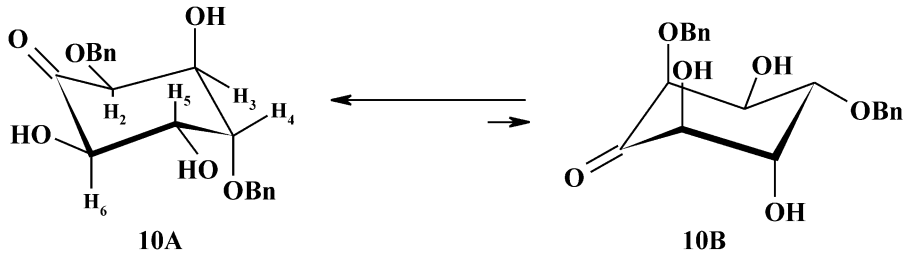
The starting material of our synthesis (Scheme 2) was the 1,5-bis-methyl glycoside **5**,[12] masked form of 2,6-di-*O*-benzyl-L-*arabino*-hexos-5-ulose recently[10] used for the diastereoselective preparation of *epi*-inositol. The preparation of two hexos-5-uloses of the L-*lyxo* series, **8**[11] and **9** was achieved by acid hydrolysis of the bis-glycosides **6** and **7**, respectively, in turn obtained by epimerization through a sequence of oxidation and stereoselective reduction[13] of the 4-*O*-acetate or the 4-*O*-benzyl ether of **5**.[14] The treatment of crude **8** and **9** with a catalytic amount of DBU in toluene–CH_2Cl_2 at 0 °C gave with high diastereoselectivity the β-hydroxy-inososes **10** and **11**, obtained pure[15] through flash chromatography with 67 and 58% isolated yield over two steps from **6** and **7**, respectively. Furthermore, their structure was confirmed by transformation into the known inosose **12**,[9] through catalytic debenzylation [H_2–Pd(C)/MeOH]. Interestingly, the stereochemical course of the intramolecular aldol condensation of **8** and **9** is identical to that we previously found for the same reaction of 2,6-di-*O*-benzyl-L-*arabino*-hexos-5-ulose,[10] the two new stereogenic centres being formed in a *cis* orientation each other and *trans* with respect to the substituent of the contiguous stereocentre (C-2 of the parent dicarbonyl precursor).

The treatment of inosose **10** with $NaBH_4$ in EtOH at −78 °C gave with good yields (78%) a crude product constituted by a main component, which, after catalytic debenzylation [H_2–Pd(C)/MeOH] and subsequent acetylation (Ac_2O/Py), led to the previously reported[16] hexa-*O*-acetyl *allo*-inositol (**13**). The high stereoselectivity of this reaction, close to that previously found[10] for the same reaction of the C-5 epimeric inosose, is in accordance with the prevalence of the steric effects in the reductions with $NaBH_4$, the hydride attack being inferred from the α face, *anti* to the substituents at the two contigous carbons.

The stereochemical course of the inosose reductions could be, however, inverted using reagents able to give intramolecular hydride delivery,[17] taking advantage from the presence of a free β-hydroxy substituent. Although in our case the presence of two free β-hydroxy groups having an opposite relative orientation (OH-3 and OH-5) could not ensure a firm prevision of the steric course of the reaction, **10** was treated with $NaBH(OAc)_3$ under standard conditions,[7a,17] (room temp, CH_3CN and AcOH). A smooth reduction took place giving, after 45 min, a crude product (about 95%) containing a sole di-*O*-benzyl inositol, which was subjected to catalytic debenzylation [H_2–Pd(C)/MeOH,



Scheme 2. Reagents and conditions: (1) (a) BnBr–NaH/DMF; (b) TPAP–NMO/CH_2Cl_2; (c) $NaBH_4$/MeOH; (ii) CF_3COOH–H_2O/CH_3CN; (iii) DBU/$C_6H_5CH_3$–CH_2Cl_2; (iv) (a) $NaBH(OAc)_3$–AcOH/CH_3CN; (b) H_2–Pd(C)/MeOH; (v) (a) $NaBH_4$/EtOH; (b) H_2–Pd(C)/MeOH; (c) Ac_2O/Py.



Scheme 3.

90%] to give the known,[4–9] completely deprotected D-*chiro*-inositol (**1**).

A tentative explanation of this satisfactory result could take in account the conformational features of inosose **10**. A high preference of the conformation **10A** (Scheme 3) could be anticipated on the basis of the presence of an unfavourable 1,3-*syn*-diaxial interaction between a benzyloxy and a hydroxy group in the alternative conformation **10B**. Furthermore, NMR[18] analysis confirms this hypothesis, as evidenced by the presence of a long-range coupling between the two α hydrogens ($J_{2,6}=1.4$ Hz) which, owing to the high vicinal coupling constant of one of them ($J_{5,6}=9.9$ Hz), may necessarily be both axially oriented, as it is in the conformation **10A**. The internal hydride transfer involves, thus, an intermediate having a β-alkoxydiacetoxyborohydride group axially oriented in position 3 and, for these reasons, it is directed on the β face, leading to the observed diastereoselectivity.

A final point of interest arising from our approach is the possible extension of the same intramolecular carbacyclization-stereoselective reduction sequence to hexos-5-uloses of the D-*lyxo* series available from recent literature reports,[19,20] opening the way to an effective synthesis of biologically relevant L-*chiro*-inositol. Our next synthetic efforts will be directed in this direction.

Acknowledgements

This work was performed with funds provided by Consorzio Interuniversitario Nazionale 'La Chimica per l'Ambiente' within the project 'Ambiente Terrestre: Chimica per l'Ambiente' financed by M.U.R.S.T. in accordance with Law no. 488/92. Partial support to G.C. from University of Pisa and M.U.R.S.T. is also acknowledged.

References and Notes

1. Berridge, M. J. *Nature* **1989**, *341*, 197. Billington, D. C. *The Inositols Phosphates—Chemical Synthesis and Biological Significance*; VCH: Weinheim, 1993.
2. Nestler, J. E.; Jakubowicz, D. J.; Reamer, P.; Gunn, R. D.; Allan, G. J. *N. Engl. J. Med.* **1999**, *340*, 1314.
3. Liu, C.; Nahorski, S. R.; Potter, B. V. L. *Carbohydr. Res.* **1992**, *234*, 107.
4. Umezawa, H.; Okami, Y.; Hashimoto, T.; Suhara, Y.; Hamada, M.; Takeuchi, T. *J. Antibiot. (Tokyo) Ser. A* **1965**, *18*, 101.
5. Anderson, A. B. *Ind. Eng. Chem.* **1953**, 593.
6. (a) Takahashi, Y.; Nakayama, H.; Katagiri, K.; Ichikawa, K.; Ito, N.; Takita, T.; Takeuchi, T.; Miyake, T. *Tetrahedron Lett.* **2001**, *42*, 1053. (b) Chung, S.-K.; Kwon, Y.-U. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2135. (c) Berlin, W. K.; Zhang, W.-S.; Shen, T. Y. *Tetrahedron* **1991**, *47*, 1.
7. (a) Takahashi, H.; Kittaka, H.; Ikegami, S. *J. Org. Chem.* **2001**, *66*, 2705. (b) Jaramillo, C.; Chiara, J.-L.; Martin-Lomas, M. *J. Org. Chem.* **1994**, *59*, 3135.
8. Kim, K. S.; Park, J. I.; Moon, H. K.; Yi, H. *Chem. Commun.* **1998**, 1945.
9. (a) Mandel, M.; Hudlicky, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 741. (b) Mandel, M.; Hudlicky, T. *J. Org. Chem.* **1993**, *58*, 2331.
10. Pistarà, V.; Barili, P. L.; Catelani, G.; Corsaro, A.; D'Andrea, F.; Fisichella, S. *Tetrahedron Lett.* **2000**, *41*, 3253.
11. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; De Rensis, F.; Goracci, G. *J. Carbohydr. Chem.* **1998**, *17*, 1167.
12. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F. *Gazz. Chim. Ital.* **1992**, *122*, 135.
13. The stereoselectivity of the reductions of the 3-ulose intermediates was very high, if not complete. A discussion of this point will be given in the full paper.
14. The 4-*O*-acetate of **5** was obtained, as previously reported,[11] by acid hydrolysis (aq AcOH) of orthoester intermediates, while the 4-*O*-benzyl ether was formed in high yield (80%) by direct benzylation of **5** with 1 equiv of benzyl bromide either with NaH–DMF or KOH/18-crown-6/THF.
15. All new compounds have been fully characterized with satisfactory elemental analyses and through analysis of routine mono- and bi-dimensional NMR spectra.
16. Motherwell, W. B.; Williams, A. S. *Angew. Chem. I.E.E.* **1995**, *34*, 2031.
17. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
18. 2,4-Di-*O*-benzyl-2L-(2,3,6/4,5)-pentahydroxycyclohexanone (**10**): mp 89–91 °C (EtOAc–hexane); $[\alpha]_D^{25}=+15.1$ (*c* 0.96, $CHCl_3$); selected NMR data (CD_3CN): δ_H (200 MHz): 4.42 (dd, 1H, $J_{2,3}=3.4$ Hz, H-2), 4.30 (dd, 1H, $J_{3,4}=4.0$ Hz, H-3), 4.29 (dd, 1H, $J_{5,6}=9.9$ Hz, $J_{2,6}=1.4$ Hz, H-6), 3.90 (dd, 1H, $J_{4,5}=3.3$ Hz, H-4), 3.78 (dd, 1H, H-5); δ_C (50 MHz): 206.39 (C-1), 80.91 (C-2), 79.64 (C-4), 77.60 (C-6), 75.46 (C-5), 71.56 (C-3).
19. Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L. *Tetrahedron Lett.* **1998**, *39*, 2021.
20. O'Brien, J. L.; Tosin, M.; Murphy, P. V. *Org. Lett.* **2001**, *3*, 3353.
21. Attolino, E.; Catelani, G.; D'Andrea, F.; Puccioni, L. *Carbohydr. Res.* **2002**, *337*, 991.