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A Versatile Route to L-Hexoses: Synthesis of L-Mannose and L-Altrose

Annalisa Guaragna,* Carmela Napolitano, Daniele D'Alonzo, Silvana Pedatella, and Giovanni Palumbo

Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, via Cynthia, 4 I-80126 Napoli, Italy

guaragna@unina.it

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ABSTRACT

An efficient route for the synthesis of orthogonally protected L-sugars has been opened up, starting from the heterocyclic homologating agent 1 and 2,3-*O*-isopropylidene-L-glyceraldehyde (2). Our synthetic path enables the synthesis of a 2,3-unsaturated-L-pyranoside, which can be suitably functionalized to afford the desired L-hexoses. In this paper, we report the synthesis of L-*manno*- and L-*altro*-pyranosides. Moreover, this strategy may be used to prepare all eight sugars and their derivatives in either enantiomeric form.

The rare L-sugars[1] are valuable compounds as precursors in the synthesis of various chemicals and also as agents in a wide range of crucial biological events. Although much less common in nature than their D-counterparts, L-hexoses (in their pyranosidic form) are key components of numerous bioactive[2] oligosaccharides, antibiotics, glycopeptides, and terpene glycosides, as well as of steroid glycosides and other clinically useful agents such as heparin.[3] Some remarkable examples are L-gulopyranoside-containing compounds such as the antitumor drug Bleomycin A_2[4] and the nucleoside antibiotic Adenomycin.[5] Moreover, L-altrose is a typical constituent of the extracellular polysaccharides from *Butyrivibrio fibrisolvens* strain CF3,[6] and L-mannose has been found in some steroidal glycosides.[7] Its phenolic derivatives are potent substrates for measuring the α-L-mannosidase activity of commercial naringinase[8] (Figure 1).

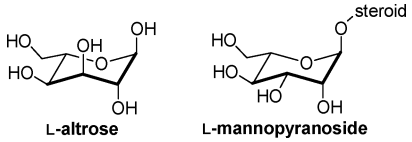

Figure 1. Bioactive L-sugars.

Not all L-hexoses are commercially available; this fact, together with the practical difficulties in obtaining these compounds from natural sources, has led chemists to develop new, general, and convenient methods for their production.

Numerous approaches to L-pyranose preparation have been reported, including homologation of shorter-chain sugars,[9] epimerization of readily available D-sugars,[10] and de novo syntheses.[11]

* Corresponding author. Phone: + 39 081 674 118. Fax: + 39 081 674 119.

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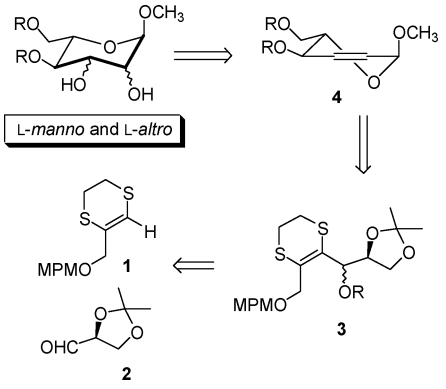
As part of our efforts working toward the synthesis of bioactive polyhydroxylated compounds, we have explored a general and efficient route for the preparation of L-hexoses (as well as their D-enantiomers) starting from L-glyceraldehyde and the three-carbon homologating agent **1** (Scheme 1). The latter has recently been employed in a versatile

Scheme 1. Retrosynthetic Path



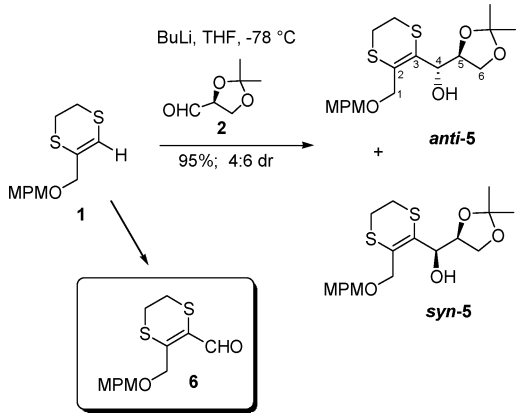
procedure to prepare both 4-deoxy-hexopyranoses[12] and 1-deoxy-iminosugars[13] belonging to the D- or L-series.

In this preliminary communication, we describe the preparation of orthogonally protected L-altro- and L-manno-pyranosides in enantiomerically pure form, testing, at the same time, the breadth of our methodology.

As shown in the retrosynthetic path (Scheme 1), our strategy comprises the following major steps: (i) preparation of **3** by a three-carbon homologation reaction, employing the heterocyclic system **1** and the well-known[14] 2,3-*O*-isopropylidene-L-glyceraldehyde (**2**); (ii) synthesis of the 2,3-unsaturated pyranoside **4** by carbon skeleton cyclization; (iii) suitable double-bond functionalization by stereoselective dihydroxylation of **4**.

The synthesis started with the coupling reaction of **1**, prepared in a few steps from methyl pyruvate,[15] with the protected aldehyde **2** to obtain a diastereoisomeric mixture of secondary alcohols **5** (Scheme 2). Oddly, our first attempts

Scheme 2. Three-Carbon Homologation



at using Ti(*O*-*i*-Pr)$_4$ as the catalyst[16] led only to the formation of a small amount of the desired alcohols; in fact, once formed, **5** readily changed, almost quantitatively and even at low temperature, into the unexpected aldehyde **6**.[17]

On the contrary, in the absence of catalysts, this side reaction proceeded much more slowly and the alcohols **5** were obtained in an excellent yield (95%) and in an anti/syn 4:6 diastereomeric ratio.[18] The slight preference for the syn compound is consistent with a nonchelation-controlled reaction[19] according to the Felkin−Anh model prediction (Figure 2).

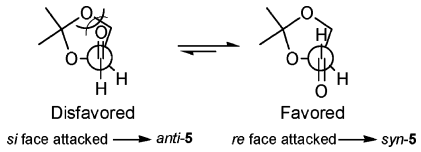


Figure 2. Felkin−Ahn models for the aldehyde **2**.

After mixture separation by SiO_2 flash chromatography, the *anti*-**5** diastereoisomer was chosen as a model to test the whole synthetic path. Benzylation of the secondary hydroxyl function, treating *anti*-**5** with NaH and BnBr, afforded **7** in almost quantitative yield (Scheme 3). Interestingly, if the reaction was carried out in the presence of an excess of NaH, the formation of an unexpected byproduct **8** in 20% yield[20] was observed besides the benzylated product **7** (65%).

4-Methoxybenzyl protecting group removal was next attempted by treating **7** with DDQ (1.2 equiv) in CH_2Cl_2/

(9) Some recent examples of homologation of shorter-chain sugars: (a) Takahashi, S.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 607−612. (b) Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1997**, *62*, 6261−6267. (c) Lubineau, A.; Gavard, O.; Alais, J.; Bonnaffé, D. *Tetrahedron Lett.* **2000**, *41*, 307−311. (d) Ermolenko, L.; Sasaki, N. A. *J. Org. Chem.* **2006**, *71*, 693−703.

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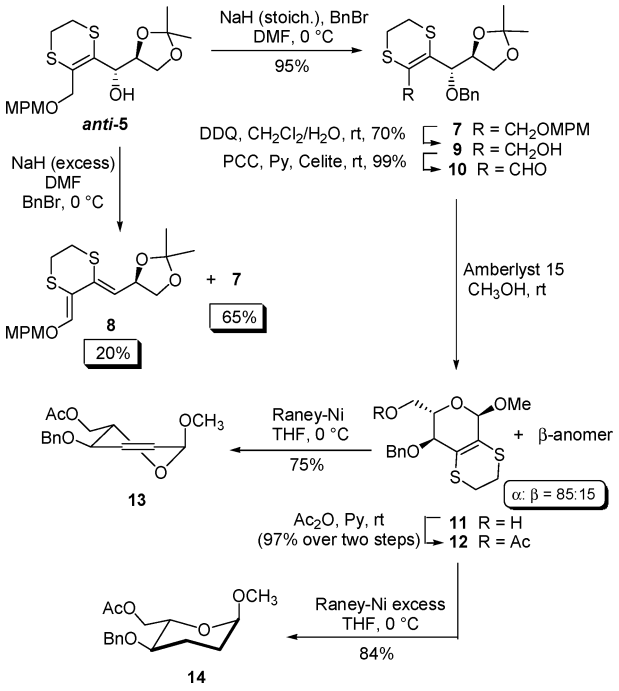
(15) Caputo, R.; Guaragna, A.; Palumbo, G.; Pedatella, S. *J. Org. Chem.* **1997**, *62*, 9369−9371.

(16) According to standard procedures carried out on the same chiral aldehyde **2**; see: Suzuki, K.; Yuki, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 1529−1532.

Scheme 3. Cyclization of the Carbon Skeleton



H_2O (18:1). As we have previously described,[12,15] with similar substrates, such removal conditions lead quantitatively to the formation of a formyl function rather than to the expected primary alcohol. To our regret, under the same conditions, **7** is converted both into **10** and into the corresponding alcohol **9** with an unsatisfactory overall yield (48%) and in a 4:6 ratio. All attempts to obtain quantitatively only the aldehyde **10** failed; therefore, a two-step reaction sequence was preferred, first converting **7** into **9** and then oxidizing **9** to **10**. The complete conversion of **7** into **9** (70% yield) was accomplished using DDQ in the presence of a higher-water percentage; on the other hand, oxidation of the primary hydroxyl function of **9** was easily performed by treatment with PCC and Celite in pyridine to afford quantitatively **10**, which was directly used in the next cyclization step.

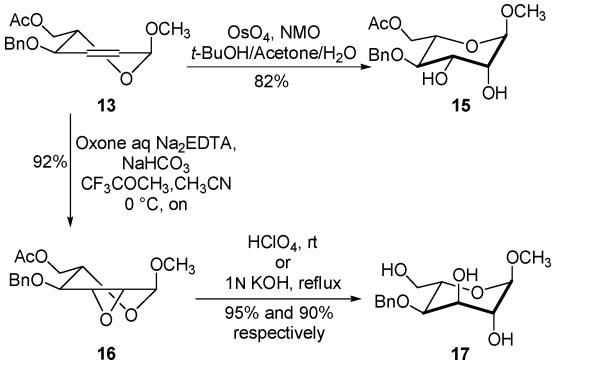
Treatment of the aldehyde **10** in the presence of Amberlyst 15 in methanol allowed, in a one-pot simple procedure, the conversion of the formyl group into its di-*O*-methyl acetal,[12] acetonide deprotection, and intramolecular transacetalation to give the unstable bicyclic compound **11**. After subsequent acetylation of the crude residue, an α/β diastereomeric mixture (85:15 dr) was obtained in 97% overall yield. Recrystallization from methanol allowed separation of the major α-anomer **12** from its β-form.

Desulfurization of the α-anomer **12** with Raney Ni in THF at 0 °C for 2 h led to the unsaturated pyranosyl derivative **13** (75% yield). Moreover, when the dithiodimethylene bridge removal was carried out with an excess of Raney Ni, the overreduction product was obtained with satisfactory yield (84%), affording the interesting 2,3-dideoxy-L-hexopyranoside **14**.[21]

To access the desired L-manno- and L-altropyranosides, we next explored the stereoselective dihydroxylation of olefin **13**. Under common Upjohn conditions (OsO_4/NMO), the L-mannopyranoside **15** was obtained as a single diastereomer in 82% yield. This result concurred with earlier investigations[11d,22] into the dihydroxylation of allylic alcohol derivatives: the osmylation reaction occurred anti to the pseudoequatorial benzyloxy group.

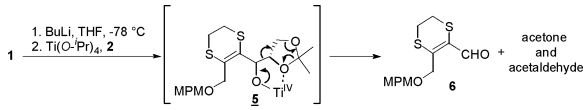
With our successful synthesis of the protected L-mannose **15**, we next attempted preparation of the L-altrose derivative by introducing an epoxy functionality.[23] For this, we treated olefin **13** with in situ[24] generated DMDO (Oxone/trifluoroacetone). The *anti*-epoxide **16** was obtained[25] exclusively in 92% yield (Scheme 4). Subsequent ring opening of the 2,3-

Scheme 4. Dihydroxylation of the Unsaturated Derivative **13**



anhydro derivative **16** either by acid-[26] or by base-catalyzed[27] hydrolysis afforded the L-altropyranoside **17** (95% and 90% yield, respectively), with C-6 O-deacetylation being observed under both conditions.

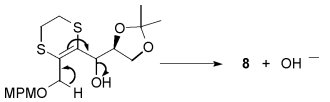
(17) This product, whose structure was unambiguously confirmed by spectroscopic data, seems to be formed by consumption of the coupling product **5** (TLC monitoring). The mechanism of such a reaction has to be proved, and it is still under investigation; nevertheless, we assume that it proceeds via the titanium complex **5** [see ref 11a]:



(18) The C-4 absolute stereochemistry was clearly established in the course of our synthesis on the basis of the $^3J_{4,5}$ of the cyclic compounds **12**, **15**, and **16**.

(19) As recently reported [Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Eur. J. Org. Chem.* **2003**, 2268−2275], steric and stereoelectronic interactions between the chiral aldehyde **2** and the nucleophile across the two diastereotopic faces of the carbonyl group do not play a significant role in determining the stereochemical outcome of the reaction, a situation that allows the nucleophilic attack on the more stable conformer leading to a slight preference for the syn compound.

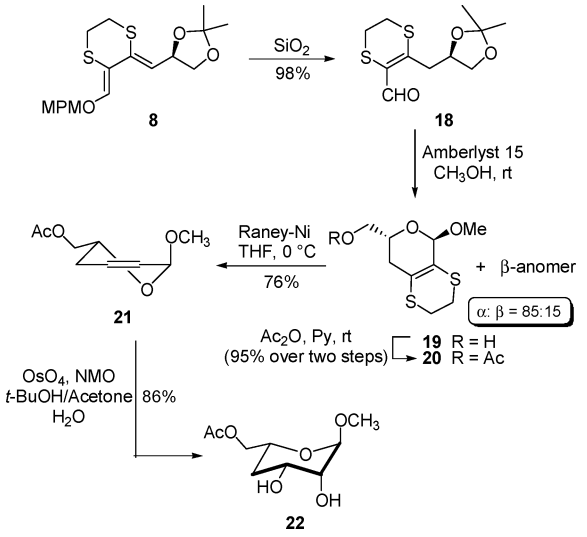
(20) The latter could presumably be generated by an allylic C-1 proton abstraction with a subsequent electronic shift, to give the thermodynamically stable **8**.



(21) For examples of bioactive 2,3-dideoxy-L-hexopyranoside-based compounds, see: Guppi, S. R.; Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 293−296. For their enantiomers, see: Groebke, K.; Hunziker, J.; Fraser, W.; Peng, L.; Diederichsen, U.; Zimmermann, K.; Holzner, A.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta* **1998**, 81, 375−474.

It is noteworthy to recall the value of diene **8**, obtained as byproduct in Scheme 3, as a useful intermediate with the purpose to prepare 4-deoxy-L-hexopyranosides. In fact, following chromatographic purification, the compound **8** afforded quantitatively the aldehyde **18** (Scheme 5). When

Scheme 5. 4-Deoxy-L-sugar Preparation Starting from **8**



this was submitted to the synthetic steps described above, it gave the intermediate **20**, which after desulfurization (76% yield) and double-bond osmylation (86% yield) led, according to our previous results,[12] to methyl 4-deoxy-L-*lyxo*-hexopyranoside **22** as a single diastereomer.

In summary, we have developed a pratical approach to the synthesis of orthogonally protected L-manno- and L-altropyranosides **15** and **17**. The versatility of our method lies in producing an intermediate bearing a double bond in C-2/C-3 positions (such as **13**), which can be suitably functionalized. We are currently investigating the appropriate conditions to achieve the remaining epimers belonging to the *gluco*-configuration. On the other hand, the use of a C-4 diastereomer of olefin **13** (coming from the *syn*-**5** intermediate) enables the preparation of all four *galacto*-epimers.

Obviously, it would be possible to synthesize D-analogues and their deoxy derivatives simply by replacing the chiral electrophile with its *ent*-**2**.

Acknowledgment. ^{1}H and ^{13}C NMR spectra were performed at Centro Interdipartimentale di Metodologie Chimico-Fisiche (CIMCF), Università di Napoli Federico II. The Varian Inova 500 MHz instrument is the property of Consorzio Interuniversitario Nazionale La Chimica per l'Ambiente (INCA) and was used in the frame of a project by INCA and M.I.U.R. (L. 488/92, Cluster 11-A).

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) In an initial experiment, the oxidation of **13** with *m*-CPBA resulted in a lower yield (70%) and a 10:1 anti/syn dr.

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(25) For similar results, see: Kim, K. S.; Moon, C. W.; Park, J., II; Han, S.-H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1341−1343.

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