

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

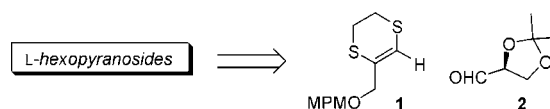
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ABSTRACT



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-sugars¹ 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 bioactive² 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 A₂⁴ and the nucleoside antibiotic Adenomycin.⁵ Moreover, L-altrose is a typical constituent of the extracellular polysaccharides from *Butyri-*

vibrio 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 naringinase⁸ (Figure 1).

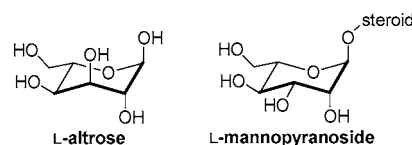


Figure 1. Bioactive L-sugars.

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

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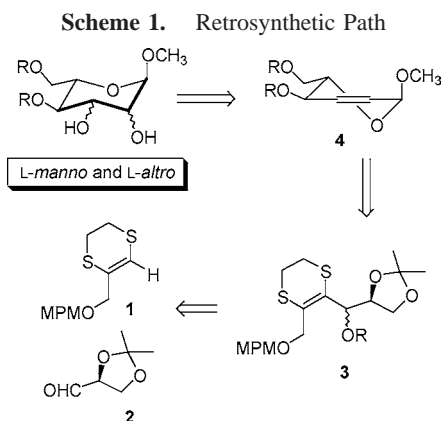
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As part of our efforts working toward the synthesis of bioactive polyhydroxylated compounds, we have explored a general and efficient route for the preparation of L-hexoses (as well as their D-enantiomers) starting from L-glyceraldehyde and the three-carbon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



procedure to prepare both 4-deoxy-hexopyranoses¹² and 1-deoxy-iminosugars¹³ belonging to the D- or L-series.

In this preliminary communication, we describe the preparation of orthogonally protected L-altro- and L-mannopyranosides 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-known¹⁴ 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**.

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(10) Some recent examples of C-5 epimerization of sugars: (a) Ojeda, R.; de Paz, J. L.; Martín-Lomas, M.; Lassaletta, J. M. *Synlett* **1999**, *8*, 1316–1318. (b) Adinolfi, M.; Barone, G.; De Lorenzo, F.; Iadonisi, A. *Synlett* **1999**, *3*, 336–338. (c) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995–3000. (d) Hung, S.-C.; Wang, C.-C.; Thopate, S. R. *Tetrahedron Lett.* **2000**, *41*, 3119–3122. (e) Boulineau, F. P.; Wie, A. *Org. Lett.* **2002**, *4*, 2281–2283.

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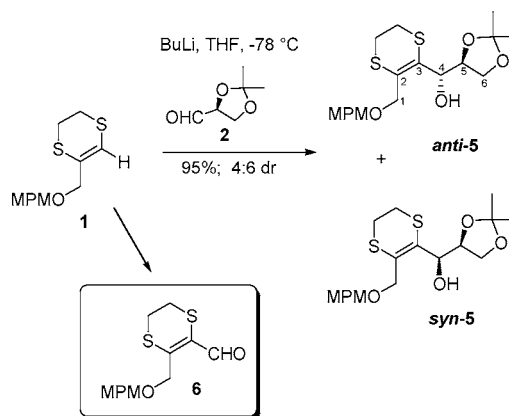
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(14) Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth.* **1995**, *72*, 1–3.

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 $\text{Ti}(\text{O}-i\text{-Pr})_4$ as the catalyst¹⁶ 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 reaction¹⁹ according to the Felkin–Anh model prediction (Figure 2).

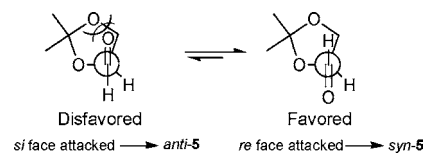


Figure 2. Felkin–Anh models for the aldehyde 2.

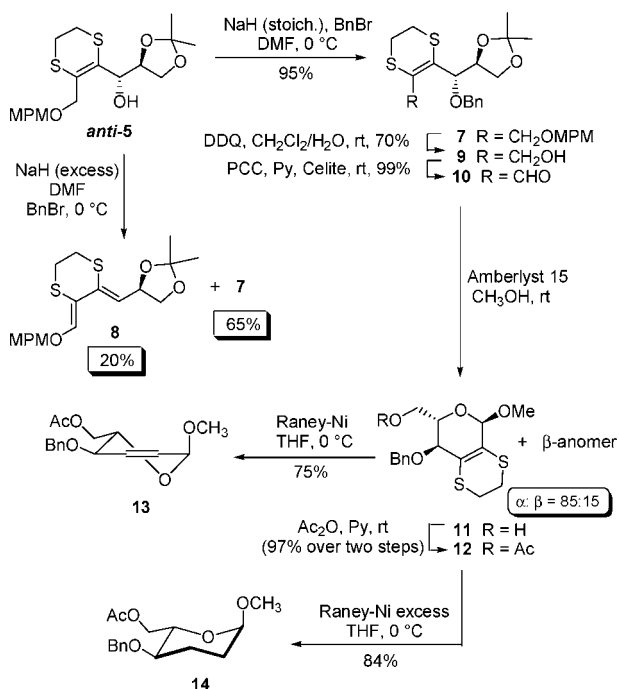
After mixture separation by SiO_2 flash chromatography, the *anti*-**5** diastereoisomer was chosen as a model to test the whole synthetic path. Benzylation of the secondary hydroxyl function, treating *anti*-**5** with NaH and BnBr, afforded **7** in almost quantitative yield (Scheme 3). Interestingly, if the reaction was carried out in the presence of an excess of NaH, the formation of an unexpected byproduct **8** in 20% yield²⁰ 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 /

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(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.

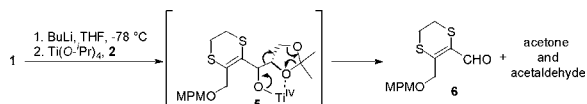
Scheme 3. Cyclization of the Carbon Skeleton



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

(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.

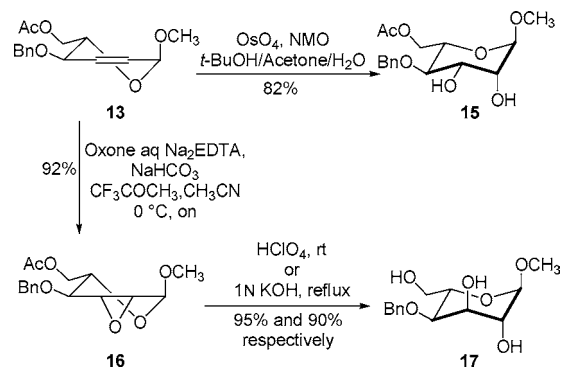
conversion of the formyl group into its di-*O*-methyl acetal,¹² acetonide deprotection, and intramolecular transacetalation to give the unstable bicyclic compound **11**. After subsequent acetylation of the crude residue, an α/β diastereomeric mixture (85:15 dr) was obtained in 97% overall yield. Recrystallization 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.

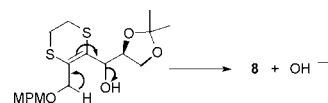
With our successful synthesis of the protected L-mannose **15**, we next attempted preparation of the L-altrose derivative by introducing an epoxy functionality.²³ For this, we treated olefin **13** with in situ²⁴ generated DMDO (Oxone/trifluoroacetone). The *anti*-epoxide **16** was obtained²⁵ exclusively 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-catalyzed²⁷ hydrolysis afforded the L-altropyranoside **17** (95% and 90% yield, respectively), with C-6 O-deacetylation being observed under both conditions.

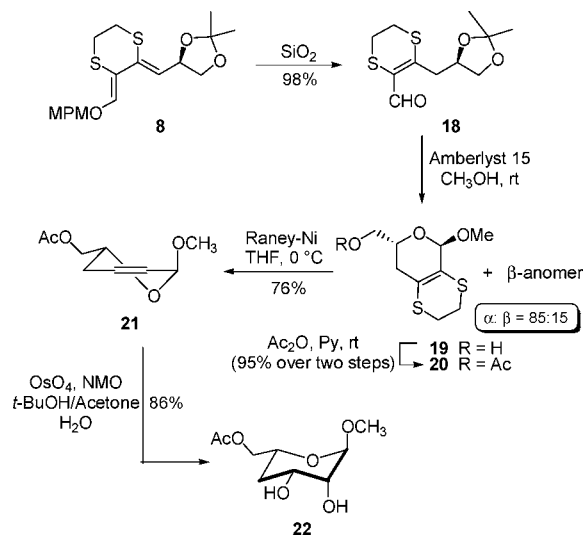
(20) The latter could presumably be generated by an allylic C-1 proton abstraction with a subsequent electronic shift, to give the thermodynamically stable **8**.



(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, accord-

(22) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255.

(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.

ing to our previous results,¹² to methyl 4-deoxy-L-lyxo-hexopyranoside **22** as a single diastereomer.

In summary, we have developed a practical 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*.

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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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