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Conversion of D-Glucals into L-Glycals and Mirror-Image Carbohydrates

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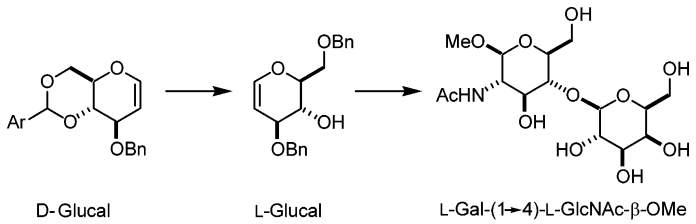
ABSTRACT



D-Glucal L-Glucal L-Gal-(1→4)-L-GlcNAc-β-OMe

L-Glycals can be prepared in seven steps from readily available D-glucals, enabling the facile construction of mirror-image carbohydrates such as the L-lactosamine derivative shown above.

Chiral intermediates derived from readily available D-glycals are frequently employed as starting materials in the synthesis of complex carbohydrates and other natural products.[1] In principle, compounds derived from these unsaturated D-sugars represent only 50% of the available chiral space; the remaining "left-handed" half can be routed by default through the antipodal L-glycals. In addition to providing direct access to a broad range of L-sugars and related glycoconjugates with medicinal value (e.g., bleomycin[2] and the aminoglycoside antibiotics[3]), L-glycals can serve as the basis set for mirror-image carbohydrates. Several intriguing hypotheses can be developed around antipodal carbohydrate ligands in the context of chiral biological systems: while their physicochemical properties would be essentially identical to those of naturally occurring sugars, their interactions with proteins and other biomacromolecules would not. In particular, the unnatural enantiomers of carbohydrates and other bioorganic structures may have the capacity to evade antibody detection and enzymatic degradation.[4] Wong and co-workers have recently described a novel strategy involving synthetic L-sugars based on this premise.[5]

While numerous synthetic routes toward L-sugars have been developed, very few have been targeted at the synthesis of L-glycals despite their broader synthetic utility. Some de novo approaches have been reported: 6-deoxy- and C5 phenyl-substituted L-glycals have been prepared by Danishefsky and co-workers via cyclocondensation of activated aldehydes and electron-rich dienes followed by enzymatic resolution.[6] 6-Deoxy-L-glycals have also been synthesized by McDonald and co-workers via endo-selective cyclization of chiral alkynols.[7] However, methods for preparing L-glycals bearing C5 hydroxymethyl groups (e.g., L-glucal and L-galactal) have so far depended on the degradation of rare or unnatural L-sugars, with obvious economical drawbacks.[8]

Here we report an efficient synthesis of L-glycals from readily available D-glucal **1** via pseudodesymmetrization of

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(6) Berkowitz, D. B.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 4518−4529.

(7) (a) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304−4309. (b) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979−3981.

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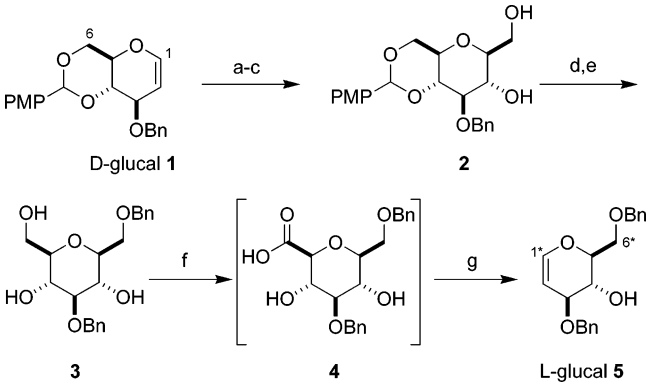
Scheme 1. Synthesis of L-Glucal 5[a]



[a] Reagents and conditions: (a) DMDO, CH_2Cl_2/acetone, 0 °C. (b) (*i*PrO)Me_2SiCH_2MgCl (3.5 equiv), CuI (0.5 equiv), THF, −10 °C. (c) 30% H_2O_2, KOH, MeOH/THF, rt (66% over three steps). (d) (*n*-Bu)$_2$SnO, BnBr, TBAI, toluene, reflux. (e) AcOH/THF/H_2O, 45 °C (90% over two steps). (f) TEMPO (5 mol %), bleach, saturated aq $NaHCO_3$, CH_2Cl_2, 0 °C. (g) *N*,*N*-Dimethylformamide dineopentyl acetal, xylenes, 150 °C (61% over two steps). PMP = *p*-methoxyphenyl.

an intermediate *C*-glycoside (see Scheme 1).[9] This method takes advantage of latent symmetry elements that are present in D-glucose to produce L-glucal and L-galactal.[10] In addition, our approach is complementary to methods that epimerize D-hexoses at the C5 stereocenter to produce other isomeric L-sugars such as L-idose and L-altrose (starting from D-glucose and D-galactose, respectively).[11−13]

D-Glucal derivative **1** (prepared from *β*-D-glucose pentaacetate in five steps and 47% overall yield)[14] was transformed into *β*-*C*-glycoside **2** on a multigram scale in 66% yield by dimethyldioxirane (DMDO) oxidation[15] and Cu^I-mediated addition of (*i*PrO)Me_2SiCH_2MgCl, followed by Tamao−Kumada oxidation (see Scheme 1).[16,17] The unsymmetrically protected *C*-glycoside **2** was converted in two steps to partially benzylated triol **3**, followed by TEMPO oxidation to carboxylic acid **4** and decarboxylative elimination to 3*,6*-*O*-dibenzyl-L-glucal **5** using *N*,*N*-dimethylformamide dineopentyl acetal (DMFDNA).[18] The latter procedure has been used previously to introduce $\Delta^{4,5}$-unsaturation into the pyranose ring of *O*-glycosides.[19,20] Overall, the conversion of D-glucal **1** to L-glucal **5** was accomplished in seven steps and 36% yield.

With respect to the mechanism of decarboxylative elimination, we note that the temperature required for the decomposition of *β*-*C*-glucuronide intermediate **4** (150 °C) is considerably higher than that for α-*O*-glucuronides, whose elimination is complete after 1 h at 120 °C.[21] This suggests that the glucuronides must first adopt geometries with trans diaxial C4 and C5 substituents such as $^1C_4$ or twist-boat conformations (see Figure 1), as opposed to the formation

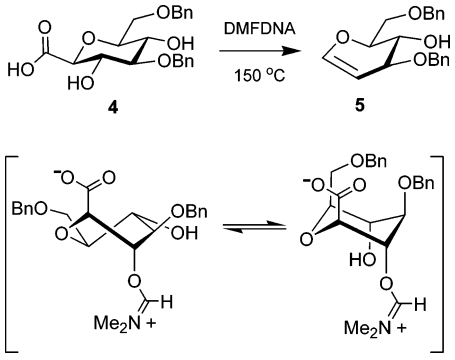


Figure 1. Possible trans diaxial conformations adopted during the decarboxylative elimination of **4**.

of a cyclic orthoamide intermediate.[22] In the case of **4**, the benzyloxymethyl group at C1 raises the barrier to interconversion and may destabilize transition-state geometries by introducing sterically unfavorable interactions.

L-Glucal **5** can be readily transformed into the antipodal isomers of several common pyranoside derivatives, and is an ideal precursor for constructing mirror-image carbohydrates. As a demonstration, we have synthesized the methyl glycoside of *N*-acetyl-L-lactosamine (L-Gal-(*β*1→4)-L-GlcNAc-*β*-OMe), whose antipode is the core disaccharide found in human blood group antigens and serves as a substrate for a number of glycosyltransferases (see Scheme 2).[23,24]

3*,6*-*O*-dibenzyl-L-glucal **5** was oxidized using the Dess−Martin periodinane and treated immediately with $NaBH_4$, affording the corresponding dibenzyl-L-galactal as the major isomer (84% yield, L-Gal/L-Glc > 30:1). Tribenzyl-L-galactal **6** was isolated in diastereomerically pure form after benzy-

(9) Pseudosymmetry of hydroxymethyl *C*-glycosides has been appreciated by others: Hoffmann, H. M. R.; Dunkel, R.; Mentzel, M.; Reuter, H.; Stark, C. B. W. *Chem. Eur. J.* **2001**, *7*, 4772−4789.

(10) L-Glucose has been previously synthesized by oxidative decarboxylation of *β*-*C*-glucuronides, in low to fair yields: (a) Shiozaki, M. *J. Org. Chem.* **1991**, *56*, 528−532. (b) Smid, P.; Noort, D.; Broxterman, H. J. G.; van Straten, N. C. R.; van der Marel, G. A.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 524−528.

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(12) Blanc-Muesser, M.; Defaye, J. *Synthesis* **1977**, 568−569.

(13) Rochepeau-Jobron, L.; Jacquinet, J.-C. *Carbohydr. Res.* **1997**, *303*, 395−406.

(14) D-Glucal **1** was prepared according to literature protocols: Fernandez-Mayoralas, A.; Marra, A.; Trumtel, M.; Veyrières, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *188*, 81−95.

(15) (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661−6666. (b) Lee, G. S.; Min, H. K.; Chung, B. Y. *Tetrahedron Lett.* **1999**, *40*, 543−544.

(16) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120−2122.

(17) The stereoselectivity of this transformation is noteworthy, as reactions between Grignard reagents and 1,2-epoxyglycals do not always proceed in high yield or with complete S_N2 selectivity: (a) Smoliakova, I. P. *Curr. Org. Chem.* **2000**, *4*, 589−608. (b) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997−2009.

(18) To maintain a consistent nomenclature, the carbons of L-glycals and derivatives thereof have been numbered 1* through 6*.

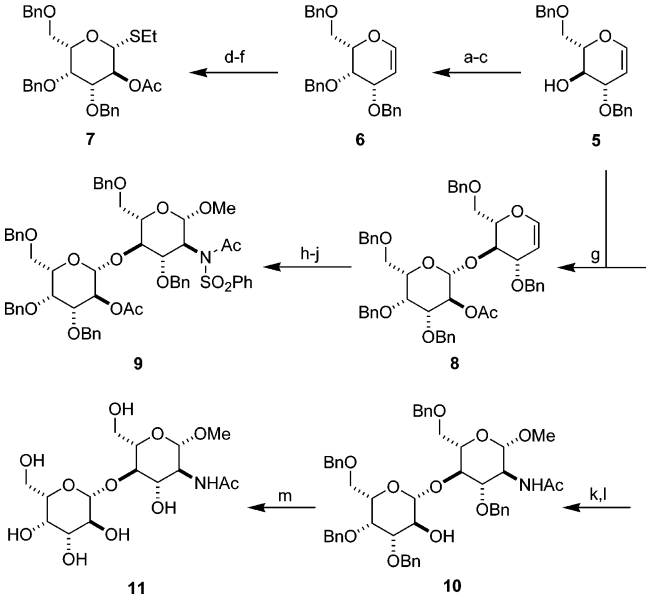
(19) Philips, K. D.; Žemlička, J.; Horwitz, J. P. *Carbohydr. Res.* **1973**, *30*, 281−286.

(20) Boulineau, F. P.; Wei, A. *Org. Lett.* **2002**, *4*, 2281−2283.

(21) We have observed that decarboxylative elimination of *β*-*O*-glucuronides also requires 1 h at 150 °C.

(22) (a) Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, *19*, 1545−1548. (b) Mulzer, J.; Brüntrup, G. *Chem. Ber.* **1982**, *115*, 2057−2075.

Scheme 2. Synthesis of *N*-Acetyl-L-lactosaminoside **11**[a]



[a] Reagents and conditions: (a) Dess−Martin periodinane, $NaHCO_3$, 4A molecular sieves, CH_2Cl_2, rt. (b) $NaBH_4$, MeOH/CH_2Cl_2, −5 °C. (c) NaH, BnBr, DMF, rt (81% over three steps). (d) DMDO, CH_2Cl_2/acetone, −55 °C. (e) EtSLi, THF, 0 °C. (f) Ac_2O, pyridine, rt (63% over three steps). (g) **7** (1.0 equiv), **5** (1.5 equiv), MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 4A molecular sieves, CH_2Cl_2 (73%). (h) $I(collidine)_2ClO_4$, $PhSO_2NH_2$, 4A molecular sieves, 0 °C. (i) NaOMe, MeOH, rt. (j) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (80% over three steps). (k) Na naphthalenide, THF, −78 °C. (l) NaOMe, MeOH, 45 °C (80% over two steps). (m) H_2, $Pd(OH)_2$/C, MeOH, rt (99%).

lation and treated with anhydrous DMDO to yield the desired α-epoxide, which was then reacted with EtSLi and acetylated to produce thioethyl *β*-L-galactoside donor **7** in 63% yield from **6**. Galactosyl donor **7** was coupled with L-glucal **5** (1.5 equiv) using the thioglycoside activation conditions described by Seeberger et al. to furnish protected L-lactal **8** in 73% yield.[25] After surveying several different conditions for installing the acetamido group at C2*, we used a slightly modified version of the sulfonamidoglycosylation procedure developed by Danishefsky and co-workers.[26] L-Lactal **8** was transformed into its 2*-*β*-iodo-1*-α-phenylsulfonamido derivative and then treated with NaOMe in MeOH to give methyl *N*-phenylsulfonyl-*β*-L-lactosaminoside, followed by acetylation to afford **9** in 80% yield after three steps. Desulfonylation with sodium naphthalenide at −78 °C cleanly produced *N*-acetyl derivative **10**, which was globally deprotected to methyl *N*-acetyl-*β*-L-lactosaminoside **11** in 79% overall yield from **9**.[27]

In summary, we have developed an expedient route to L-glycals and mirror-image oligosaccharides from D-glucals. We anticipate that in addition to preparing L-sugars such as those described here, the decarboxylative elimination of pyranosides may have broad utility in the stereocontrolled synthesis of highly substituted dihydro- and tetrahydropyrans.

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Supporting Information Available: Experimental details and analytical data for the preparation of L-glucal **5** from D-glucal **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Methyl *N*-acetyl-*β*-L-lactosamine **11** was found to be spectroscopically identical to its enantiomer but opposite in optical activity. **11**: $[\alpha]^{20}_D$ +24.0° (*c* 0.5, MeOH). *ent*-**11** (synthesized from the corresponding D-glycals): $[\alpha]^{20}_D$ −23.4° (*c* 0.5, MeOH).