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A general stereodivergent strategy for the preparation of carbasugars. Syntheses of 5a-carba-α-D-glucose, α-D-galactose, and β-L-gulose pentaacetates from D-mannose

Ana M. Gómez,* Eduardo Moreno, Serafín Valverde and J. Cristóbal López*

Instituto de Química Orgánica General, C.S.I.C., Juan de la Cierva 3, 28006 Madrid, Spain

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Abstract—A stereodivergent approach to 5a-carba-D- and L-pyranoses has been applied to the preparation of 5a-carba-α-D-gluco-, 5a-carba-α-D-galacto-, and 5a-carba-β-L-gulopyranose pentaacetates. The strategy, by which a single precursor can be transformed into three different carbasugars, features a stereoselective reduction followed by deoxygenation of a key polyoxygenated methylcyclohexanone intermediate. The latter is readily available by 6-*exo-dig* radical cyclization of a D-mannose derivative.
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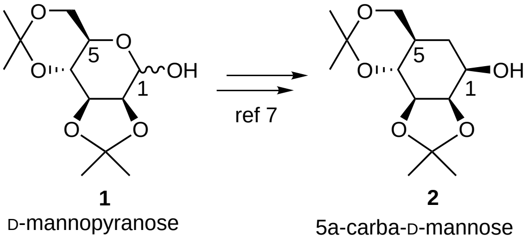
More than 30 years ago McCasland and coworkers synthesized the first sugar in which a methylene group replaced the oxygen ring.[1] Owing to their close resemblance to the parent carbohydrate,[1] many of these substances, now termed carbasugars,[2] were found to possess an interesting range of biological activities,[3] which has triggered the development of different synthetic approaches for their preparation.[1,4,5] In this context we have recently reported two synthetic strategies for such an approach.[6–8] These methods, based on radical cyclizations of monosaccharide derivatives,[9] were designed to *directly correlate* a given carbohydrate, **1**, with its corresponding carbasugar, **2** (Scheme 1).

More recently, unlike in our previous work,[6,7] we have focused on a stereodivergent strategy for the preparation of D- and L-carbasugars from a single carbocyclic intermediate. In this communication, we disclose the syntheses of 5a-carba-α-D-galacto **21**, 5a-carba-β-L-gulo, **24**, and 5a-carba-α-D-glucopyranose, **30**, pentaacetates from a polyoxygenated methyl cyclohexanone, e.g. **6** (Scheme 2b). The latter is readily available by ozonation of a methylenecyclohexene, e.g. **5**, prepared by 6-*exo-dig* radical cyclization of a D-mannose derived precursor **3** (Scheme 2a).



Scheme 1.

Our approach takes advantage of the observation that selective deoxygenation of a polyoxygenated intermediate[10] (e.g. **7**, Scheme 3) at C-4 or at C-5a could afford either a 5a-carba-L-sugar derivative, **8**, or a 5a-carba-D-sugar derivative **9**, respectively.

When the above-mentioned deoxygenation is combined with the stereoselective reduction of a carbonyl group in a polyoxygenated cyclohexanone, e.g. **10**, the latter can be correlated with up to three different carbasugars (Scheme 4). Accordingly, ketone **10**, could be transformed into epimeric polyols **11** and **12**, which upon deoxygenation either at C-5a or at C-4 would afford carbapyranoses **13**, **14** and **15**.

Along these lines, carbonate **5** (Scheme 5) was treated with potassium carbonate in methanol to afford alkene **16**, which upon ozonolysis and reduction at C-5a afforded diol **17**. Compound **19**, in which the 4-OH had already been differentiated, was prepared by benzylation of **16** followed by chemoselective acetal hydrolysis and regioselective silylation at the primary hydroxyl

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* Corresponding authors. Tel.: +34 91 5622900; fax: +34 91 5644853; e-mail: anago@iqog.csic.es; clopez@iqog.csic.es

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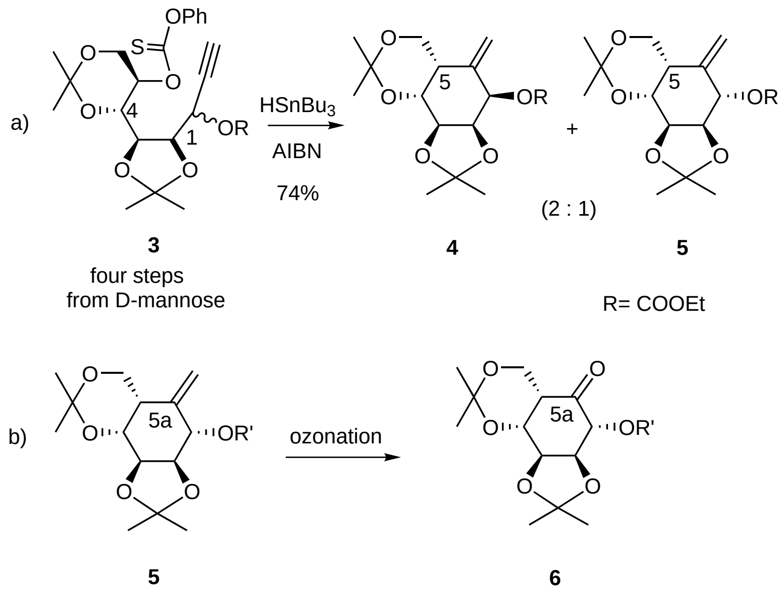
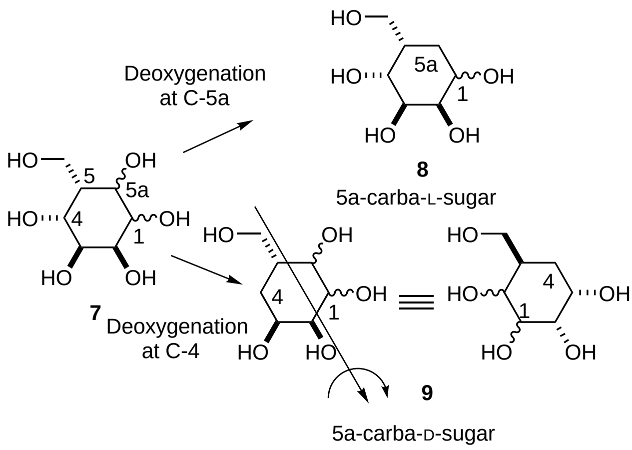


Scheme 2.

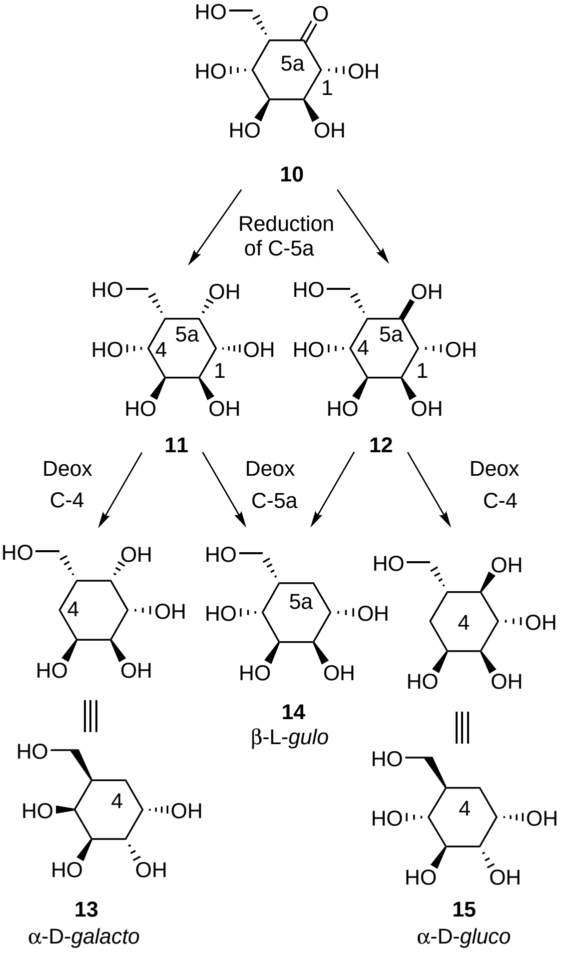
group. Deoxygenation at C-4, was carried out via the corresponding xanthate by treatment with tri-*n*-butyltin hydride,[11] and led to 5a-carba-galactose derivative **20**. Deprotection steps, followed by acetylation yielded 5a-carba-α-D-galactose pentaacetate **21**[12–14] ($[\alpha]_D^{21}$ +35.8 (*c* 0.4, CHCl$_3$), Lit. Ref. 13a ($[\alpha]_D^{20}$ +35.2 (*c* 1.77, CHCl$_3$).

Compound **16** was benzylated at 1-OH and submitted to ozonation and reduction of the ensuing carbonyl group to afford **22** (Scheme 6) in 40% yield (its C-5a epimer was also obtained (3:1 mixture)). Deoxygenation[11] of **22** yielded gulose-derivative **23** which was submitted to routine deprotection steps and acetylation to yield 5a-carba-β-L-gulose pentaacetate **24**[15] ($[\alpha]_D^{21}$ +18.7 (*c* 0.4, CHCl$_3$), Lit. Ref. 15a ($[\alpha]_D^{20}$ +20.5 (*c* 1.0, CHCl$_3$).

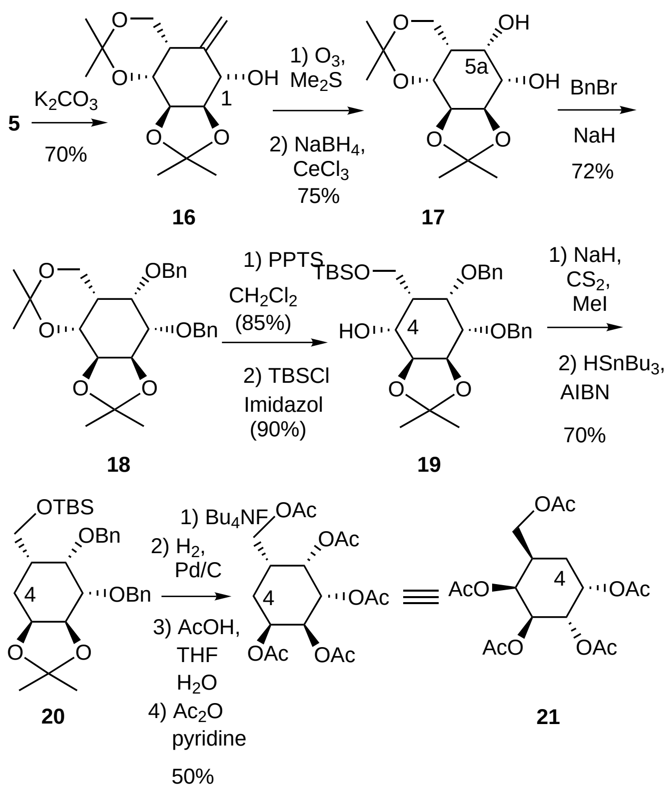
The synthetic process for the preparation of 5a-carba-D-glucose implied: (a) preparation of an equatorial 5a-OH, rather than an axial one as in **17**, and (b) deoxygenation at C-4 (as in Scheme 4). Extensive experimentation was carried out on the reduction of cyclohexanones **25a** and **25b**, which showed a preferred facial approach of the incoming reducing agent



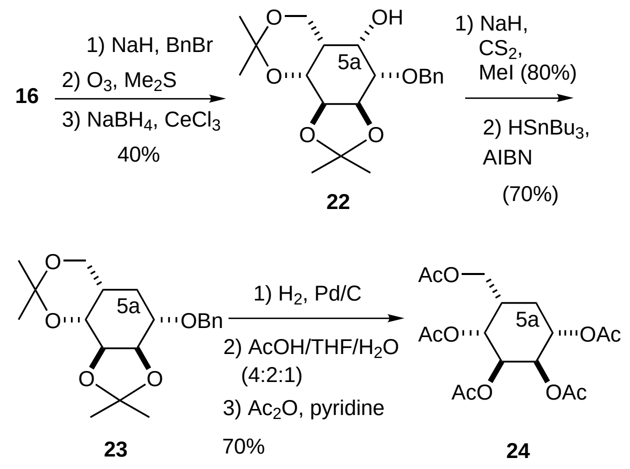
Scheme 3.



Scheme 4.



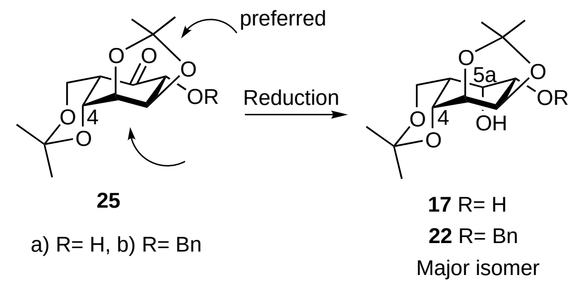
Scheme 5.



Scheme 6.

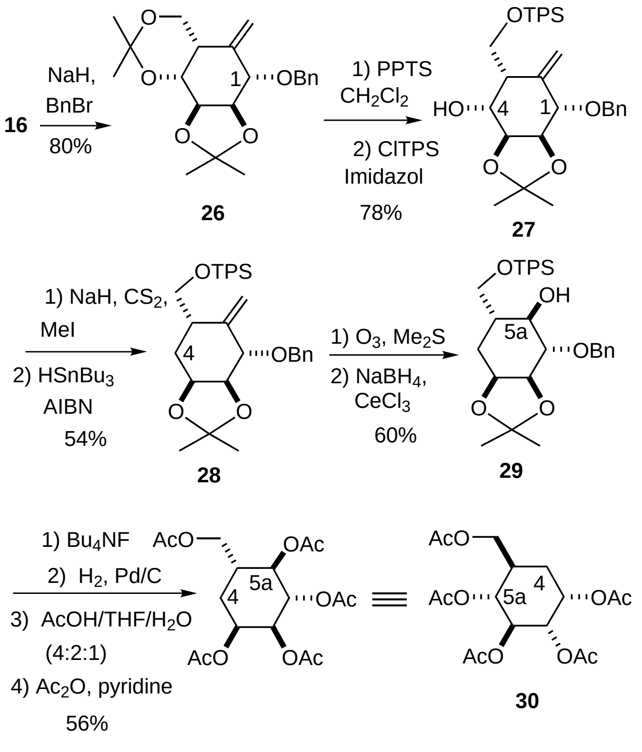
(Scheme 7) leading to axial C-5a derivatives. Finally, removal of the isopropylidene acetals and deoxygenation at C-4 prior to reduction of the carbonyl group allowed us to obtain the desired 5a-OH epimer as a major isomer (vide infra).

Chemoselective deprotection of the acid labile primary isopropylidene acetal in **26** (Scheme 8), followed by regioselective protection of 6-OH afforded compound **27**, in which the 4-OH group was now differentiated. Deoxygenation via the corresponding xanthate, as above, resulted in the formation of olefin **28**. Ozonation of the latter, followed by reduction of the resulting carbonyl group led to the desired isomer, **29**, as the major isomer (2.5:1 ratio). Conventional deprotection steps on **29**, and acetylation led to 5a-carba-α-D-glucose pentaacetate **30**[14c,16,17] ($[\alpha]_D^{21}$ +32.1 (*c* 0.4, $CHCl_3$), Lit. Ref. 16a ($[\alpha]_D^{21}$ +37 (*c* 0.90, $CHCl_3$), Ref. 16b ($[\alpha]_D^{21}$ +57 (*c* 0.90, $CHCl_3$).



Scheme 7.

In summary, we have reported a stereodivergent strategy for the preparation of carbasugars based on the combination of a stereoselective reduction and a site-selective deoxygenation of a polyoxygenated intermediate. The latter is readily available from D-mannose upon 6-*exo-dig* radical cyclization. We have illustrated the synthetic potential of this approach with the preparation of three carbasugars **21**, **24**, and **30** from a single synthetic intermediate, **5**. Similar chemistry carried out with major isomer **4** (Scheme 2), might have led to 5a-carbasugars of the α-D-allo-, α-L-gulo-, and α-D-gulo series. The scope of this strategy can still be enhanced



Scheme 8.

by the use of different monosaccharide starting materials, or by the use of carbocyclic key intermediates with different stereocenters at C-5, and C-1, while maintaining the stereochemical integrity, at positions C-2, C-3 and C-4, in derivatives arising from D-mannose.[7] Use of the above strategy for the preparation of additional carbasugars and derivatives thereof is underway in our laboratory and will be described in due course.

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