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A stereodivergent approach to carbahexofuranoses: synthesis of carba-α-D-glucofuranose, carba-β-D-altrofuranose, carba-α-D-allofuranose, carba-β-D-idofuranose, carba-α-D-galactofuranose and carba-β-D-talofuranose

Mukund G. Kulkarni *, Ajit S. Borhade, Yunnus B. Shaikh, Attrimuni P. Dhondge, Deekshaputra R. Birhade, Nagorao R. Dhatrak

Department of Chemistry, University of Pune, Pune, Maharashtra 411 007, India

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ABSTRACT

A stereodivergent route, starting from D-glyceraldehyde derivative, employing Wittig olefination–Claisen rearrangement protocol is reported for the synthesis of six novel carbahexofuranoses—carba-α-D-glucofuranose, carba-β-D-altrofuranose, carba-α-D-allofuranose, carba-β-D-idofuranose, carba-α-D-galactofuranose and carba-β-D-talofuranose in enantiomerically pure form.

A group of carbohydrate mimetics,[1] called *carbasugars*[2] are obtained by replacing ring oxygen atom of a sugar with a methylene group.[3] They have comparatively higher lipophilicity and hence are potentially beneficial for increasing oral efficiency and cell wall penetration. Further, due to lack of acetal functionality, the compounds containing carbasugar moiety are more resistant to the endogenous degradative enzymes. As a consequence of this carbasugars have higher affinity and selectivity for their cognate receptors as compared to their natural saccharide counterparts.[4] Carbasugars, in their chiral form, can be versatile intermediates for synthesis of aminocarbasugars,[5] carbaoligosaccharides[6] and carba-nucleosides[7] (Fig. 1). Carbafuranoses are present as subunits of natural carbanucleosides, such as aristeromycin[8] and neplanocin-A[9] and synthetic carbanucleosides like Carbovir[10] and Cyclaradine[11] are potent antitumour and antiviral agents. Carbasugars required for synthesis of such carba-nucleosides are available only through a complex multistep chiral synthesis.[12–15]

Several novel and interesting synthetic strategies have been reported for the synthesis of various carbafuranoses,[12] especially, carbapentofuranoses employing either achiral starting materials[13] or chiral substrates like carbohydrates.[14] However, only a few approaches have been reported for the synthesis of carbahexofuranoses.[15] Therefore, there is enough scope to develop novel, general and more efficient routes for synthesis of carbahexofuranoses. Such synthetic routes will be more appealing if they allow the preparation of all possible stereoisomers of carbahexofuranoses. We herein report such an approach while achieving the first synthesis of six isomeric D-carbahexofuranoses.

Wittig olefination of aldehydes or ketones to get allyl vinyl ethers[16] followed by a Claisen rearrangement[17] is a convenient protocol for the generation of 4-pentenals which serve as versatile synthetic intermediates. Such 4-pentenals have been applied to the synthesis of terpenes, alkaloids and heterocycles.[18] As a part of the continued interest towards the application of this protocol, a practical approach for the synthesis of novel carbahexofuranoses has been designed.

2,3-*O*-cyclohexylidene-D-glyceraldhyde[19] **1** was treated with allyloxymethylenetriphenylphorane to get the corresponding allyl vinyl ether **2** (Scheme 1) as an inseparable mixture of *E*- and *Z*-isomers in 1:1.5 ratio. The allyl vinyl ethers **2** underwent Claisen rearrangement in refluxing xylene to afford aldehyde **3a** and **3b** as an inseparable mixture of diastereomers. The ratio of the aldehydes was estimated to be 1:2.7 from the proton NMR spectrum. Reduction of the diastereomeric mixture of aldehyde **3a** and **3b** with $NaBH_4$ gave chromatographically separable mixture of alcohols **4a** and **4b** in the ratio of 1:2.7. The structures of these alcohols were established by converting them to the known alcohols.[20,21]

Proceeding towards the synthesis of carbahexofuranoses, alcohol **4a** was oxidized with PCC in CH_2Cl_2 at 0 °C to aldehyde **3a** $[\alpha]_D^{29} = -18.40$ (*c* 6.60, $CHCl_3$) (Scheme 2). Grignard reaction of aldehyde **3a** with vinyl magnesium bromide gave the dienol **5a** as an

* Corresponding author. Tel.: +91 20 25601394; fax: +91 20 25601728.
E-mail address: mgkulkarni@chem.unipune.ac.in (M.G. Kulkarni).

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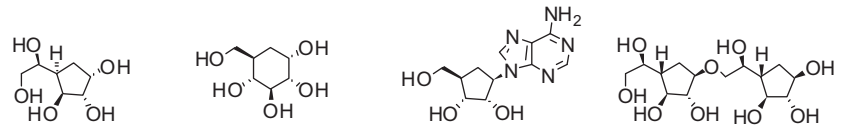
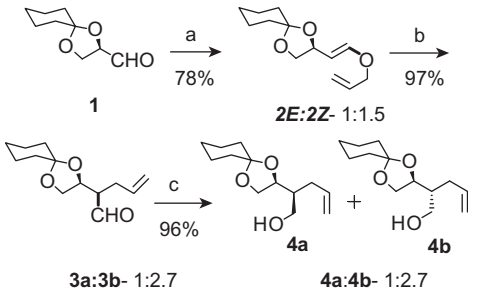


Figure 1. Structure of carbasugars, carba-nucleoside and carbadisaccharide.



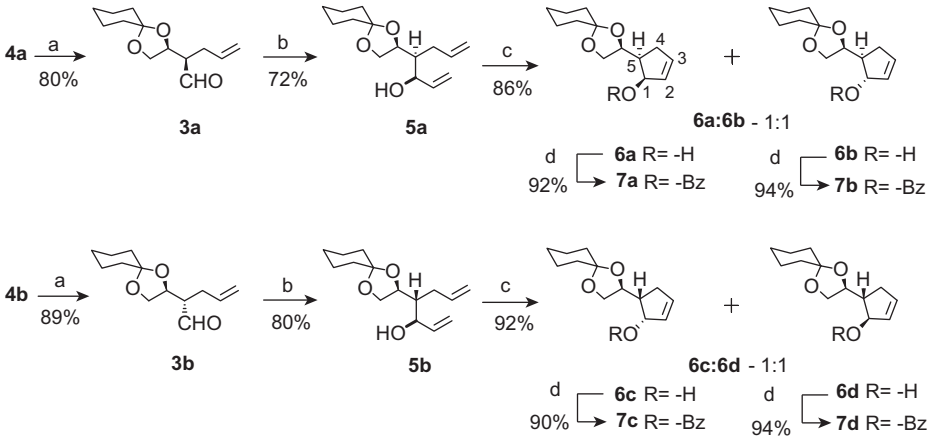
Scheme 1. Reagents and conditions: (a) $CH_2CHCH_2OCH_2Ph_3P^+Cl^-$, *t*-$BuO^-Na^+$, THF, 50–55 °C, 1 h; (b) Xylene, reflux, 6 h; (c) $NaBH_4$, aq Methanol, rt, 35 min.

inseparable mixture of diastereoisomers. This distereomeric mixture of dienol **5a**, under ring closing metathesis conditions with Grubbs' second generation catalyst, gave a mixture of diastereomeric cyclopentenols which on chromatographic separation gave cyclopentenols **6a** $[\alpha]_D^{29} = -16.10$ (*c* 0.35, $CHCl_3$) and **6b** $[\alpha]_D^{29} = +38.66$ (*c* 1.89, $CHCl_3$) in equimolar quantities. Stereochemical assignment to the cyclopentenol **6a** was based on the NOESY NMR experiment, which showed the NOE correlation between protons on carbon C-1 and C-5. This also established the stereochemistry of the cyclopentenol **6b**. In a similar fashion the alcohol **4b** was oxidized to aldehyde **3b** $[\alpha]_D^{29} = -5.22$ (*c* 5.86, $CHCl_3$) and converted to the cyclopentenols **6c** $[\alpha]_D^{29} = +16.61$ (*c* 6.54, $CHCl_3$) and **6d** $[\alpha]_D^{29} = -48.64$ (*c* 4.50, $CHCl_3$) in 1:1 ratio. In the NOESY NMR spectrum of cyclopentenol **6c**, NOE correlation between the protons on carbon C-1 and C-5 confirmed the stereochemical assignment to the compound. This also established the stereostructure of cyclopentenol **6d**. The hydroxyl group in cyclopentenols **6a–d** was protected as their benzoate esters **7a–d**, respectively.

cis-Dihydroxylation of the cyclopentene benzoate **7a** using potassium osmate followed by protection of diol with 2,2-dimethoxy propane gave carbasugar derivative **8a** $[\alpha]_D^{29} = -29.61$ (*c* 2.51, $CHCl_3$) in 60% yield (Scheme 3). Stereochemical assignment of the carbasugar derivative **8a** was based on NOESY NMR experiment. The NOESY spectrum did not show any NOE correlation between the protons on carbon C2 and C3 this indicates that the *cis*-dihydroxylation of double bond in the cyclopentene benzoate **7a** took place exclusively from the opposite face of the alkoxy groups, which is in accordance with Kishi's principle.[22] The cyclopentene benzoate **7b** on dihydroxylation and further protection of the resulting diol gave the fully protected derivatives of carbahexofuranose **8b** $[\alpha]_D^{29} = -10.05$ (*c* 6.61, $CHCl_3$) and its diastereoisomer **8c** $[\alpha]_D^{29} = +57.09$ (*c* 2.77, $CHCl_3$) in the ratio of 2:1. The stereostructure of compound **8c** was confirmed by NOESY wherein a NOE correlation between protons on carbon C-2 and C-3 was observed. This also established the absolute stereochemistry of the diastereomer **8b**. Following a similar protocol, cyclopentene benzoates **7c** and **7d** were transformed to their corresponding carbasugar derivatives. Cyclopentene benzoate **7c** gave exclusively the carbahexofuranose derivative **8d** $[\alpha]_D^{29} = +9.22$ (*c* 4.57, $CHCl_3$). The stereochemical assignment was based on the NOESY NMR experiment and was in accordance with Kishi's principle.[22]

The cyclopentene benzoate **7d** gave the fully protected derivatives of carbahexofuranose **8e** $[\alpha]_D^{29} = -7.10$ (*c* 1.17, $CHCl_3$) and its diastereomer **8f** $[\alpha]_D^{29} = -44.42$ (*c* 6.72, $CHCl_3$) in the ratio of 2:1. The NOESY NMR spectrum of compound **8f** showed NOE correlation between protons on carbon C-2 and C-3. This confirmed the stereostructure of the compound **8f**. This also established the stereostructure of the other diastereomer **8e**.

Finally, to complete the synthesis of carbahexofuranoses, the carbasugar derivatives **8a–8f** were treated with NaOH in aqueous methanol followed by acid mediated hydrolysis of acetals to afford carba-α-D-glucofuranose 9a $[\alpha]_D^{32} = +0.52$ (*c* 2.71, H_2O), carba-β-D-altrofuranose 9b $[\alpha]_D^{32} = -0.27$ (*c* 1.13, H_2O), carba-α-D-allofuranose 9c $[\alpha]_D^{32} = +3.57$ (*c* 2.68, H_2O), carba-β-D-idofuranose 9d $[\alpha]_D^{32} = -10.42$ (*c* 2.34, H_2O), carba-α-D-galactofuranose 9e $[\alpha]_D^{32} = -2.10$ (*c* 3.34, H_2O) and carba-β-D-talofuranose 9f $[\alpha]_D^{29} = -7.24$ (*c* 3.36, H_2O), respectively in enantiomerically pure form (Scheme 4).



Scheme 2. Reagents and conditions: (a) PCC, CH_2Cl_2, 0 °C, 4 h; (b) Vinyl magnesium bromide, THF, rt, 20 min; (c) Grubbs' catalyst second generation, CH_2Cl_2, rt, 3 h; (d) BzCl, DABCO, pyridine, CH_2Cl_2, rt, 6 h.