Synthesis of 4a-carba-α-D-lyxofuranose from 2,3-*O*-isopropylidene-L-erythruronolactone *via* Tebbe-mediated cascade reaction†

Girija Prasad Mishra, G. Venkata Ramana and B. Venkateswara Rao*

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A new, efficient and highly diastereoselective approach for the synthesis of 1,2,3,5-tetraacetylcarba-α-D-lyxofuranose 14 from D-ribose is reported *via* one-pot conversion of 5 to 1 using Tebbe reagent which involves a cascade reaction sequence of methylenation, cleavage of isopropyl group, carbocyclization and again methylenation.

Polyoxygenated carbasugars are a common feature of many interesting biologically active compounds such as carbocyclic nucleoside analogues[1] and a number of enzyme inhibitors. Conversion of readily available carbohydrates to these polyfunctionalized carbocyclic derivatives is an attractive route adopted by many synthetic chemists.[2,3] Among these, intramolecular ring-closure of carbohydrates to give carbocycles is a highly useful transformation which gives direct access to the densely substituted cyclitols. Grosheintz and Fisher first reported the conversion of carbohydrates to carbocycles utilizing intramolecular aldol reaction.[4] Ferrier and co-workers developed an efficient approach for the synthesis of polyhydroxy cyclohexanone derivatives starting from hex-5-enopyranoside *via* regiospecific hydroxymercuration and aldol-like intramolecular cyclization.[5,6] This approach provided a practical route to many cyclohexitols. Dalco and Sinay developed an interesting approach where a 5-enohexopyranose was converted to cyclohexitols using TIBAL.[7] In this process the transposition of oxygen atom takes place with the exocyclic carbon without cleaving the anomeric C–O bond and also TIBAL reduces the carbonyl group generated during the intramolecular cyclization to give cyclohexitols. Later on this transformation was carried out with [$TiCl_3$(O*i*Pr)] under mild conditions.

The above methods are generally useful for making six-membered carbapyranoses, but to the best of our knowledge none of these approaches are used for the transformation of furanosides to cyclopentitols since the molecule has to undergo an unfavourable 5-(enolendo)-*exo-trig* cyclization.[7] The solution for this challenging problem was given by Belanger and Prasit, where the five-membered enolactone was converted to a cyclopentanone derivative using $LiAlH(O^tBu)_3$.[8] Recently Gree *et al*. developed an another interesting approach which involves tandem isomerisation–aldolactonisation of vinyl sugars to cyclopentenone using 5% $Fe(CO)_5$ and photoirradiation.[9]

Organic Division III, Indian Institute of Chemical Technology, Hyderabad, India 500007. E-mail: drb.venky@gmail.com, venky@iict.res.in; Tel: 91-40-27193003

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In continuation of our work in conversion of carbohydrates to carbocycles[10] herein we report an attractive alternative route to cyclopentitols from 5-enofuranoside.

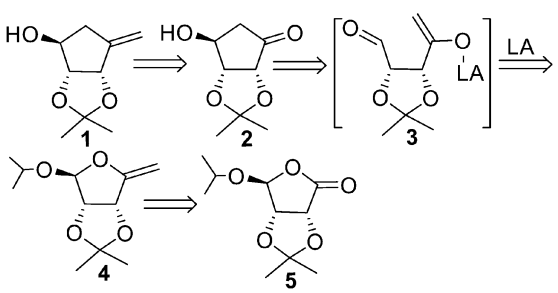
Cyclopentitols of varying nature and complexities form an integral part of a broad class of natural products. Some examples are the glycoside inhibitors such as mannostatin A, allosamizoline, trehalostatin, carbafuranoses and carbonucleosides such as neplanomycin, aristeromycin *etc*.[11]

After analyzing the retrosynthesis of some of the cyclopentitols it was realized that the olefinic cyclopentane derivative **1** can be a suitable intermediate for their synthesis. Since compound **1**, to the best of our knowledge, is not reported in the literature, therefore we envisaged a novel approach for its synthesis.

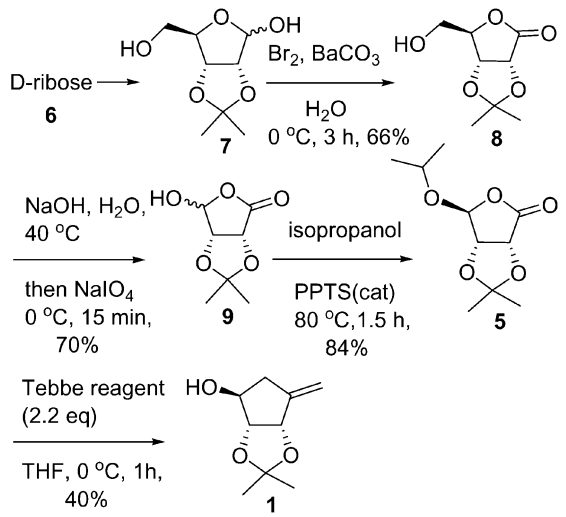
Based on retrosynthesis (Scheme 1), it was felt that compound **2** is a logical precursor for **1**, which in turn can be prepared from the enofuranoside **4** *via* ring-opening followed by intramolecular aldol reaction. The enofuranoside **4** can be synthesized from lactone **5** through a one-carbon extension.

In principle, we require a methylenation reagent for two one-carbon extension steps and a Lewis acid for cleavage of isopropyl group for carbocyclization to complete all the transformations of lactone **5** to olefin alcohol **1**. It was felt that Tebbe reagent is a suitable one for the conversion of **5** to **1**, and is very well known for one-carbon extension of carbonyl compounds, esters, lactones *etc*.[12] The bimetallic Tebbe reagent and its dissociated byproducts are known to have acidic properties. Generally this Lewis acidity is a drawback in conventional functional group transformations whereas here, we took the advantage of this property.[13]

In order to implement the above assumption, we undertook the synthesis of 4a-carba-α-D-lyxofuranose **13** which is a very important precursor for accessing carbonucleosides[1] whose synthesis is not as simple as one might presume. For this, the required lactone **9** was prepared from the 2,3-*O*-isopropylidene-D-ribose **7** based on the reported protocol[14–17] with good overall yield. Compound **9** was converted to its isopropyl



Scheme 1 The retrosynthesis of compound **1**.



Scheme 2 Synthesis of key intermediate **1** from D-ribose.

glycoside (**5**) using isopropanol and catalytic PPTS (Scheme 2).

When compound **5** was treated with Tebbe reagent (2.2 eq.) in THF solution at 0 °C for 1 h, it smoothly yielded the expected compound **1** in 40% yield, $[\alpha]^{20}_{D}$ −125.24 (*c* 2.67, $CHCl_3$).[18] The newly created hydroxyl center is confirmed as *anti* to the existing alkoxy groups, through extensive NMR studies (Fig. 1). The stereoselectivity of the reaction could be rationalized through a seven-membered transition state (**Y**) or through the transition state (**Z**) where the carbonyl group is located away from the isopropylidene, thus generating the *trans* hydroxy functionality in the cyclized product.

In the conversion of **5** to required compound **1**, four transformations are taking place sequentially in one-pot. These are methylenation of lactone **5** to give **4**, cleavage of the isopropyl group in isopropyl enofuranoside **4** to give **3**, intramolecular aldol reaction of **3** to give **10** and again methylenation of **10** to give **1**. First activation of the enol oxygen in **4** by Lewis acid helped the cleavage of the ring C–O bond instead of the anomeric C–O bond and the strategic presence of the isopropyl unit on the anomeric oxygen led to its facile cleavage, later thus facilitating the ring-opening reaction to afford intermediate **3**. The intramolecular cyclization occurred *via* a disfavoured 5-(enolendo)-*exo-trig* pathway[19] under Lewis acid catalysed condition (Scheme 3).

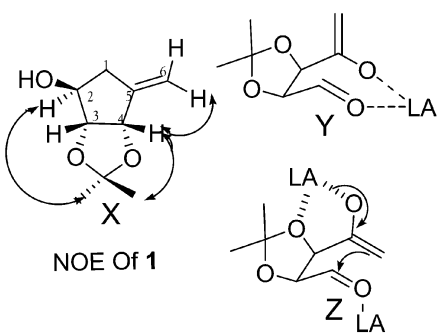
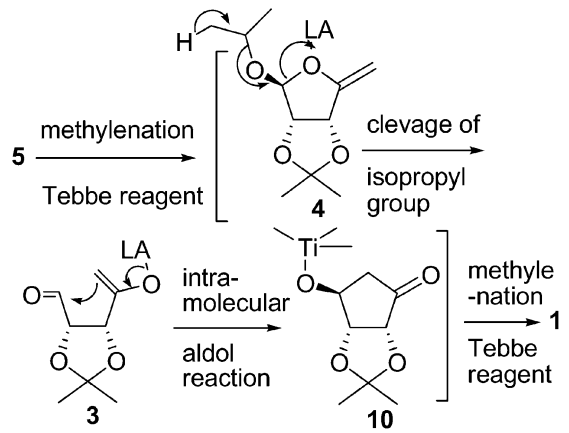


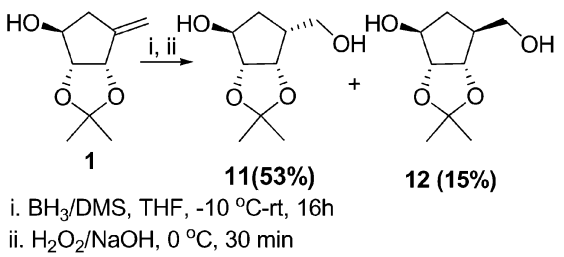
Fig. 1 **X** NOEs showing the relative stereochemistry of compound **1**; **Y** and **Z** are the possible seven-membered transition states.



Scheme 3 The proposed mechanism for the synthesis of the key intermediate **1**.

After achieving the five-membered carbocycle product **1** successfully, we turned our efforts for the transformation of **1** to carbafuranose **11** by functionalizing the exocyclic double bond.

The olefinic compound **1** on stereoselective reduction[20] with BH_3·DMS and followed by oxidative hydrolysis with H_2O_2–NaOH yielded the 2,3-*O*-isopropylidene 4a-carba-α-D-lyxofuranose **11** and 2,3-*O*-isopropylidene 4a-carba-α-L-ribofuranose **12** in 3.5 : 1 ratio (Scheme 4). The ^1H, ^{13}C NMR and specific rotation $[\alpha]^{20}_{D}$ +38 (lit $[\alpha]^{20}_{D}$ = +40) values of the major compound **11** matched with the reported values.[21] The stereochemistry was further confirmed by NOE studies (Fig. 2).



Scheme 4 Stereoselective reduction of key intermediate **1**.

Diol **11** on acidic hydrolysis with MeOH–HCl afforded 4a-carba-α-D-lyxofuranose **13**. For the convenience of purification the crude product (tetraol) was converted to its acetylated derivative **14** using Ac_2O–Et_3N (Scheme 5). The spectral and physical data of **14** were in good agreement with the reported values.[19]

In conclusion we have developed a novel strategy for the transformation of a five-membered carbohydrate lactone to cyclopentitol using Tebbe reagent and synthesized 4a-carba-

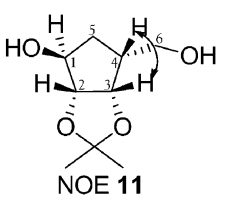
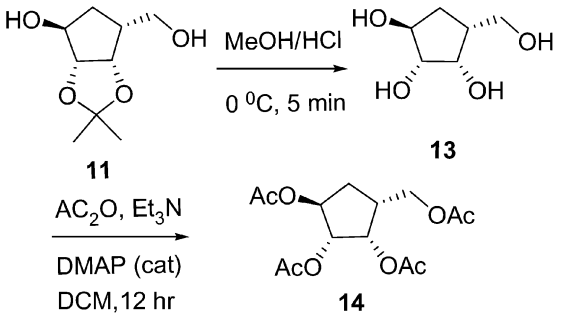


Fig. 2 The NOEs showing the relative stereochemistry of compound **11**.



Scheme 5 Deprotection and acetylation of major compound **11**.

α-D−lyxofuranose **13** an important carbasugar. Further studies on application of this strategy for the synthesis of different five- and six-membered carbasugars are underway.

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