Tetrahedron xxx (2016) 1–12

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of some carbahexopyranoses using Mn/$CrCl_3$ mediated domino reactions and ring closing metathesis

Bejugam Santhosh Kumar, Girija Prasad Mishra, Batchu Venkateswara Rao *

Organic and Biomolecular Chemistry Division, CSIR- Indian Institute of Chemical Technology, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 14 December 2015
Received in revised form 28 January 2016
Accepted 19 February 2016
Available online xxx

Keywords:
Carbasugars
Aminocarbasugars
Reductive elimination
Nozaki–Hiyama–Kishi reaction
Ring closing metathesis

ABSTRACT

An efficient and common method for the synthesis of 5a-carba-α-D-mannopyranose **5**, 5a-carba-β-D-mannopyranose **6**, (+) methyl shikimate **9**, (+) methyl-5-*epi*-shikimate **10**, validamine analogue **15** and valiolamine analogue **16** from D-mannose, formal synthesis of Tamiflu **17** from D-ribose and also synthesis of 5a-carba-α-D-glucopyranose **1**, 5a-carba-β-D-glucopyranose **2**, 5a-carba-β-L-altropyranose **7** and 5a-carba-α-L-altropyranose **8** from D-xylose is described using Nozaki–Hiyama–Kishi (NHK) condition and ring closing metathesis (RCM). In this transformation 5-deoxy-5-halo-manno/ribo/xylo furanoside undergoes reductive elimination in the presence of Mn/$CrCl_3$ to give corresponding olefin-aldehyde which was trapped by nucleophile under the same condition to afford diolefinic species which on metathesis reaction with appropriate Grubbs catalyst produced required carbocycles.

1. Introduction

Carbasugars or pseudosugars are carbocyclic analogues of monosaccharides in which the ring oxygen is replaced by methylene.[1] If C-1 OH in carbasugars is replaced by amino group then they are called as aminocarbasugars. These compounds are excellent glycosidase inhibitors and shows interesting biological activity such as *anti*-cancer, *anti*-diabetic, *anti*-HIV, etc.[1,2]

Some of the important carbasugars and their derivatives are depicted in Fig. 1. Racemic pseudo-α-D-glucopyranose **1** shows inhibition of glucose stimulated-insulin release and islet glucokinase activity.[3] (±) Carbasugar **2** is a substrate of the cellobioside phosphorylase of *cellvibro gilvuse*,[4] and also the taste of (±) carba-β-DL-glucopyranose **2** is same as that of D-glucose.[5] Carba-glucotropaeolin **3** is a 5a-carba analogue of β-D-glucopyranose and is a good inhibitor of myrosinase.[6] Pseudo-sergliflozin **4** is a carba analogue of sergliflozin, a phase II drug and is a potent and selective inhibitor of sodium-dependent glucose cotransporter 2 (SGLT2) for the treatment of Type 2 diabetes and its IC_{50}=2.45 nm.[7] Shikimic acid is a key intermediate in the synthesis of aromatic amino acids by plants, fungi and microorganisms. Shikimic acid and their derivatives such as methyl shikimate **9** and methyl-5-*epi*-shikimate **10** are biologically important compounds.[8] Moreover several carbasugars and aminocarbasugars have been synthesised starting from shikimic acid and their intermediates.[1a]

Some of the important aminocarbasugars are depicted in Fig. 2. These are valienamine **11,** validamine **12** and valiolamine **13**, which are secondary metabolites of various microorganisms showing glycosidase inhibitory activity. Valiolamine **13** shows activity against maltase and sucrase.[9] Voglibose **14** is the chemical modification of valiolamine currently used for the treatment of diabetes.[10] Tamiflu **17** is related to aminocarbasugar structure and is widely used for the treatment of H5N1 influenza as well as H1N1 influenza.[11]

In continuation of our efforts towards the synthesis of carbohydrate mimics such as carbasugars,[12] aminocarbasugars[13] and iminosugars,[14] herein we report the synthesis of 5a-carba-α-D-mannopyranose **5**,[15] 5a-carba-β-D-mannopyranose **6**,[15b,c,d,h] (+) methyl shikimate **9**,[16] (+) methyl-5-*epi*-shikimate **10**,[16] validamine analogue **15**[13b,17a,b] and valiolamine analogue **16**[13b,17c,d] from D-mannose and formal synthesis of Tamiflu[18] from D-ribose. Also we present here synthesis of 5a-carba-α-D-glucopyranose **1**,[15a,b,c,19] 5a-carba-β-D-glucopyranose **2**,[9c,9e,15a,19g] 5a-carba-β-L-altropyranose **7**[19d,20] and 5a-carba-α-L-altropyranose **8**[21] from D-xylose. The key step in the synthesis of above molecules is one pot reductive ring opening of 5-deoxy-5-iodomanno/ribo/xylo furanoside and C–C bond formation using allyl bromide under NHK[22] condition to get the diene precursor for RCM reaction.[23]

2. Results and discussions

Reductive elimination of 5-deoxy-5-halofuranosides under Bernet-Vasella[24] protocol giving chiral 4-pentenals, has many

* Corresponding author. E-mail address: venky@iict.res.in (B.V. Rao).

http://dx.doi.org/10.1016/j.tet.2016.02.044
0040-4020/

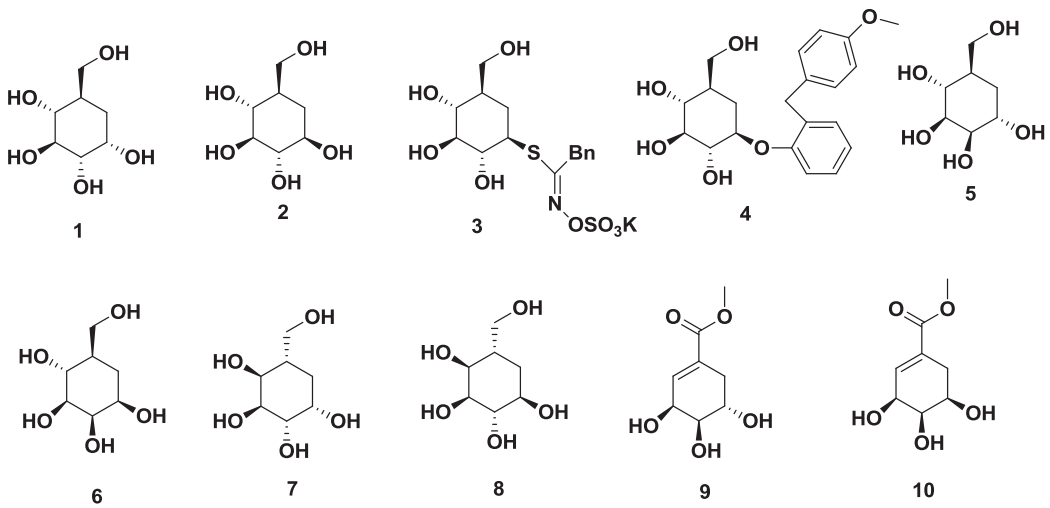


Fig. 1. Carbasugars and their derivatives.

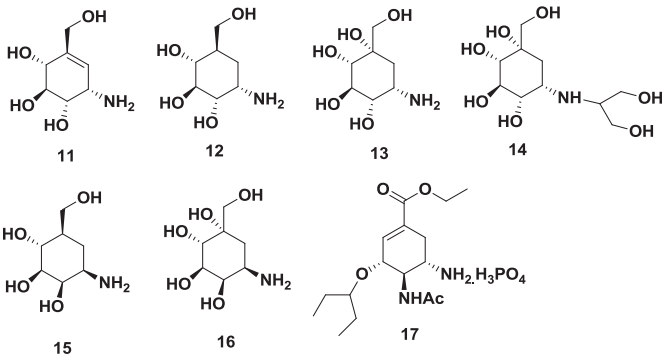
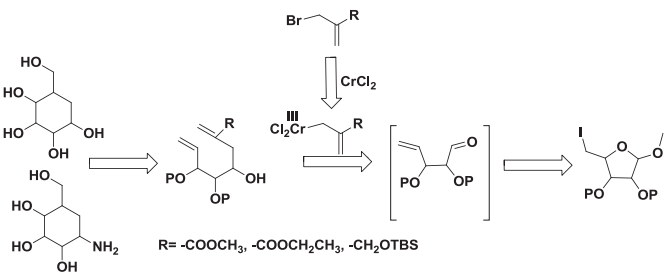


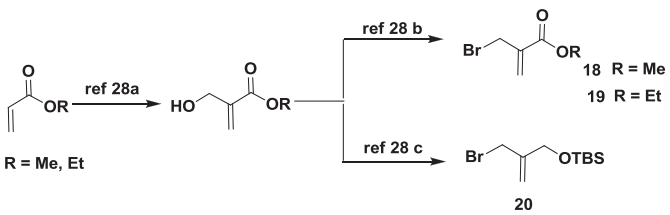
Fig. 2. Some important aminocarbasugars.

synthetic applications.[25] The reductive elimination can be carried out with different metallic reagents such as Zn,[24a,b] In,[25d] $CrCl_2$,[26a] SmI_2,[26b] $Mn/PbCl_2$,[26c] BuLi[24a,b] and acetyliron.[24g] Reductive ring opening of 5-deoxy-5-halofuranosides followed by intermolecular C–C bonding coupling in one pot have been performed by using Zn[25c–f] and In[25d] under ultrasonication. Our group has earlier developed $CrCl_3/Zn$ condition for the generation of olefin-aldehyde in which Zn is used for the conversion of $CrCl_3$ to $CrCl_2$ and the aldehyde was trapped by vinyl chromium (NHK reaction) to form diene precursor for the RCM, which was carried further for the synthesis of carbafuranoses.[12a] Later for this purpose,[12b] we utilized Furstner's modified NHK condition for the generation of $CrCl_2$ from $CrCl_3$ using Mn as reductant which remains inert throughout the reaction.[27] Herein we wish to describe the synthetic utility of our domino NHK and RCM strategy for the synthesis of various carbapyranoses from 5-deoxy-5-halo manno/ribo/xylo furanosides. The retrosynthetic analysis was depicted in Scheme 1.



Scheme 1. Retrosynthetic analysis.

The 5-deoxy-5-iodo furanosides can be obtained from respective sugar such as mannose, ribose and xylose. The nucleophiles **18, 19** and **20** required for the NHK reaction are prepared from methyl/ethyl acrylate[28] (Scheme 2).



Scheme 2. Allyl nucleophiles for NHK reaction.

For the synthesis of (+) methyl shikimate **9**, (+) methyl-5-*epi*-shikimate **10**, pseudo-α-D-mannopyranose **5** and pseudo-β-D-mannopyranose **6** (Scheme 3), the iodo compound **21**[29] obtained from D-mannose was treated with $Mn/CrCl_3$ (20:1) for 8 h in THF/DMF. The change in colour from violet to pale blue confirmed the formation of $CrCl_2$. After the consumption of starting iodo compound (confirmed by TLC), catalytic amount of $NiCl_2$, methyl 2-(bromomethyl)acrylate **18** followed by TMSCl at 50 °C were added to carry out the NHK reaction. The reaction completed in 5 h and gave an inseparable mixture of diastereomers **22** and **23** in 1:1 ratio in 75% yield (over 2 steps). Mixture of **22** and **23** were reacted with Hoveyda-Grubbs second generation catalyst to afford compounds **24** and **25** in 96% yield which were separated using column chromatography. The compound **24** on oxidation with Dess–Martin periodinane followed by stereo selective reduction with $NaBH_4$ produced compound **25** exclusively. Though NHK reaction gave two diastereomeric alcohols in 1:1 ratio, the oxidation and reduction strategy provided a way for obtaining the single diastereomeric compound **25**. Deprotection of **24** and **25** independently using aqueous TFA afforded (+) methyl shikimate **9** and (+) methyl-5-*epi*-shikimate **10,** respectively. The physical and spectral data of compound **9**[16i,j] and **10**[16h] are in accordance with the reported values. For the synthesis of pseudo-α-D-mannopyranose **5** and pseudo-β-D-mannopyranose **6**, first the ester functionalities in compounds **24** and **25** were reduced using DIBALH to furnish alcohols **26** and **29**, respectively. Next the compounds **26** and **29** on stereoselective hydroboration/oxidation afforded triol compounds **27** and **30**, respectively. Deprotection of acetonide functionality in