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Chemoselective Nozaki–Hiyama–Takai–Kishi and Grignard reaction: short synthesis of some carbahexopyranoses†

Allam Vinaykumar,*[a] Banothu Surender[b] and Batchu Venkateswara Rao ●*[b]

A common, divergent, efficient, stereoselective and short approach for the total syntheses of some carbahexopyranoses namely, MK7607, (−)-gabosine A, (−)-conduritol E, (−)-conduritol F, 6a-carba-β-ᴅ-fructopyranose and other carbasugars using chemoselective Grignard or Nozaki–Hiyama–Takai–Kishi (NHTK) reactions and RCM. Herein, the Grignard and NHTK reactions are able to differentiate the reactivity difference between lactol or lactolacetate and aldehyde of **2** & **6** under given conditions to give the desired skeleton chemoselectivity.

Introduction

Carbasugars, the carbocyclic analogues of sugars, constitute an important class of natural products. These carbasugars were stable to enzymatic hydrolysis in biological systems and display a diverse range of biological activities.[1] Their inhibition activity has enormous potential for the treatment of many diseases.[2] Carbohydrates are involved in various cellular signaling pathways, therefore there is a great interest in synthesis and biological exploration of carbasugars and their synthetic analogues. Many carbasugar-type natural products have polyoxygenated methyl or hydroxymethyl cyclohexane as a common structural feature, which are classified under C7-cyclitols. Gabosines belongs to this class and they are secondary metabolites isolated from several *Streptomyces* strains and also known as ketocarbasugars. They are known to display a wide range of interesting bioactivities, such as antibiotic,[3] anticancer,[4] inhibition of cholesterol biosynthesis,[3b] and DNA binding properties.[5] Gabosine derivatives are also considered as very potent and emerging antitumor agents due to their glutathione S-transferases (GST) inhibition activity.[6] In addition gabosine related derivatives have been used as intermediates for the synthesis of biologically active compounds such as an ʟ-fucosyltransferase inhibitor,[7a] valienamine and its derivatives,[7b] and pseudo sugar C-disaccharides.[7c] Some secondary metabolites with the gabosine structural pattern were isolated from natural sources and shown to have important biological activity. These are MK7607, streptol (also named valienol), uvamalol A and uvacalol A (Fig. 1).

Another interesting class of cyclitols are conduritols or 1,2,3,4 cyclohexene tetrols. Several conduritol derivatives possess antifeedant, antibiotic, antileukemic, and growth-regulating activity.[8] Conduritol epoxides and amino-conduritols act as inhibitors of glycosidases,[9] Also, conduritols have been widely used as intermediates in chemical syntheses of inositols,[10] deoxyinositols,[11] conduritol epoxides,[9a,c] amino-conduritols,[9a,c,12] cyclophellitol,[13] pseudosugars,[14] amino sugar analogs,[15] *etc.* Some more interesting compounds under this class are 6a-carba-β-ᴅ-fructopyranose which could be used as a non-nutritive sweetener since it has a sweet taste[16] which is also active carba-isostere of topiramate, a useful antiepileptic drug.[17] (−)-Uvarirufol A isolated from *Uvariarufa* and similar polyhydroxy cyclohexene derivatives showed a wide range of biological activities such as anti-tumor, anti-malarial, anti-leukemic, and pesticidal.[18]

The structural diversity and promising biological activities of these molecules have triggered several approaches for their synthesis. Synthesis of gabosines was reviewed by Mac[19a] and co-workers. The isolation, structural determination, biogenetic studies, biological evaluation, and synthesis of gabosines and related molecules have been reviewed by Bayon and Figueredo.[19b] Later, recently some novel interesting approaches for these molecules have been reported.[20] In continuation of our interest in this area, the structural diversity and promising biological activities of MK7607, (−)-gabosine A, (−)-conduritol E, (−)-conduritol F, 6a-carba-β-ᴅ-fructopyranose and other carbasugars motivated us to develop a common strategy for their synthesis. These molecules have a common stereochemical arrangement, therefore a common strategy was envisaged for their synthesis.

(−)-Gabosine A was isolated from the *Streptomyces* strain,[3a,b] shows DNA binding activity and it is an important synthetic

[a]Fluoro-Agrochemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad, India. E-mail: vinaykumar@iict.res.in

[b]Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, India. E-mail: drb.venky@gmail.com
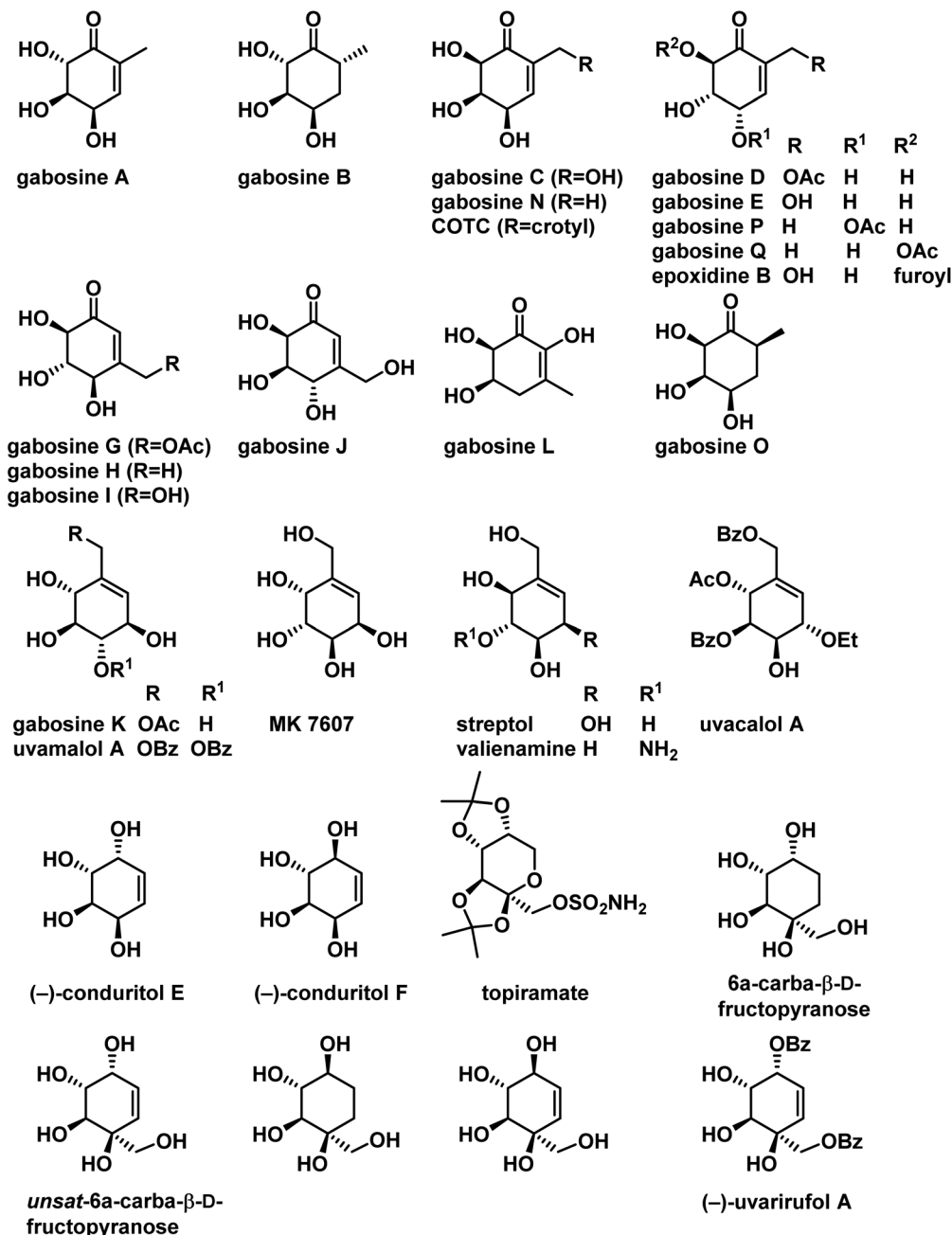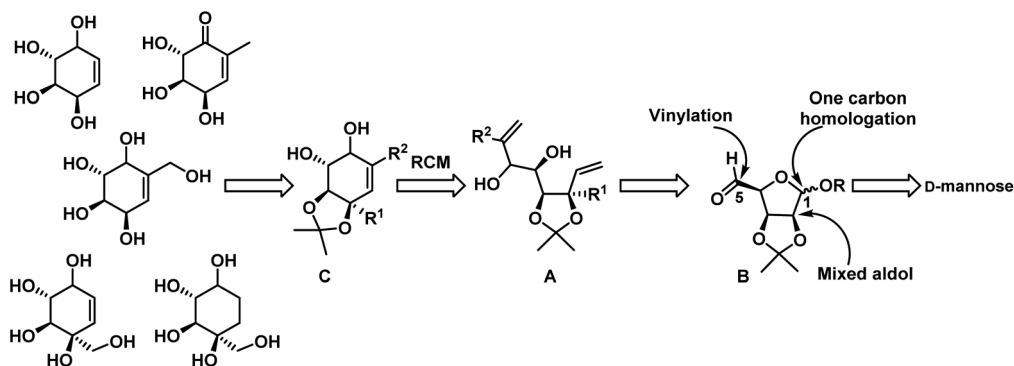
Fig. 1 Some of the naturally occurring carbasugars belongs to gabosine family and its related compounds.

target.[20b,c,21] (+)-MK7607 is a natural isomer, an α-galactose mimic, isolated from the culture of *Curvularia eragrostidis* D2452 and was found to have effective herbicidal and antimicrobial activities. The first total synthesis of MK7607 was reported in racemic form by Mehta *et al.*[22a] in 2000 from norbornane system. Later, many synthetic chemists focused their attention for the synthesis of (+)-MK7607,[22a] (−)-MK7607 (ref. 20b and 20c) and its epimers.[20b,22] The synthesis of (−)-MK7607 was reported by Shing *et al.*[22c] from (−)-shikimic acid and Sureshan *et al.*[20b] from D-pinitol. The synthesis of conduritol from cyclohexadiene-*cis*-1,2-diols have been accomplished in both racemic and enantioselective manner. Hudlicky

group reported the enantiocontrolled synthesis of conduritols (+)-E and (−)-F from bromobenzene in 1991.[23a] Next year, Carless[23b] applied a similar sequence of chemical transformations to reach conduritol E and reported optical rotation for (−)-conduritol E and pointed out the erroneous assignment in the Hudlicky synthesis. Also, some enantiopure conduritols have been prepared by employing chiral starting materials such as carbohydrates[23c] and diethyl L-tartrate.[23d]

Enantiomerically pure carba-β-D-fructopyranose has been synthesized previously from a chemically resolved Diels–Alder adduct of furan and acrylic acid,[24a] also from (−)-quinic acid,[24b] L-arabinose[24c] and an enzymatically resolved homochiral
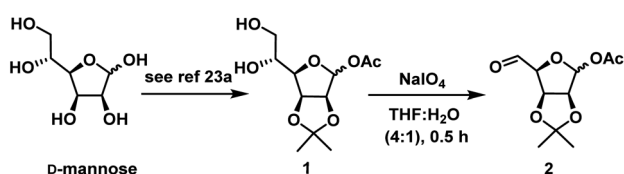
Scheme 1 Retrosynthetic analysis.

building block derived from cyclohexene.[24d] Additionally, the enantiomer of carba-β-D-fructopyranose ie 6a-carbab-L-fructopyranose has been targeted by different groups.[24e,f] So far there is no report on unsaturated analog of carba-β-D-fructopyranose **30** and other carbasugars **31** & **35**. Only few reports are present on enantiomer of **30** *i.e.* unsaturated analog of carba-β-L-fructopyranose from microbial oxidation of benzoic acid[24e] and chiral starting material (−)-shikimic acid.[24f] Herein, we would like to present the chemoselective nucleophilic addition methodology for the synthesis of above molecules. Our approach is a short and efficient which involves chemoselective Grignard and NHTK reactions from a single common intermediate. Our basic strategy is depicted in Scheme 1.

To synthesize RCM precursor **A**, from D-mannose in a classical way generally we need to carry protection and deprotection steps at C-1 and C5 positions. To minimize these steps in the synthesis and to avoid harsh conditions in deprotection steps, we envisaged a chemoselective NHTK reaction and vinyl Grignard addition on C-5 aldehyde of **B** in presence of hemiacetal followed by one carbon homologation at C-1 will give the required diene precursor for RCM. This can be elongated to the cyclohexene core **C**, a key intermediate for the synthesis of target molecules.

As per our strategy, we started our synthesis from D-mannose which is a cheap and commercially available. D-Mannose was converted to diol **1** using reported method[25a] in 65% overall yield. When diol **1** was subjected to oxidative degradation with NaIO₄ in THF : H₂O (4 : 1) for 0.5 h afforded compound **2** (Scheme 2). The next step is the chemoselective nucleophilic addition at C-5 aldehyde in presence of anomeric acetate. Later the anomeric acetate of the resultant adduct can be easily hydrolysed to lactol and Wittig reaction of the resultant lactol should give the diene for RCM reaction.
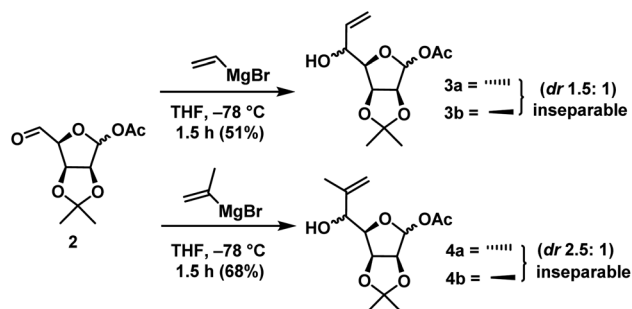
Chemoselective vinyl Grignard addition on intermediate 2

As mentioned above, the compound **2** has two functional groups which are reactive towards Grignard reagents one is free aldehyde and the other is anomeric acetate. It was felt that the selectivity can be achieved by reducing the reagent reactivity and minimizing its concentration in the reaction medium. After studying some conditions, it was found that the slow addition of Grignard reagent (1 equiv.) to **2** at −78 °C for 1 h gave the desired products in good yields. Vinylmagnesium bromide addition gave a mixture of ene compounds **3a** & **3b** as an inseparable mixture in the ratio of 1.5 : 1 (*anti* : *syn*) in 51% yield. When compound **2** was subjected to isopropenylmagnesium bromide for the synthesis of (−)-gabosine A under the above-mentioned conditions gave the mixture of ene compounds **4a** & **4b** as an inseparable mixture in the ratio of 2.5 : 1 (*anti* : *syn*) in 68% yield (Scheme 3).

A possible chelation controlled transition state for the Grignard addition was given in Fig. 2. Where one face is blocked by the acetonide group. Also it was found that the structurally bulky isopropenyl group gave better facial selection when compared to vinyl.

For the synthesis of (−)-MK7607, to introduce '3C' unit the compound **7** having protected hydroxymethyl part is not a practical choice for Grignard reaction. Therefore, it was thought to use NHTK reaction for the chemoselective introduction of 3C unit. The vinylchromium reagent generated in

Scheme 2 Construction of acetate aldehyde intermediate **2**.

Scheme 3 Chemoselective vinyl Grignard addition on intermediate **2**.
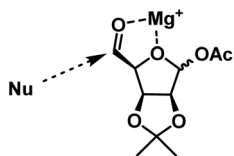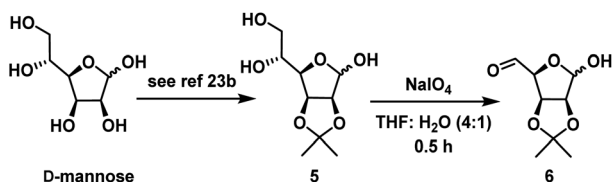
Fig. 2 Chelation controlled transition state. The configuration of the newly generated chiral centers in **3a** & **3b** were confirmed after completing the synthesis of target molecules and comparing the spectral data with the reported data.

Scheme 4 Construction of hemiacetal aldehyde intermediate **6**.

NHTK reaction is less reactive when compared to Grignard reagent. Therefore, it was further envisaged that on the substrate like **6** having aldehyde and lactol, the vinyl chromium should able to add chemoselectivity on the aldehyde. This strategy further eliminates the protection and deprotection steps at anomeric positions. For this, D-mannose was converted to diol **5** using the reported literature method[25b] in two steps in 50% overall yield. Compound **5** on oxidative cleavage with $NaIO_4$ in THF and H_2O in 4 : 1 ratio at 0 °C gave the aldehyde **6** (Scheme 4).

Compound **6** has two aldehyde groups, one is in free form at C5 and the other is in hemiacetal form at C1. When we treat the compound **6** with strong nucleophiles, such as alkyl lithium, magnesium, copper and other organometallic compounds may result in C–C bond formation at both the places. The NHTK reaction[26] is a very mild and highly chemoselective method for forming carbon–carbon bonds[27] with aldehydes in natural product synthesis. The NHTK reaction shows exceptional chemoselectivity in nucleophilic addition towards aldehydes over other functional groups. But to the best of our knowledge, we haven't find chemo selectivity addition of NHTK nucleophile on aldehydes in presence of lactol as in **6**. When, we carried out NHTK reaction on compound **6**, the addition of alkenyl chromium nucleophile (generated from **7**)[28] has taken place
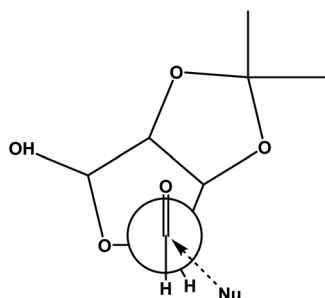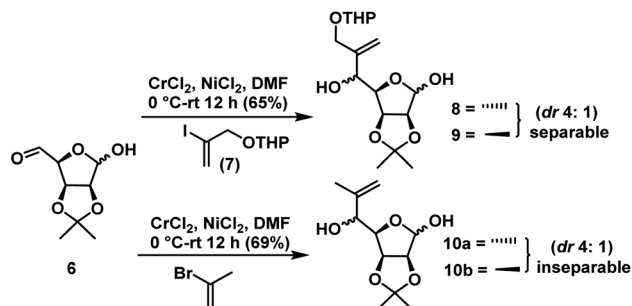

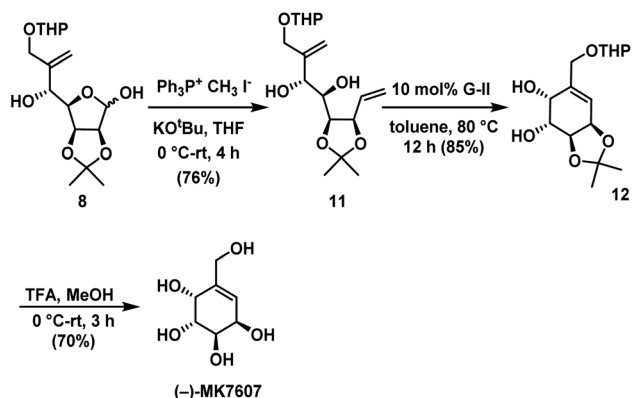**Fig. 3** Felkin–Anh model where nucleophile is organochromium.

Scheme 5 Chemoselective organochromium addition on intermediate **6**.

selectively on the free aldehyde to afford the alkenes **8** and **9** in the ratio of 4 : 1 (*anti* : *syn*) in 65% yield (from NMR) for two steps (Fig. 3). This is due to pronounced chemoselectivity and poor nucleophilicity of organochromium reagents. In NHTK reaction, the nucleophilic addition has taken place in a non-chelation mode due to the weak chelating property of chromium salt to give *anti* isomer **8** as the major. Only major isomer **8** was separated by column chromatography, whereas the minor isomer **9** was not separated in pure form, every time it was eluted as a mixture along with major isomer (Scheme 5). In order to see validity again we tried with 2-bromopropene under NHTK condition on compound **6** for the synthesis of (−)-gabosine A which gave **10a** and **10b** as an inseparable mixture in the ratio of 4 : 1 (*anti* : *syn*) in 69% yield for two steps.
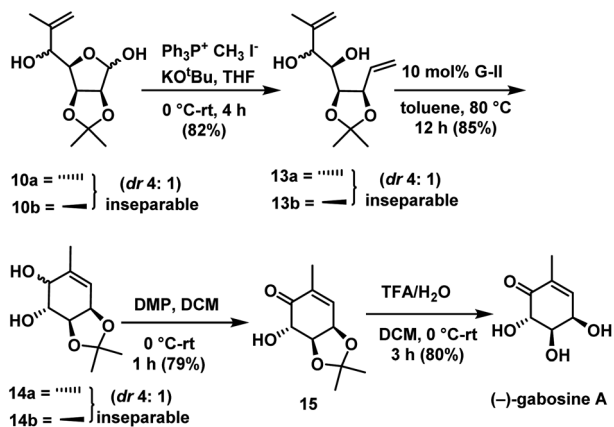
The major *anti*[27a] isomer was further confirmed after completing the synthesis of (−)-MK7607 **2** by comparing the spectral data with the reported one.

The next step is to utilize addition products for the synthesis of target compounds. To make diene precursor for RCM for the synthesis of (−)-MK7607 one-carbon homologation of lactol **8** using Wittig olefination[29] afforded the terminal olefin compound **11** in 76% yield. Ring-closing metathesis reaction was carried out on **11** using Grubbs II generation catalyst[28] to give substituted cyclohexene **12** in 85% yield. Finally, deprotection of acetonide in **12** under acidic conditions gave the target molecule (−)-MK7607 in 70% yield (Scheme 6).

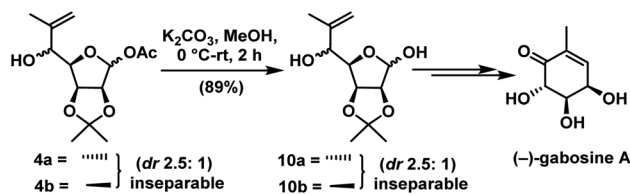**Scheme 6** Synthesis of (−)-MK7607.

Scheme 7 Synthesis of (−)-gabosine A.

Scheme 8 Synthesis of (−)-gabosine A.

Scheme 9 Synthesis of (−)-conduritol E and (−)-conduritol F.

One carbon Wittig olefination on the mixture of **10a** & **10b** afforded the diolefins compounds **13a** & **13b** as an inseparable mixture in the ratio of 4 : 1 in 82% yield. Ring-closing metathesis was carried out on a mixture of **13a** & **13b** using Grubbs II generation catalyst[30] to give substituted cyclohexenes as an inseparable mixture of **14a** & **14b** in the ratio of 4 : 1 in 85% yield. Allylic alcohol was selectively oxidized to ketone in compound **14a** & **14b** with DMP in DCM for a period of 1 h to give ketone compound **15**. Deprotection of acetonide in **15** under acidic conditions gave the target molecule (−)-gabosine A in 80% yield (Scheme 7).
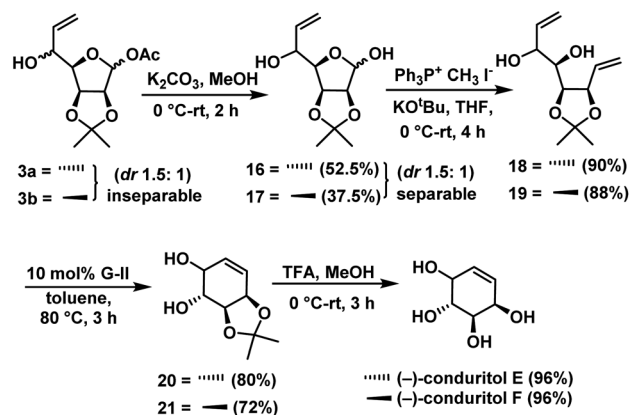
Deacylation in compounds **4a** & **4b** was done with K_2CO_3 in MeOH to give the inseparable mixture of hydroxyl compounds **10a** & **10b** in the ratio of 2.5 : 1 (*anti* : *syn*) in 91% yield. Then mixture was carried to the synthesis of (−)-gabosine A as shown in Scheme 7.

Deacylation of compounds **3a** & **3b** gave lactol **16** (52.5%) & **17** (37.5%) as separable diastereomers in the ratio of 1.5 : 1 (*anti* : *syn*). Wittig olefination on compounds **16** & **17** independently gave dienes **18** (90%) & **19** (88%). Next we focused our attention on its ring-closing olefin metathesis. Compounds **18** and **19** were subjected to RCM using Grubbs 2nd generation catalyst[30] independently to give cyclohexenes **20** (72%) and **21** (80%). Finally, removal of protecting groups in **20** & **21** was achieved independently by treating with TFA/H_2O in methanol, for a period of 3 h to give the (−)-conduritol E (96%) and (−)-conduritol F (96%) (Scheme 9), whose spectral data were in good agreement with the reported data.

For the synthesis of 6a-carba-β-D-fructopyranose & other three carbasugars we need to introduce hydroxymethyl unit. For this, compounds **16** & **17** were subjected to the mixed aldol
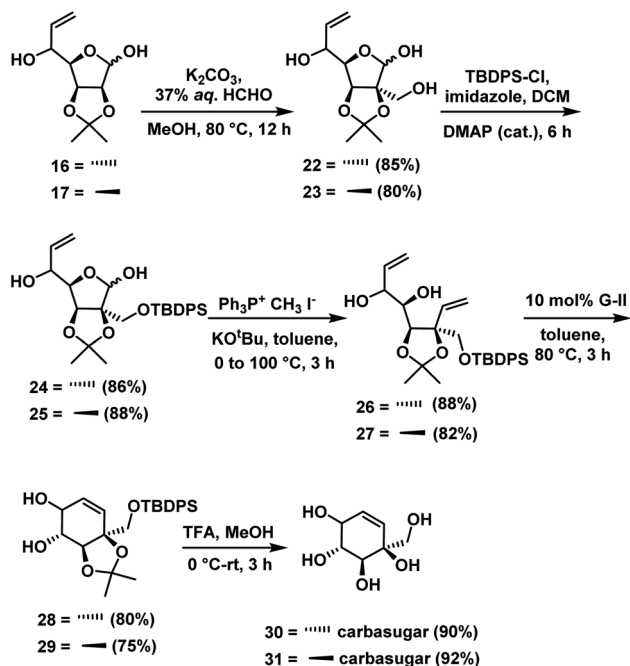
reaction[31] independently with excess 37% aqueous formaldehyde to give the 1,3 diols **22** (85%) & **23** (80%). To make diene precursor, we tried Wittig olefination on compounds **22** & **23** which failed to give the desired products and every time the starting materials were recovered. The inertness of substrates **22** & **23** towards Wittig olefination even with excess reagent might be due to the presence of a free hydroxyl group adjacent to the lactol (see Table 1). To circumvent this, we protected the primary alcoholic group in **22** & **23** as TBDPS ether to get **24** & **25** by treating with TBDPS-Cl, imidazole, and DMAP (cat.) for 6 h in 86% & 88% yields respectively (Scheme 8). Wittig olefination[32] under forced conditions on compounds **24** & **25** independently gave the dienes **26** (86%) & **27** (88%).

Compounds **26** and **27** were subjected to RCM using Grubbs 2nd generation catalyst independently to give cyclohexene intermediates **28** (80%) and **29** (75%). Finally, removal of protecting groups in cyclohexene derivative was achieved by treating the compounds **28** & **29** independently with TFA/H_2O in methanol, for a period of 3 h to give the carbasugar **30** (90%) and carbasugar **31** (92%) (Scheme 10), whose spectral data were in good agreement with the reported data in the case of **30** and assigned structure in the case of **31**.
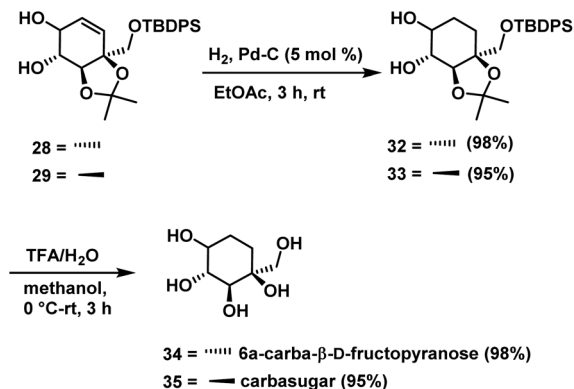
Table 1 Wittig olefination on compounds **22**, **23**, **24** and **25** nr = no reaction

Compound	Wittig salt (equivalents)	Potassium *tert*-butoxide (equivalents)	Temp (°C)	Time (h)	Yield (%)
22	6	5	rt	12	nr
23	6	5	rt	12	nr
24	6	5	100	3	86
25	6	5	100	4	88

Scheme 10 Synthesis of carbasugars **30** and **31**.

Scheme 11 Synthesis of 6a-carba-β-D-fructopyranose **34** and carbasugar **35**.

Hydrogenation of cyclohexene compounds **28** & **29** independently over palladium on activated carbon gave cyclohexane derivatives **32** (98%) & **33** (95%). Finally, deprotection of the acetonide in **32** & **33** with TFA/H$_2$O in methanol for a period of 3 h afforded compound 6a-carba-β-D-fructopyranose **34** (98%) and carbasugar **35** (95%) (Scheme 11), whose spectral and physical data were in agreement with the reported data in the case of **34** and assigned structure in the case of **35**.

Conclusions

We have successfully developed a common and short strategy for the synthesis of MK7607, (−)-gabosine A, (−)-conduritol E, (−)-conduritol F, 6a-carba-β-D-fructopyranose **34** and carbasugars **30**, **31** & **35** using chemoselective nucleophilic addition (Grignard, NHTK) reaction and RCM. To best of our knowledge

there is no report so far such type of chemoselectivity, where Grignard or NHTK reaction can differentiate the reactivity between lactol or lactolacetate and aldehyde. This approach is useful to make different carbasugars in a short time.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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