Synthesis of Carbasugars Based on Ring Closing Metathesis: 2000-2006

Joaquín Plumet[†,*], Ana M. Gómez[‡,*], and J. Cristóbal López[‡]

[†]*Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain*

[‡]*Instituto de Química Orgánica General (*CSIC*), Juan de la Cierva 3, 28006 Madrid, Spain*

Abstract: Carbasugars (a term coined for the carbocyclic analogues of carbohydrates) play a prominent role within the broad field of carbohydrate mimetics. Natural carbasugars, either as single molecules or as subunits of more complex molecules, have shown to display interesting biological activities. On the other hand, synthetic carbasugars have also shown similar biological activities. Normally, the construction of the carbocyclic framework is regarded as the key step in the synthesis of carbasugars. In this context, the use of ring closing metathesis (RCM) has proven to be of great value in recent synthetic approaches to carbasugars, owing to the discovery of easy to handle, robust, well defined, recyclable catalysts compatible with multiple functionalities. In this manuscript, we have focused on synthetic approaches to carbasugars and more complex derivatives that illustrate the usefulness of RCM reactions in the preparation of carbocyclic frameworks from sugar dienes.

1. INTRODUCTION

From 1966 to 1968, Professor G. E. McCasland's group prepared a series of derivatives in which the ring-oxygen of a monosaccharide had been replaced by a methylene group [1-3], and they coined the term *pseudosugars* for this family of compounds, that are currently known as **carbasugars** [4]. They postulated that their structural resemblance to the parent sugars would facilitate their recognition by enzymes or other biological systems in place of the related *true* sugars. This subtle change constituted an appealing possibility since, while guaranteeing a high similarity with the *true* sugar, it would lead to compounds more stable toward endogenous degradative enzymes. Notably, seven years later, 5a-carba-α-D-galactopyranose was isolated as a *"true"* natural product from a fermentation broth of *Streptomyces* sp. MA-4145 [5].

1.1. Carbasugars. Their Role as Carbohydrate Mimics

The interaction of cells with hormones, toxins, antibodies, bacteria, viruses and other cells involves carbohydrates. As a consequence, carbohydrate structures play critical roles in many biological functions. The increase of new discoveries on the biological functions of carbohydrates led to the development of an emerging field, glycobiology, which combines chemistry, biochemistry and molecular biology of carbohydrates [6]. Regarding the intervention of carbohydrates in the biosynthesis of the cellular membrane, their interaction with two types of enzymes is required. One of them, glycosyl transferases, catalyzes the glycosylation of a particular acceptor at a specific position. The other group of enzymes, glycosidases, catalyzes the hydrolytic cleavage of glycosidic linkages involved in the process. Thus, inhibitors of these enzymes should be considered as potential inhibitors of deseases associated with the biosynthesis of the cellular membrane and may act as potential antibacterial, antiviral, antimetastatic, antidiabetic, anthyperglycemic or immuno-stimulatory agents. Sugar mimetics able to "trick" these enzymes may be such inhibitors [7], and as mentioned above, carbasugars fall in this category together with other carbohydrate analogs such as iminosugars and thiosugars. All of them might be considered as carbohydrate mimetics, Fig. (**1**) [8].

In the case of carbasugars a plethora of monosaccharide and oligosaccharide mimics with enzymatic inhibitory activity have been described. However, a detailed discussion of this aspect falls beyond the scope of this review. Only, as an illustrative example, the enzymatic inhibitory activity of some carbapyranoses is displayed in Fig. (**2**), together with other therapeutic activities [9-17].

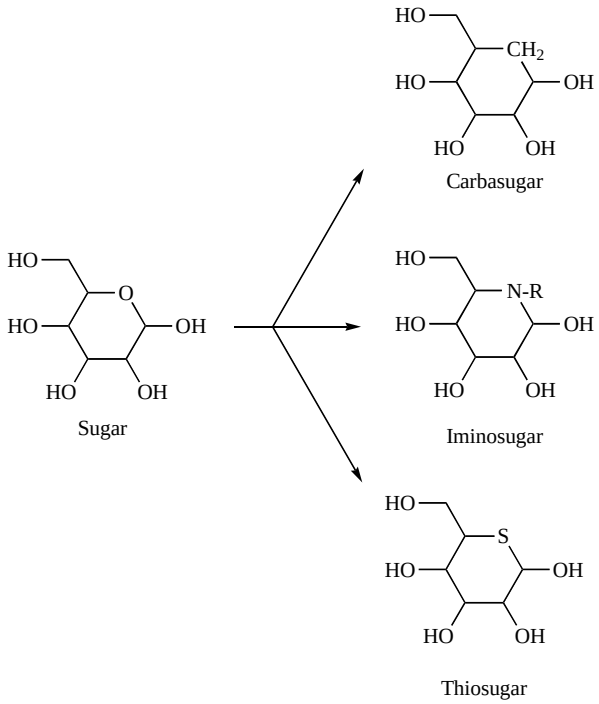

Fig. (1). Sugar mimetics.

From a synthetic standpoint, many different methods starting from carbohydrate or non-carbohydrate precursors have been developed. Among them, the metathesis reactions, both in the variant of ring closing metathesis (RCM) or cross-metathesis (CM) (see below), have emerged as convenient and versatile synthetic alternatives to other existing methods. Thus, before describing the application of these methodologies to the synthesis of carbasugars, a short overview on the scope and limitations of the metathesis reactions as synthetic tools appears to be pertinent.

1.2. Metathesis Reactions: Tools of the New Age of Organic Synthesis

A metathesis reaction, a process where a carbon-carbon double or triple bond is broken and rebuilt in the presence of an organometallic catalyst has revolutionized the organic synthesis during the last decade [18]. Applications of this synthetic technology range from their use in the synthesis of complex natural products [19] to the preparation of liquid crystalline polymers [20].

The classical variants of the metathesis reactions, ring-opening metathesis polymerization (ROMP) [21], ring closing metathesis (RCM) [22], acyclic diene metathesis polymerization (ADMET) [23],

*Address correspondence to these authors at the Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain; E-mail: plumety@quim.ucm.es; iqog106@iqog.csic.es

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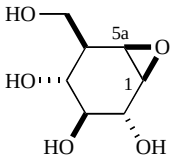
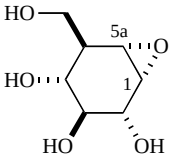
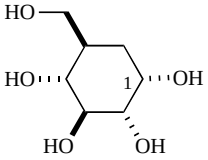


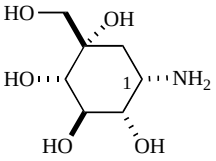
Cyclophellitol (ref. 9)
Inhibitor of β-glucosidases
(ref. 10)
Anti HIV and antimetastatic agent
(ref. 11)



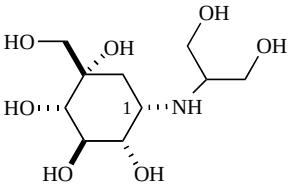
1-epi,5a-epi-Cyclophellitol (ref. 12)



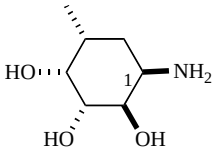
5a-carba-α-D,L-glucopyranose
Glucokinase inhibitor (ref. 13)



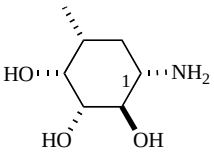
Valiolamine
α-glucosidase inhibitor (ref. 14)



Voglibose
Glycohydrolase inhibitor (ref. 15)
Marketed as antidiabetic agent since 1994.



5a-carba-α-D,L-fucopyranosylamine
α-L-fucosidase inhibitor (ref. 15)



5a-carba-α-D,L-fucopyranosylamine
β-L-fucosidase inhibitor (ref. 16)

Fig. (2). Enzymatic inhibitory activity of some carbapyranoses.

ring-opening metathesis (ROM) [24] and cross-metathesis (CM) [25] Fig. (**3**), constitute the basis for the application of this synthetic method.

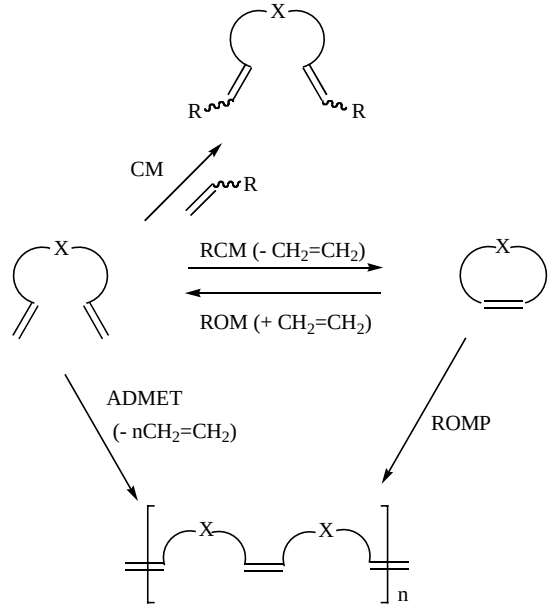


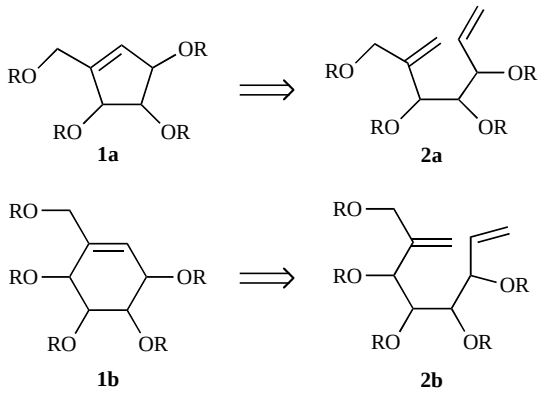
Fig. (3). Types of metathesis reactions.

1.3. Metathesis Reactions in Carbohydrate Chemistry

Olefin metathesis, in particular RCM and CM reactions, has been extensively applied in the field of carbohydrate chemistry and the topic has been reviewed several times in different contexts [26]. Regarding the preparation of carbasugars, the RCM variant of the metathesis reactions has proven to be particularly useful and several examples were collected in Madsen's [26a] and Roy's [26b] reviews. In this account we will cover the literature on the topic in the period 2000-2006, including the synthesis of carbafuranoses and carbapyranoses. It should be pointed out however, that RCM reactions have also been used in synthesis of some cyclopentene derivatives that are useful starting materials in the preparation of carbocyclic nucleosides with potential antiviral activity [27]. However, this last aspect will not be the subject of this review. On the other hand, the synthetic approachs to cyclitols and related compounds using metathesis procedures have also been previously reviewed [28].

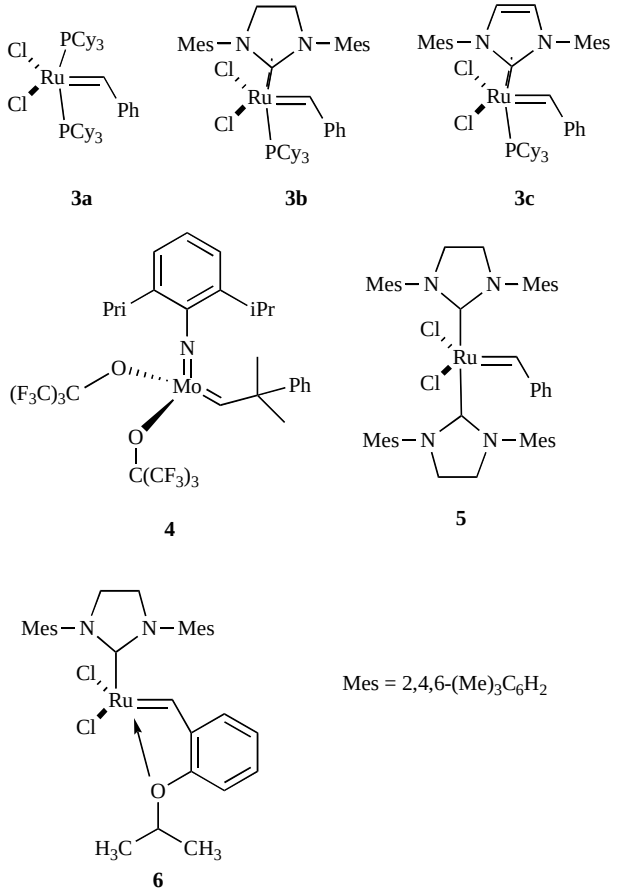
A retrosynthetic analysis for carbafuranoses and carbapyranoses reveal that these compounds could be obtained from a RCM reaction of a diene precursor (**2**) [29] (generally assembled from carbohydrate sources) followed by appropriate manipulation of the resulting cyclopentene or cyclohexene derivative (**1**) (Scheme **1**).

A key issue in the use of metathesis reactions in organic synthesis is the proper selection of the catalyst to be used. In fact, many applications of the metathesis reactions have only become possible because of the development of easy to handle well defined catalysts that are tolerant with most functional groups [30]. Among others, first generation



Scheme 1. Retrosynthesis of cyclopentenes and cyclohexenes, convenient precursors for carbafuranoses and carbapyranoses.

Grubbs' [31] and Schrock's [32] carbene complexes (**3a**) and (**4**), respectively (Fig. **4**) are the most popular commercially available catalysts. Catalysts based on the substitution of the PCy_3 ligand by a *N*,*N'*-disubstituted-2,3-dihydro-1*H*-imizazol-2-ylidene (**3b**, **3c** and **5**) fall into the category of "stable"-*N*-heterocyclic carbenes (NHC), showing significantly higher reactivity that the parent carbene (**3a**) and being close to or even surpassing that of the Schrock's Mo-alkylidene complex (**4**) [33]. On the other hand, a catalyst such as (**6**), with a coordinated bond to the metallic center [34], has gained considerable popularity. This complex is able to regenerate itself at the end of the catalytic cycle and can be recycled by conventional flash chromatography.



Mes = 2,4,6-$(Me)_3C_6H_2$

Fig. (4). Metathesis catalysts.

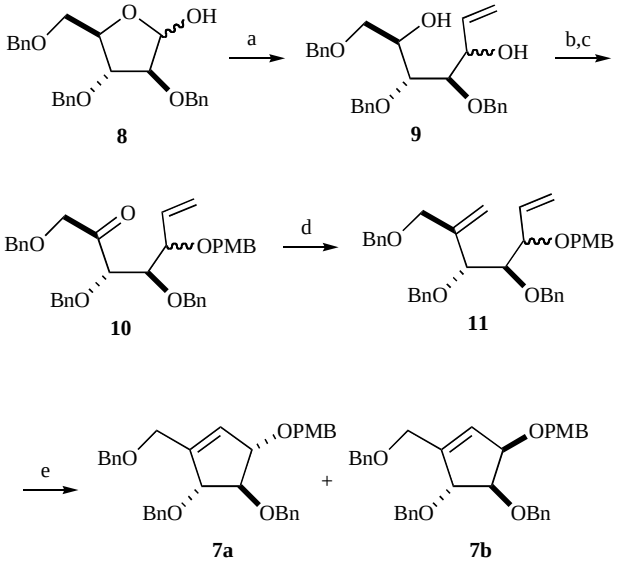
2. SYNTHESIS OF CARBAFURANOSES BY RCM REACTIONS

To the best of our knowledge, only carba-D-ribo-, carba-D-arabino-, and carba-D-xylofuranose together with trehazolamine have been synthesized using a RCM reaction as the key ring forming step, during the period covered by this review. These synthetic approaches are summarized as follows.

2.1. Carba-D-arabinofuranose

The importance of these compounds lies in their use as arabinofuranosyl transferase inhibitors. These enzymes play a key role in the biosynthesis of components of the mycobacterial cell-wall called arabinanes. Considering that infection by mycobacteria such as *Mycobacterium tuberculosis* is the origin of the tuberculosis in human [35], arabinosyltransferase inhibitors containing modified arabino-furanosyl residues [36] constitute a promising approach to the treatment of the disease [37].

Sepersaud and Al-Abed [38] synthesized diastereomeric p-methoxybenzyl carba-D-arabinofuranosides (**7a**) and (**7b**) from commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**8**) as shown in Scheme **2**. Reaction of (**8**) with vinylmagnesium bromide afforded an inseparable mixture of diastereomers (**9**). Selective protection of the allylic alcohol of (**9**) followed by Swern oxidation gave (**10**) which was transformed into the key diene (**11**) using Wittig chemistry. The diene (**11**) was refluxed in the presence of Schrock's catalyst (**4**) [39] (85 °C, 10h) to give a mixture of cyclopentenes (**7a**) and (**7b**) which was separated by flash chromatography (95% yield, **7a**:**7b** = 38:62). Since compound (**7b**), had previously been converted to 4a-carba-β-D-arabinofuranose via diastereoselective hydrogenation [40] this sequence constitutes a formal synthesis of the indicated carbasugar.

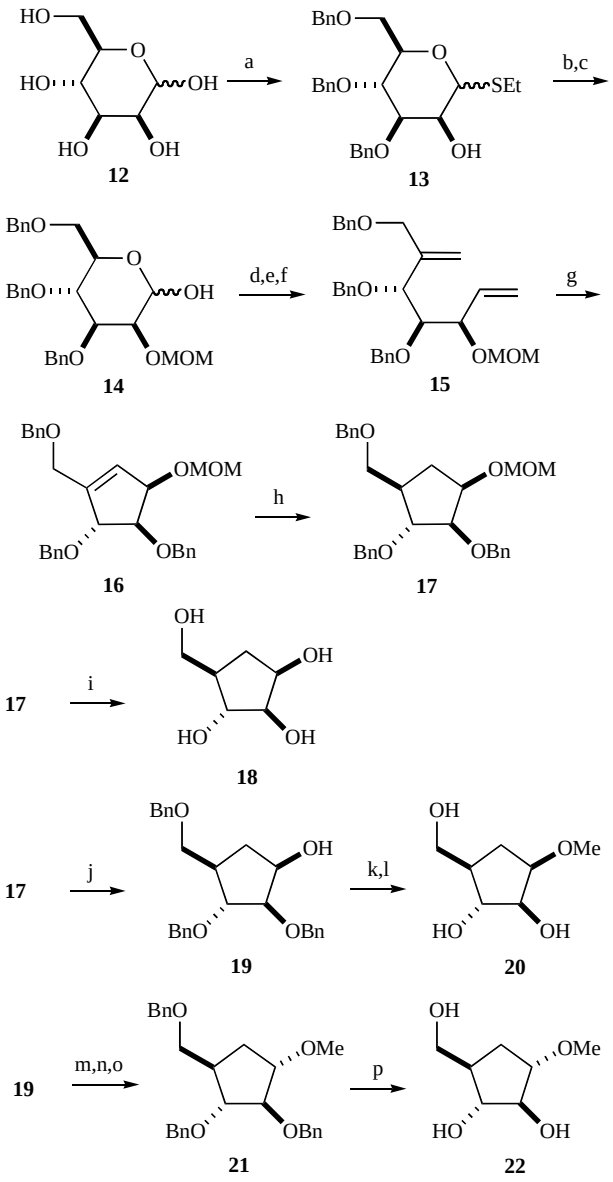


Reagents and conditions: (a) Vinylmagnesium bromide, THF, 87%; (b) p-methoxybenzyl chloride (PMBCl), NaH, DMF, 0 °C; (c) $(COCl)_2$, DMSO, Et_3N. Overall yield (two steps) 64%; (d) methyltriphenylphosphonium bromide, *n*-BuLi, 89%; (e) catalyst (***4***) (0.4 eq) 95%; (e) flash chromatography.

Scheme 2. Sepersaud and Al-Abed synthesis of carba-D-arabinofuranoside precursors.

Callam and Lowary [41] synthesized methyl-4a-carba-α- D- and β-D-arabinofuranosides and 4a-carba-β-D-arabinofuranose (**22**, **20** and **18**, respectively) starting from D-mannose (**12**) (Scheme **3**). Their synthetic route started with the transformation of the latter to the known protected thioglycoside (**13**) (six steps and 58% overall yield) [42]. Protection of the free hydroxy group of (**13**) was followed by oxidative

hydrolysis of the anomeric ethyl-1-thio group (NIS, AgOTf) to give hemiacetal (**14**). Wittig olefination, followed by oxidation and an additional Wittig homologation yielded the key diene (**15**). The conversion of (**15**) into cyclopentene (**16**) was explored using catalysts (**3a**) (**3b**) (**3c**) and (**4**). Catalyst (**3a**) gave poor results under a range of conditions, (Table **1**).



Reagents and conditions: (a) Six steps, 58% overall yield; (b) methoxymethyl chloride (MOMCl), NaH, THF; (c) NIS, AgOTf, CH_3CN-H_2O, 79% (two steps); (d) Ph_3PCH_2Br, n-BuLi, THF, -78 °C to rt; (e) PCC, NaOAc, 4Å MS, CH_2Cl_2; (f) Ph_3PCH_2Br, n-BuLi, THF, -78 °C to rt; (g) See Table 1; (h) $(Ph_3P)_3RhCl$ (30 mol%), H_2, $PhCH_3$, 88%; (i) H_2, Pd-C; (j) trace concd-HCl, MeOH, 95%; (k) CH_3I, NaH, THF; (l) H_2, Pd-C, MeOH, AcOH, 94% (two steps); (m) DEAD, PPh_3, p-$O_2NC_6H_4CO_2H$, $PhCH_3$; (n) NaOMe, MeOH; (o) CH_3I, NAH, THF, (p) H_2, Pd-C, MeOH, AcOH, 73%, (four steps).

Scheme 3. Callam and Lowary synthesis of carba-D-arabinofuranoses.

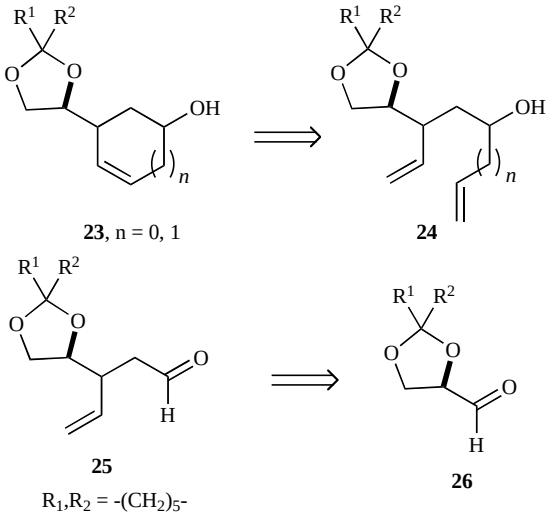
The obtained results were consistent with previous reports [43] which pointed out that catalyst (**3a**) does not provide good results in the RCM reaction of trisubstituted olefins (Table **1**, entries 1-3). Better results were obtained with (**3b**), (**3c**) and (**4**), the yields obtained with these three catalyst being very similar (Table **1**, entries 4-6). Taking into consideration that strictly anhydrous and air-free conditions are necessary for the use of (**4**), reactions in the presence of (**3b**) or (**3c**) were recommended since they are substantially more air-stable than (**4**), thus avoiding the need for a glove box.

Table 1. Ring Closing Metathesis of 15 to Give 16. Catalysts and Conditions

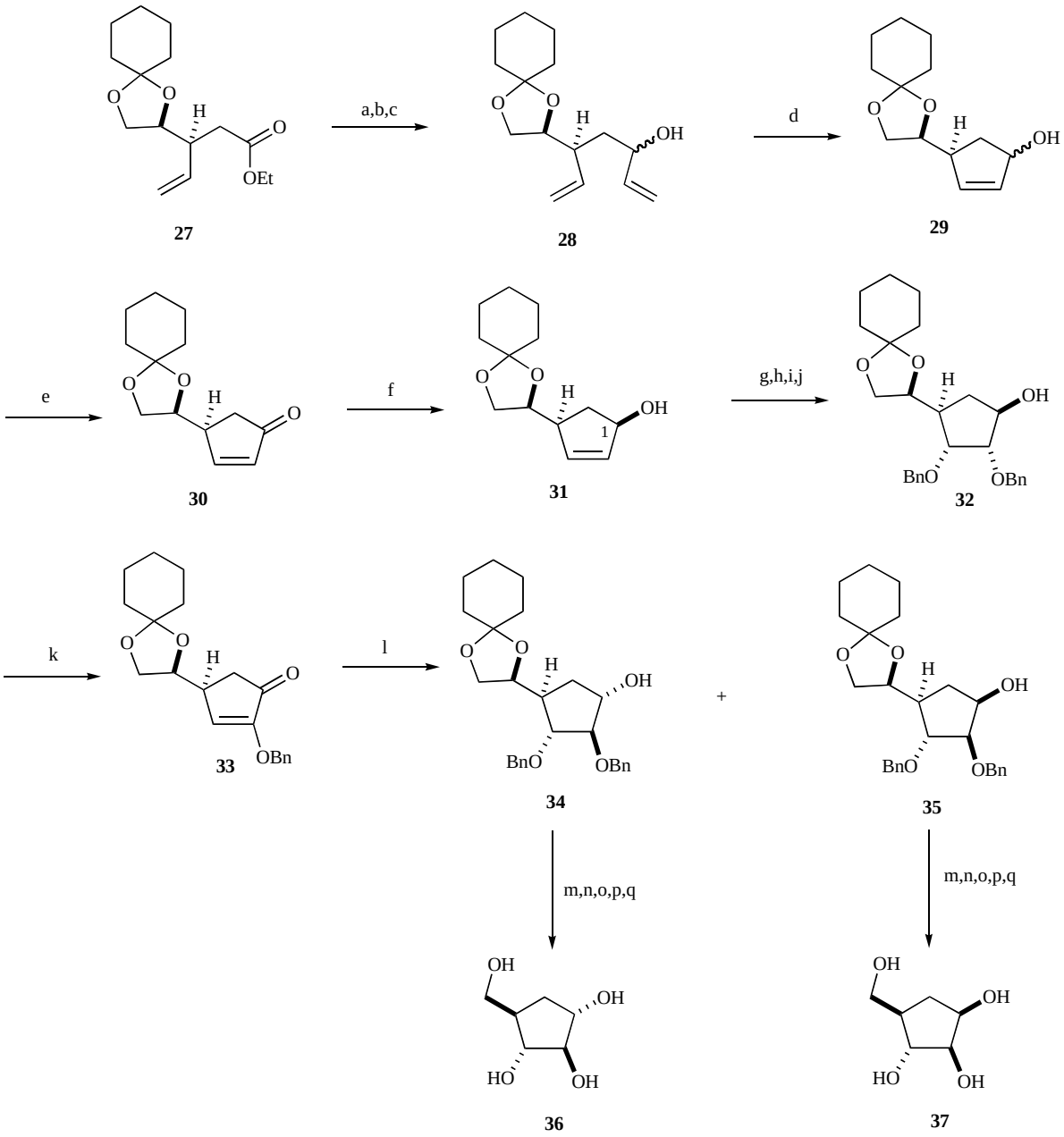
Entry	Catalyst/(mol%)	Conditions	Isolated Yield (%)
1	(**3a**) (5)	CH_2Cl_2, 24h	12
2	(**3a**) (10)	$PhCH_3$, 60 °C, 33h	19
3	(**3a**) (10)	xylenes, reflux, 48 h	0
4	(**4**) (20)	$PhCH_3$, 60 °C, 2h	74
5	(**3b**) (10)	$PhCH_3$, 60 °C, 2h	78
6	(**3c**) (10)	$PhCH_3$, 60 °C, 1,5h	74

Stereoselective hydrogenation of (**16**) was carried out upon reaction with Wilkinson's catalyst [$(Ph_3P)_3RhCl$] [39,44] under an atmosphere of hydrogen, giving (**17**) which was fully deprotected to 4a-carba-β-D-arabinofuranose (**18**). That confirms the strict stereochemical control of the hydrogenation reaction. On the other hand, removal of the MOM protecting group of (**17**) afforded alcohol (**19**) from which methyl 4a-carba-β-D-arabinofuranoside (**20**) was obtained after methylation followed by hydrogenolysis of the benzyl protecting groups. In order to prepare the epimeric carbasugar (**22**), alcohol (**19**) was subjected to Mitsunobu conditions followed by deacylation and further methylation. Final deprotection of (**21**) yielded methyl 4a-carba-α-D-arabino-furanoside (**22**).

More recently, Ghosh *et al.* have described a stereodivergent approach to carbasugars that has allowed the preparation of carba-α-D- and carba-β-D-arabinofuranoses (**36**) and (**37**), respectively (see Schemes **4** and **5**) [45]. Their general approach, also useful for the preparation of carba-D-ribofuranoses and carba-L-gulopyranoses (*vide infra*), is outlined in Scheme **4**. They reasoned that carbaanalogues of pentoses and hexoses could be prepared from carbocyclic enols of general structure (**23**) (Scheme **4**) by stereocontrolled introduction of the hydroxyl groups. In their approach, the ketal moiety at the allylic center is the source of chirality as well as the source of the hydroxymethyl group. The cyclic alkenols (**23**) were available by RCM of dienols (**24**), which in turn are readily prepared from the unsaturated aldehyde (**25**) on addition of an alkenyl metal having the required number of methylenes for its transformation into either carbapentoses or carbahexoses. The unsaturated aldehyde (**25**) was readily available from (*R*)-(+)-glyceraldehyde derivative (**26**).



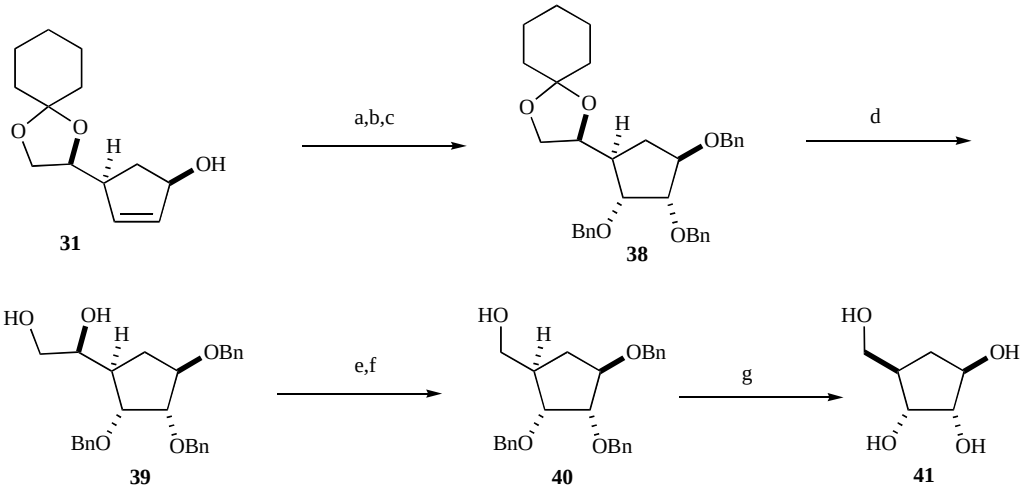
Scheme 4. Ghosh *et al.* retrosynthesis of carbapentoses and carbahexoses by RCM.



Reagents and conditions: (a) LAH, Et_2O, 0 °C, 90%; (b) Swern oxdn, 82%; (c) vinylmagnesium bromide, THF, 70 °C, 70%, (1:1 mixture); (d) Grubbs' I catalyst (***3a***), CH_2Cl_2, 83%; (e) Jones reagent, acetone, 0 °C, 86%; (f) LAH, Et_2O, -60 °C, 75%; (g) TBSCl, DMAP, Et_3N, imidazole, CH_2Cl_2, 83%; (h) OsO_4, NMO·H_2O, acetone:H_2O (4:1), 96%; (i) NaH, BnBr, THF, 0 °C to rt, 91%; (j) TBAF, THF, 0 °C to rt, 90%; (k) Swern oxdn, 82%; (l) BH_3, THF, -10 °C to 20 °C, then 3N NaOH, 30% H_2O_2, -10 °C to rt, (***34***) 20%, (***35***) 54%; (m) NaH, BnBr, THF, 0 °C to rt, 85% from (***34***), 86% from (***35***); (n) AcOH:H_2O (4:1); (o) $NaIO_4$, MeOH:H_2O (3:1), 0 °C; (p) $NaBH_4$, MeOH, 0 °C; (q) 10% Pd-C, H_2, MeOH, 96%.

Scheme 5. Ghosh *et al*. synthesis of carbaarabinofuranoses by RCM.

Their synthesis of 4a-carba-α-D-arabinofuranose (**36**) and 4a-carba-β-D-arabinofuranose (**37**) is outlined in Scheme **5**. Ester (**27**), prepared from glyceraldehyde derivative (**26**) (R^1,R^2 = -$(CH_2)_5$-) (see Scheme **4**) according to a procedure described by the same authors [46], was transformed to a 1:1 mixture of dienols (**28**), which underwent RCM with Grubbs I Ru-catalyst (**3a**) to yield cyclopentenols (**29**). The authors, however, devised a stereocontrolled route to allylic alcohol (**31**) by stereoselective reduction of a cyclopentenone (**30**) prepared by oxidation of cyclopentenols (**29**). Reduction of (**30**) with $LiAlH_4$ gave major isomer (**31**) in 79% yield (together with its C-1 diastereomer, in a 16:1 ratio). Conversion of allylic alcohol (**31**) to di-*O*-benzyl derivative (**32**) was carried out through a sequence involving silylation, stereocontrolled osmylation, benzylation, and desilylation. Next, Swern oxidation of (**32**) furnished cyclopentenone (**33**) in excellent yield, probably through a NEt_3-mediated elimination of the benzyloxy group *β*- to the carbonyl



Reagents and conditions: (a) NaH, BnBr, THF, 0 °C to rt, 92%; (b) OsO_4, NMO·H_2O, acetone:H_2O (4:1), 90%; (c) NaH, BnBr, THF, 0 °C to rt, 85%; (d) AcOH:H_2O (4:1), 75%; (e) $NaIO_4$, MeOH:H_2O (3:1), 0 °C, 94%; (f) $NaBH_4$, MeOH, 0 °C, 95%; (g) 10% Pd-C, H_2, MeOH, 96%.

Scheme 6. Ghosh *et al.* synthesis of 4a-carba-β-D-ribofuranose (**41**).

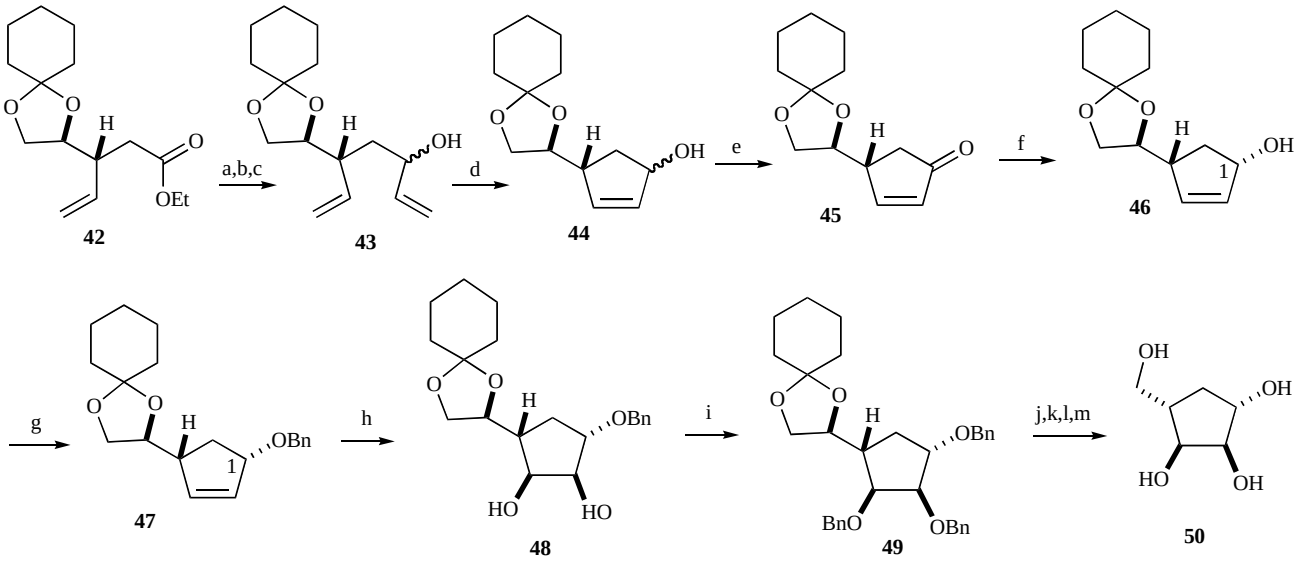
of an initially formed cyclopentanone, as suggested by the authors. Hydroboration of (**33**) gave a mixture of diastereomeric diols (**34**) and (**35**) in 20 and 54% yields, respectively. Finally, these diols, (**34**) and (**35**), were benzylated, deketalyzed, submitted to periodate cleavage, reduced and hydrogenolysed to 4a-carba-α-D-arabinofuranose (**36**) and 4a-carba-β-D-arabinofuranose (**37**), respectively.

2.2. Carba-D- and L-Ribofuranoses

Ghosh *et al.* also used their protocol (see Scheme 4) in the synthesis of 4a-carba-β-D-, 4a-carba-β-L-, and 4a-carba-α-D-ribofuranoses. The synthesis of carba-D-ribofuranose (**41**) employed previously used allylic alcohol (**31**) and is depicted in Scheme **6**. Benzylation of (**31**) followed by stereoselective osmylation and benzylation yielded tri-*O*-benzyl derivative (**38**). Acid-induced deketalyzation of (**38**) afforded the diol (**39**) which upon periodate cleavage of the ensuing diol and reduction of the resulting aldehyde afforded the polyoxygenated cyclopentane (**40**). Finally, hydrogenolysis led to 4a-carba-β-D-ribofuranose (**41**).

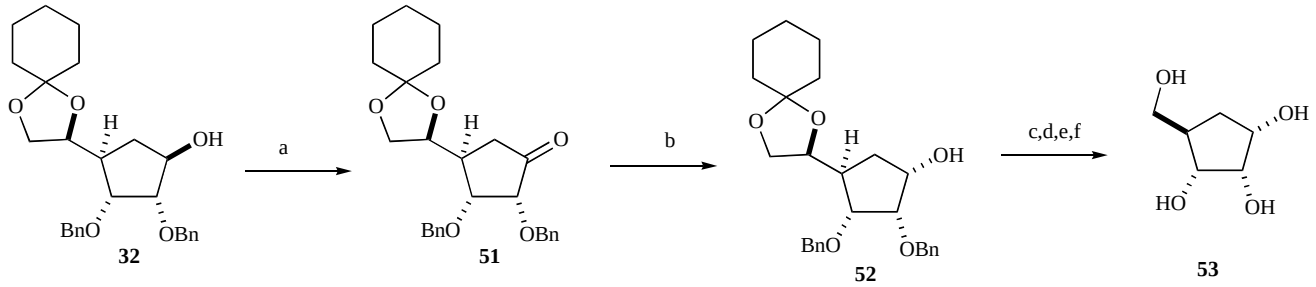
Their synthesis of carba-L-ribofuranose (**50**) is outlined in Scheme **7**. The protocol started with unsaturated ester (**42**), an epimer of compound (**27**) previously used in their preparation of carbaarabinofuranoses (**36**) and (**37**) (see Scheme **5**). A route similar to that in Scheme **5** permitted the preparation of allylic alcohol (**46**), a diastereomer of (**31**), from which osmylation and protecting group manipulations followed by glycol cleavage, reduction of the ensuing aldehyde and hydrogenolylsis yielded 4a-carba-β-L-ribofuranose (**50**) (Scheme **7**).

The polyoxygenated cyclopentane (**32**) was transformed into 4a-carba-α-D-ribofuranose (**53**) (Scheme **8**). The required inversion of the configuration at C-1 was achieved by an oxidation-reduction protocol. Oxidation of the cyclopentanol (**32**), with Jones reagent, afforded



Reagents and conditions: (a) LAH, Et_2O, 0 °C, 90%; (b) Swern oxdn, 82%; (c) vinylmagnesium bromide, THF, 70 °C, 70%, (1:1 mixture); (d) Grubbs' I catalyst **(3a)**, CH_2Cl_2, 83%; (e) Jones reagent, acetone, 0 °C, 86%; (f) LAH, Et_2O, -60 °C, 75%; (g) NaH, BnBr, THF, 0 °C to rt, 84%; (h) OsO_4, NMO·H_2O, acetone:H_2O (4:1), 80%; (i) NaH, BnBr, THF, 0 °C to rt, 88%; (j) AcOH:H_2O (4:1); (k) $NaIO_4$, MeOH:H_2O (3:1), 0 °C; (l) $NaBH_4$, MeOH, 0 °C; (m) 10% Pd-C, H_2, MeOH, 96%.

Scheme 7. Ghosh *et al.* synthesis of 4a-carba-β-L-ribofuranose (**50**).



Reagents and conditions: (a) Jones oxdn, 87%; (b) LAH, Et_2O, -60 ºC, 60%; (c) AcOH:H_2O (4:1), 60%; (d) $NaIO_4$, MeOH:H_2O (3:1), 0 ºC, 87%; (e) $NaBH_4$, MeOH, 0 ºC, 87%; (f) 10% Pd-C, H_2, MeOH, 94%.

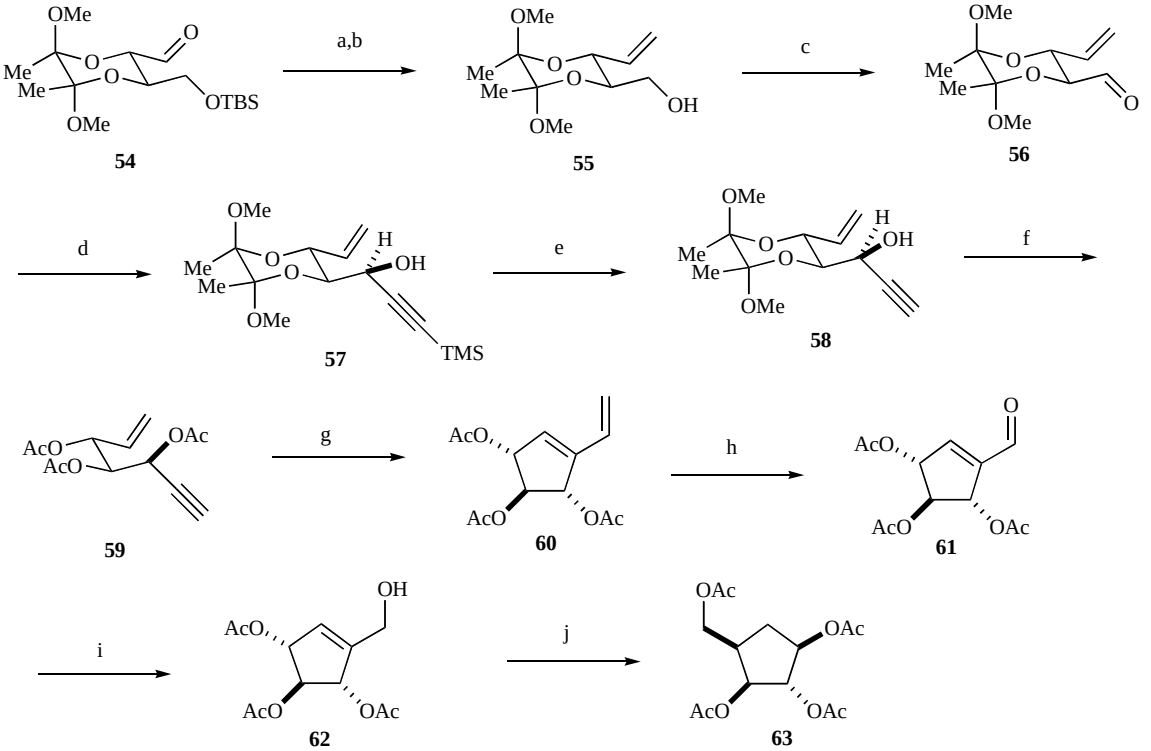
Scheme 8. Ghosh *et al*. synthesis of 4a-carba-α-D-ribofuranose (**53**).

ketone (**51**) in 87% yield. Reduction of the latter with $LiAlH_4$ took place with addition of the hydride predominantly from the side opposite to the C2 and C3 benzyloxy groups to afford the cyclopentanol (**52**) in 60% isolated yield, along with 9% yield of the epimeric (**32**). The ketal group was then converted to a hydroxymethyl group using the three-step protocol (deketalyzation, glycol cleavage and reduction) previously described in Schemes **5**, **6** and **7**. Final hydrogenolysis led to 4a-carba-α-D-ribofuranose (**53**).

2.3. Carba-D-xylofuranose [47]

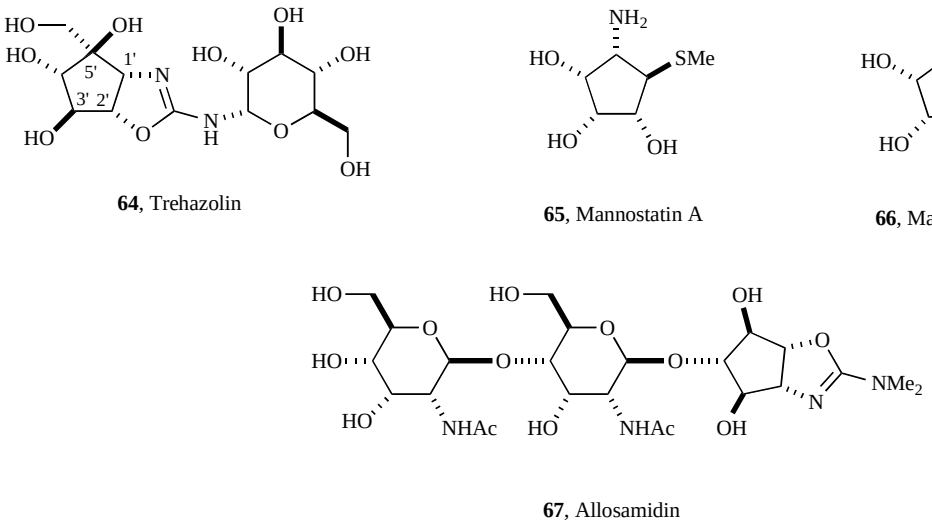
The most important feature in the synthesis of the title compound was the use of a ring closing enyne metathesis [48] for the construction of the functionalized cyclopentene derivative precursor of (**63**). The starting material was the known aldehyde (**54**) [49], and the appropriate enyne functionality was created in five steps, as indicated in Scheme **9**.

Olefination of (**54**), following a previously described protocol [50], and subsequent deprotection of the hydroxy group gave (**55**) which was oxidised (Swern) to aldehyde (**56**). The nucleophilic addition of trimethylsilyl acetylide to (**56**) was highly diastereoselective affording (**57**) in 86% *de* (70% isolated yield). Desilylation of (**57**) yielded enyne (**58**) which was converted into triacetate (**59**). The transformation of (**59**) into cyclopentene (**60**) by RCM was carried out using the Grubbs' catalyst (**3a**). Finally, conversion of (**60**) into (**63**) was achieved in three steps including the hydrogenation reaction of compound (**62**) in the presence of Wilkinson's catalyst (see below) as the last step. It should be pointed out that the appropriate selection of the solvent was critical for this reaction. Thus, the use of dichloromethane as solvent resulted in the exclusive formation of enyne (**59**). The authors suggested that the



Reagents and conditions: (a) NaH, DMSO, Ph_3PCH_3I, 2h; (b) TBAF, AcOH, THF, 50 ˚C, 3h; 86% (two steps) (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ˚C; (d) TMS acetylene, Mg, EtBr, THF, -78 ˚C, 1h; 65% (two steps); (e) TBAF, THF, 0.5-1h, 100%; (f) 3M HCl, MeOH, 24h, then Ac_2O, py, DMAP, 84% ; (g) **3a**, CH_2Cl_2, 10h, 89%; (h) OsO_4-$NaIO_4$, 2,6-lutidine, acetone-H_2O (1:1), 2h, 45%; (i) $NaBH_4$, AcOH, THF, 20h, 91% ; (j) Ph_3PRhCl (30mol %), H_2 (1atm), $PhCH_3$, 83%.

Scheme 9. Synthesis 4a-carba-β-D-xylofuranose tetraacetate (**63**).



64, Trehazolin

65, Mannostatin A

66, Mannostatin B

67, Allosamidin

Fig. (5). Biologically important aminocyclopentitol derivatives.

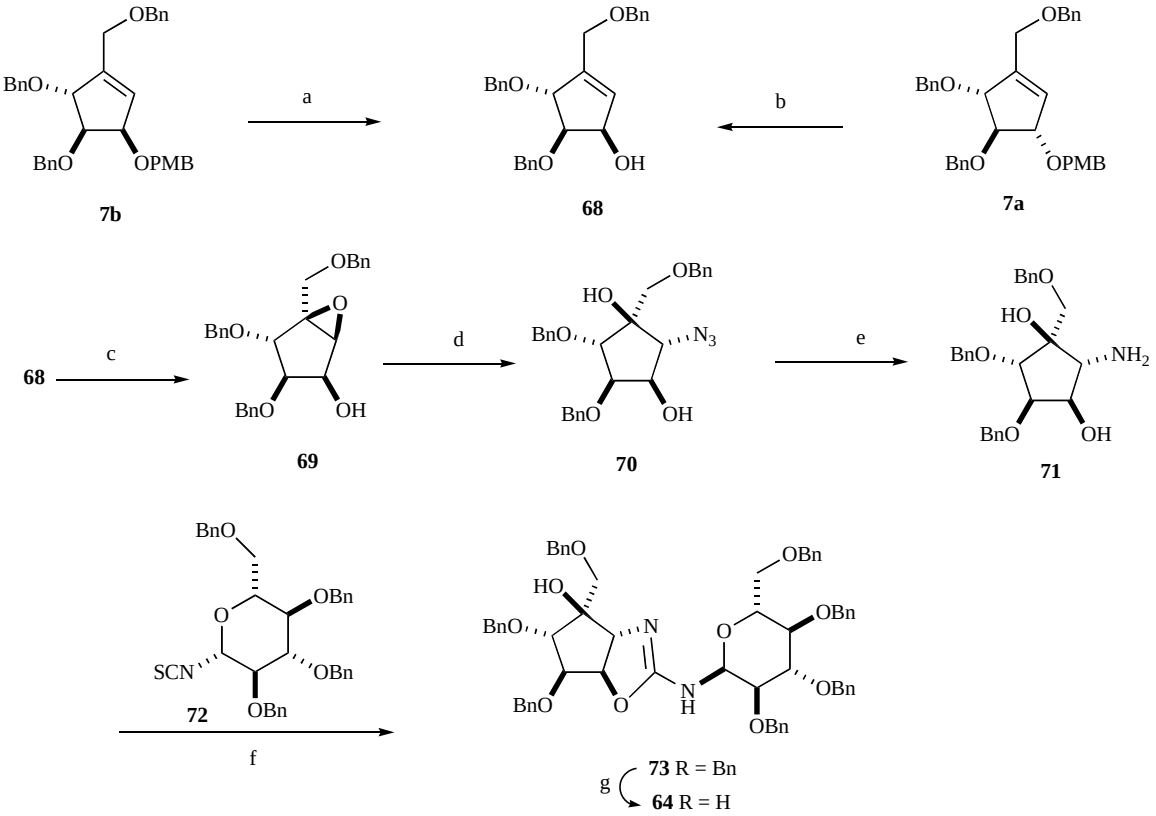
Wilkinson's catalyst was able to react with dichloromethane affording a rhodium carbene which, by reaction with (**62**) induced a ROM reaction to give (**59**). Finally, the hydrogenation reaction was carried out in toluene on the peracetylated derivative of (**62**), giving (**63**) in 83% yield.

For a synthesis of 4a-carba-α-L-xylofuranose, see Section 3.3.

2.4. Trehazolamine

Several naturally occurring glycosidade inhibitors contain an aminocyclopentitol unit in their structures. That is the case of compounds such as trehazolin (**64**), mannostatins A (**65**) and B (**66**) and allosamidines (**67**), Fig. (**5**). The biological activity and synthetic routes to these aminocyclopentitol glycosidase inhibitors have been reviewed [51].

All the previously described trehazolin syntheses used the coupling of the aminocyclopentitol moiety (trehazolamine, generally in a protected form) with a D-glucose derivative at the end of the sequence. Thus, the synthesis of trehazolamine always constitutes a formal synthesis of trehazolin (**64**). Two strategies to trehazolamine that use a RCM reaction as the key step are described below.



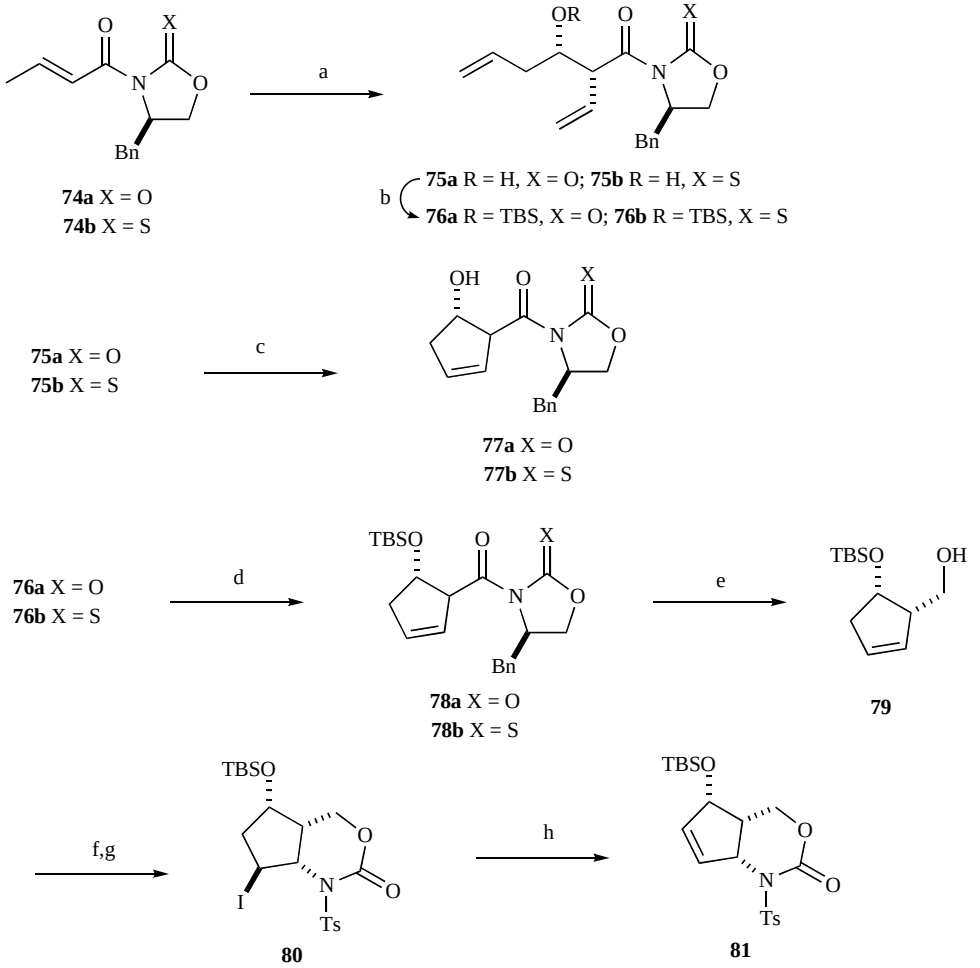
Reagents and conditions: (a) DDQ, CH_2Cl_2, H_2O, 84%; (b) (i) DDQ, CH_2Cl_2, H_2O; (ii) PPh_3, DEAD, $PhCO_2H$, NaOMe, 80% (two steps); (c) MCPBA, CH_2Cl_2, 89%; (d) NaN_3, DMF 97%; (e) PPh_3, THF, 98%; (f) Tf_2O, pyridine; (g) Pd-C, H_2, (yields not given).

Scheme 10. Al-Abed and Seepersaud's synthesis of trehazolin (**64**).

In the synthesis of Al-Abed and Seepersaud [52] (Scheme 10) an epimeric (C-4) mixture of cyclopentenes (**7a**) and (**7b**) (see Scheme **2** and ref. 38) was employed as starting materials. Accordingly, deprotection of the p-methoxybenzyl group of (**7b**) and analogous deprotection and Mitsunobu inversion in (**7a**) yielded allylic alcohol (**68**). This compound was transformed into the epoxide (**69**) in a totally diastereoselective fashion, exploiting the directive effect of the free allylic hydroxy group [53]. In this context, it should be pointed out that the epoxidation of protected compound (**7b**) yielded the diastereomeric epoxide [54]. The ring opening reaction of oxirane (**69**) with NaN_3 in DMF produced azido-alcohol (**70**) that upon reduction yielded amino-alcohol (**71**). The latter was then converted to trehazolin (**64**) following Chiara's protocol [55]. Thus, reaction of (**71**) with α-glucosylisothiocyanate (**72**), in the presence of triflic anhydride and pyridine, afforded protected aminooxazoline (**73**) which was hydrogenolyzed to give (**64**).

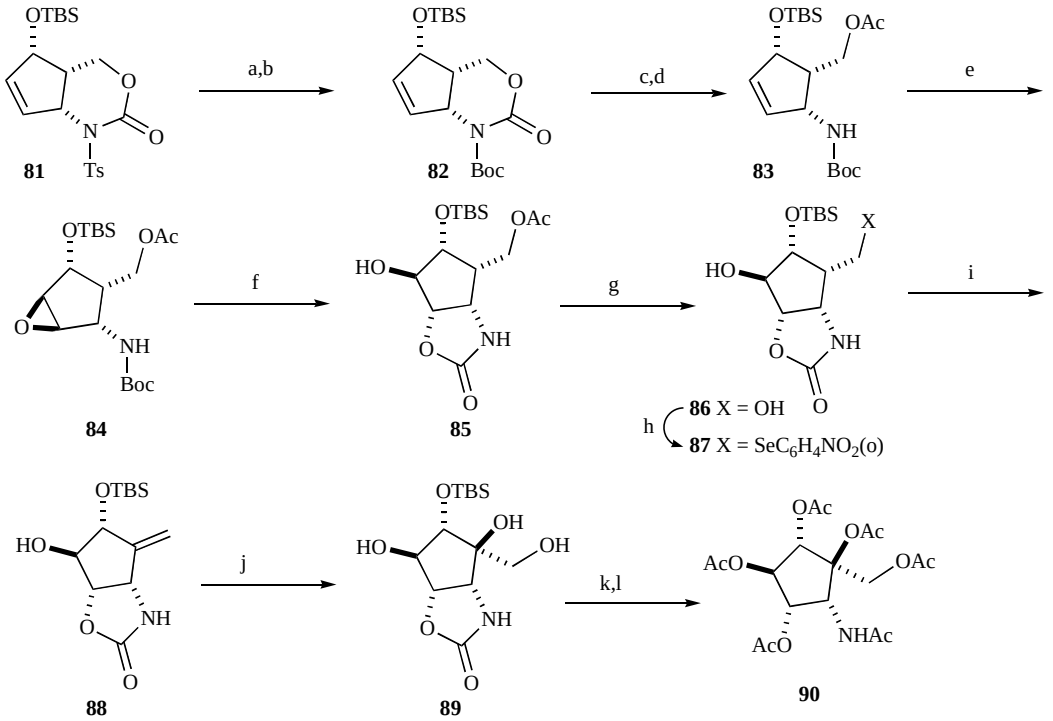
In the approach of Crimmins and Tabet (Scheme **11**) [56] the starting material used was oxazolidinone (**74a**) [57]. Accordingly, the aldol of (**74a**) reaction following the Evans' protocol (diallyl boron triflate) [57a] in the presence of 3-butenal yielded alcohol (**75a**). Similarly the related *N*-acyloxazolidinethione (**74b**) gave the adduct (**75b**) by reaction with $TiCl_4$-(-)-sparteine and subsequent treatment with 3-butenal [58]. For comparative studies, the silylated derivatives (**76**) were prepared. The RCM reactions of (**75a**) or (**75b**) using catalyst (**3a**) afforded low yields (less than 50% conversion) of the expected cyclopentenes (**77a**) and (**77b**). The authors ascribed these disappointing results to the coordination of the homoallylic alcohol to the metal center of the catalyst [59]. Accordingly, the silyl ether derivatives (**76**) were next studied and their RCM reactions using catalyst (**3a**) afforded cyclopentenes (**78a**) and (**78b**) in excellent yields. Removal of the chiral auxiliary gave (**79**). The incorporation of the amino group with concomitant isomerization of the double bond was carried out in two steps, namely iodine induced electrophilic cyclization to give (**80**) [60] followed by treatment with DBU to produce (**81**).

Once the stereocenter bearing the amino group had been established, the authors set to introduce the stereocenters at C2' and C3' (trehazolin numbering) as indicated in Scheme **12**. Reductive removal of the sulfonamide in (**81**) followed by nitrogen protection with di-*tert*-butyldicarbonate gave carbamate (**82**) which, after hydrogenolysis and protection of the alcohol with Ac_2O yielded ester (**83**). The epoxidation of (**83**) took place from the less hindered face leading to (**84**) as the only diastereomer. The acid-induced nucleophilic ring opening of the epoxide by the carbamate carbonyl oxygen produced oxazolidinone (**85**). The last stage was the introduction of the stereocenter at C5' (trehazolin numbering) which was accomplished as follows: deprotection of the primary hydroxyl group led to (**86**) that was transformed to a primary selenide (**87**) which was oxidised to an



Reagents and conditions: (a) For (**74a**): Bu_2OTf, Et_3N, 3-butenal, 65%; For (**74b**): $TiCl_4$, (-)-sparteine, CH_2Cl_2, 3-butenal, 75%; (b) catalyst (**3a**), incomplete conversion. Ratio (starting diene : product) 56:44; (c) TBSOTf, 2,6-lutidine. Yields: (**76*a***): 92%; (**76b**): 70%; (d) catalyst (**3a**), CH_2Cl_2, Yields: (**78a**): 98%; (**78b**): 91%; (e) $LiBH_4$, MeOH. Yields: from (**78a**): 83%; from (**78b**): 75%; (f) TSNCO; (g) I_2, K_2CO_3, Et_2O, 77% (two steps); (h) DBU, C_6H_6, 91%.

Scheme 11. Crimmins and Tabet's approach to trehazolin intermediate (**81**).



Reagents and conditions: (a) Na, Naphthalenide, THF, -78 ºC; (b) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 88% (two steps); (c) Cs_2CO_3, MeOH, 94%; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95%; (e) dimethyldioxirane, acetone, 77%; (f) camphorsulfonic acid, CH_2Cl_2, 83%; (g) K_2CO_3, MeOH, 98%; (h) o-NO_2-C_6H_4SeCN, nBu_3P; (i) H_2O_2, THF, 71% (two steps); j) OsO_4, NMO, acetone-H_2O, 75%; (k) 2N KOH, EtOH; (l) Ac_2O, pyridine, DMAP, 86% (two steps).

Scheme 12. Crimmins and Tabet's formal synthesis of trehazolin.

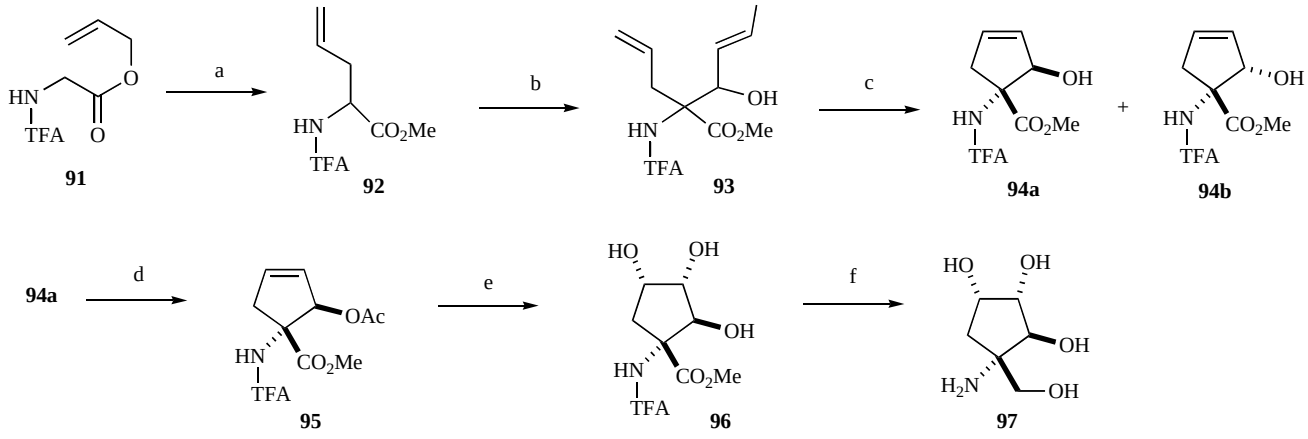
exocyclic alkene (**88**). The formal synthesis of trehazolin was finished by *bis*-hydroxylation of (**88**) to triol (**89**) which, after basic hydrolysis and peracetylation yielded compound (**90**), a known intermediate in a previous synthesis of trehazolin [50].

2.5. 4-Amino-4-(hydroxymethyl)-cyclopentane-1,2,3-triol

The synthesis of carbafuranoses and aminocarbafuranoses *via* RCM reactions normally uses carbohydrates as synthetic precursors of the appropriate dienes. However, the synthesis of compound (**97**) from an aminoacid derivative constitutes an interesting exception (Scheme **13**) [61]. The protected glycine derivative (**91**) was subjected to a chelate-enolate Claisen rearrangement [62] to give (**92**). The reaction of (**92**) with crotonaldehyde in the presence of $ZnCl_2$ gave (**93**) as a diastereomeric *anti-syn* mixture (OH-NHTFA) in a (3:1) ratio. This mixture was allowed to react with catalyst (**3a**) giving compounds (**94a**) and (**94b**) that were separated by flash column chromatography. Enzymatic resolution [63] of (**94a**) (*Candida Antarctica*) afforded acetate (**95**). *Bis*-hydroxylation of (**95**) paved the way to diol (**96**) which was deprotected and reduced to (**97**).

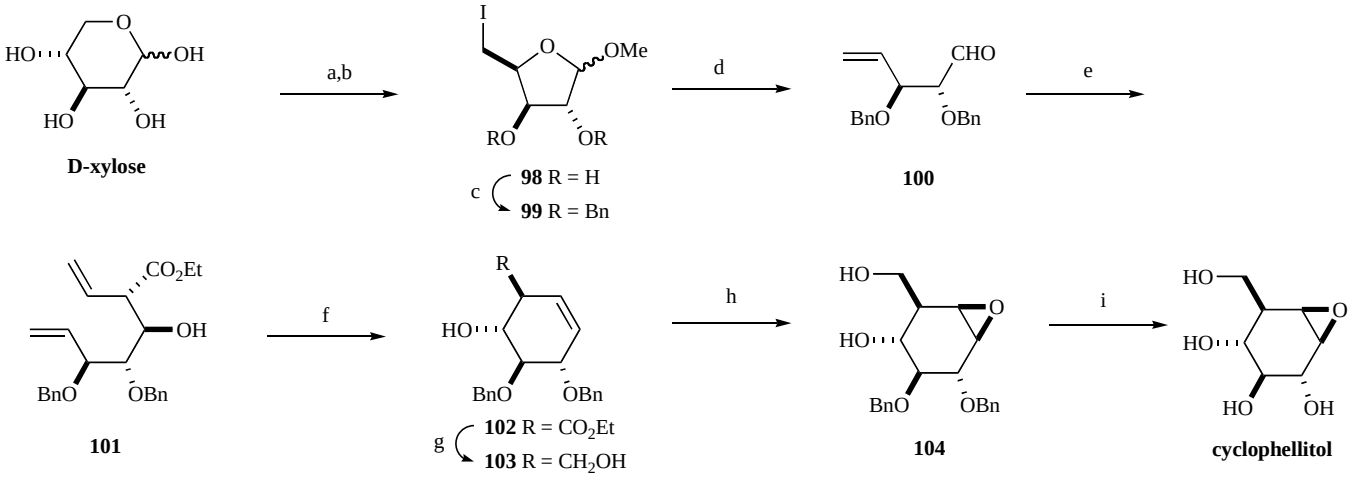
3. SYNTHESIS OF CARBAPYRANOSES BY RCM REACTIONS

The first synthesis of a carbasugar derivative from a carbohydrate using the RCM reaction as the key ring forming step was reported in 1998 by Ziegler and Wang in their approach to cyclophellitol from D-xylose [64]. Since then a great deal of work concerning the synthesis of



Reagents and conditions: (a) Chelate-enolate Claisen rearrangement: (b) (i) LHDMS, $ZnCl_2$, -78 ºC; (ii) crotonaldehyde, -78 ºC, 72%; (c) catalyst (**3a**), 75%; (d) from (±)-(**94a**): immobilized Novozyn®, vinyl acetate, 99% *ee*, 47%, (e) K_2OsO_4 (cat), NMO, acetone-H_2O, 91%; (f) $NaBH_4$, $CaCl_2$, THF-EtOH, 93%.

Scheme 13. Kummeter and Kazmaier's synthesis of (**97**).



Reagents and conditions: (a) MeOH, HCl, 5 °C; (b) I_2, PPh_3, imidazole, 74% (two steps); (c) $BnOC(=NH)CCl_3$, TfOH, dioxane, 90%; (d) Zn, THF, H_2O, ultrasound, 78%; (e) ethyl-4-bromocrotonate, In powder, $La(OTf)_3$, H_2O, 85%; (f) catalyst (**3b**), CH_2Cl_2, 91%; (g) DIBAL-H, THF, 0 °C to rt; then $NaBH_4$, H_2O, 64%; (h) MCPBA, CH_2Cl_2, 40 °C, 56%; (i) $Pd(OH)_2$, H_2, MeOH, 100%.

Scheme 14. Madsen's synthesis of (+)-cyclophellitol.

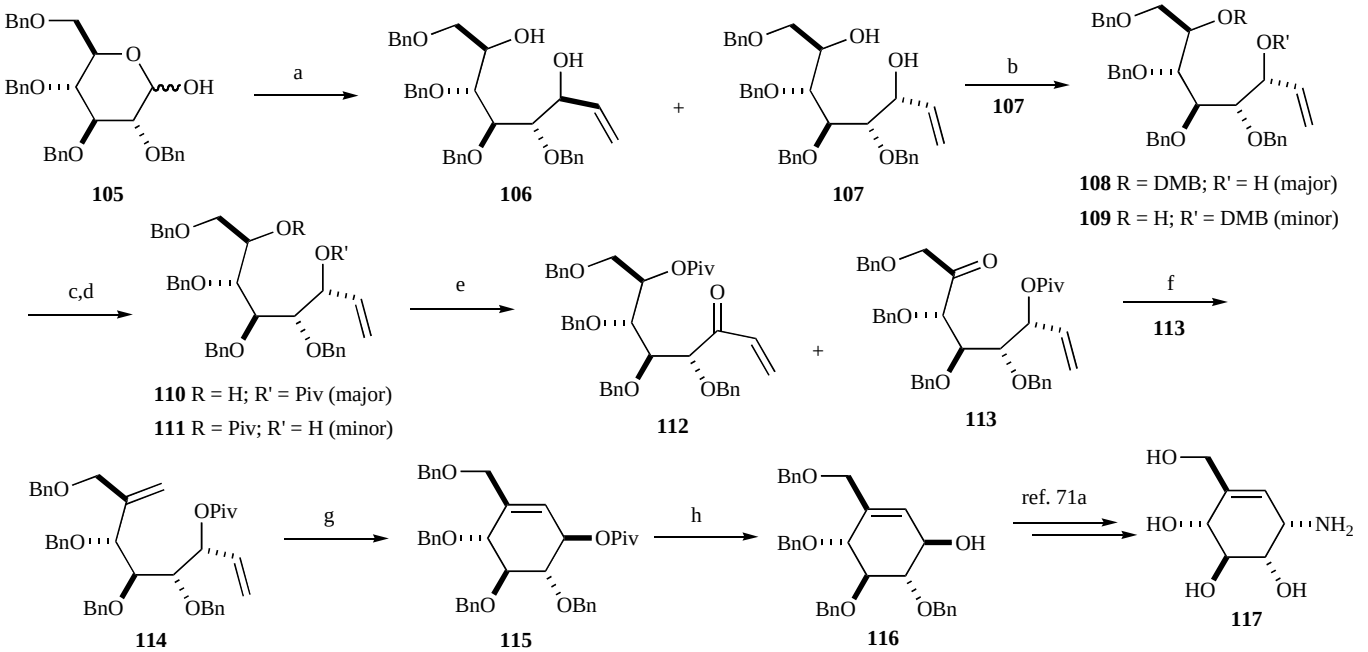
polyhydroxylated six-membered rings systems using this technology have been reported [26b]. In this account, the most significant synthetic approaches to carbapyranoses are presented.

3.1. Cyclophellitol

Cyclophellitol [1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-hydroxymethyl-7-oxabicyclo 4,1,0] heptane-2,3,4-triol) is an interesting compound that has been found to be a specific inhibitor of β-glucosidases [65]. The more recent synthesis of cyclophellitol using RCM as the key step was that reported by Madsen's group (Scheme **14**) [66]. The starting material in their synthesis was aldehyde (**100**), prepared in three steps from D-xylose [67]. Thus, reaction of D-xylose with acidic methanol, followed by iodination afforded methyl 5-deoxy-5-iodo-furanoside (**98**) that upon benzylation and reaction with Zn gave (**100**). This compound was diastereoselectively alkylated [68] with ethyl-4-bromo crotonate in the presence of indium to give diene (**101**). RCM reaction of the latter using Grubbs' second generation catalyst (**3b**) yielded cyclohexene (**102**) in 91% yield. Reduction of the ester functionality followed by diastereoselective epoxidation of the resulting diol (**103**) yielded oxirane (**104**) that upon deprotection afforded (+)-cyclophellitol. Madsen's synthesis requires only nine steps and takes place with a remarkable 14% overall yield.

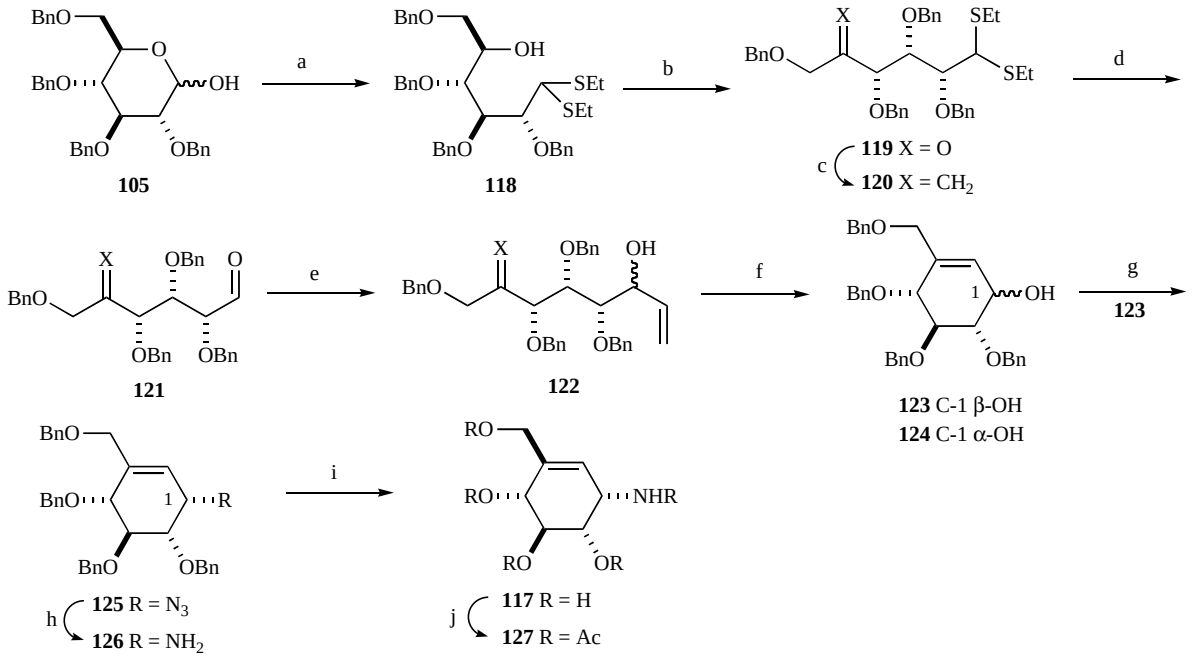
3.2. Valienamine

Since the isolation of this unsaturated aminocarbasugar [69] different syntheses of the enantiomerically pure compound have been developed using L-quebrachitol [70], D-glucose or derivatives [71], or



Reagents and conditions: (a) vinylmagnesium bromide, THF, 0 °C, 94%, ratio (**107**):(**106**) = 2.2:1; (b) from (**107**): dimethoxybenzyl chloride (DMBCl), DMF, NaH, 0°C, 57%; ratio (**108**):(**109**) = 10:1; (c) PivCl, pyridine, DMAP, 93% (mixture of diastereoisomers); (d) CAN, MeCN, H_2O, 0° to rt, 74% (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, (**112**) 7%, (**113**) 81%; (f) PPh_3CH_3Br, THF, NaHDMS, -78 °C, 63% from (**113**); (g) catalyst (**3b**), $PhCH_3$, 60 °C, 65%; (h) NaOMe, MeOH, 99%.

Scheme 15. Cumpstey's approach to valienamine (**117**).



Reagents and conditions: (a) EtSH, TFA, 77%; (b) DMSO, Ac_2O, 94%; (c) PPh_3CH_3Br, KOt-Bu, C_6H_6, 88%; (d) $HgCl_2$, HgO, CH_3CN-H_2O; (e) vinylmagnesium bromide, THF, -78 ºC, 63% (two steps); (f) catalyst (***3b***), CH_2Cl_2, 86%, 61% as ***123***; (g) (i) DPPA, DBU, $PhCH_3$, 0 ºC, then (ii) NaN_3, 60 ºC, 83% from (**123**) (two steps); (h) PPh_3, NH_4OH, pyridine, 80%; (i) Na, liq NH_3, THF, -78 ºC; (j) Ac_2O, pyridine, 71% (two steps).

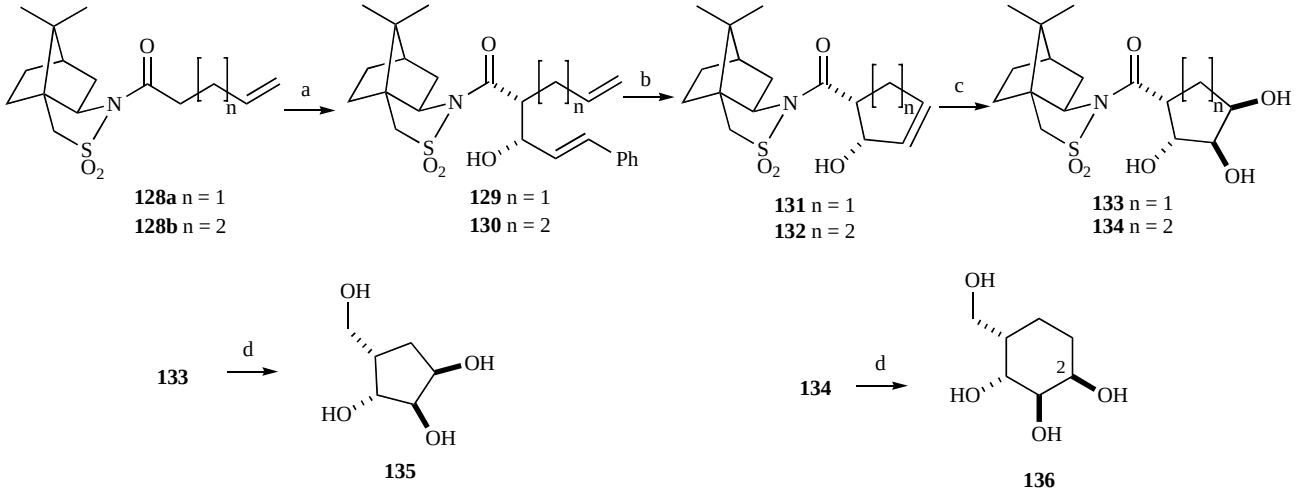
Scheme 16. Jeon, Kim and coworkers approach to valienamine (**117**).

quinic acid [72] as starting materials. In other cases, the cyclohexane unit was created by Diels-Alder cycloaddition [73].

Vasella *et al.* applied, in 1999, the RCM reaction of a diene prepared from tetra-*O*-benzyl-D-glucose (**105**) as the key step in their synthesis of valienamine [74]. During the time covered by this review two new synthetic approaches have been reported.

Cumpstey reported a formal synthesis of valienamine from commercially available tetra-*O*-benzyl-D-glucose (**105**) (Scheme **15**) [75]. Treatment of (**105**) with vinylmagnesium bromide afforded allylic alcohols (**106**) and (**107**) in a (2.2:1) ratio in favour of the desired (*R*)-isomer (**107**) [76]. The reaction of (**107**) with 3,4-dimethoxybenzyl chloride gave the desired (**108**) together with (**109**) in a 9:1 ratio [77]. Treatment of this mixture with pivaloyl chloride and removal of the dimethoxybenzyl group gave compounds (**110**) and (**111**) as an inseparable mixture that was subjected to Swern oxidation to yield ketones (**112**) and (**113**). After flash column chromatography, the desired ketone (**113**) could be isolated in 81% yield. Wittig methylenation of (**113**) followed by RCM reaction using catalyst (**3b**) afforded carbasugar (**115**). After deacetylation of the pseudoanomeric center, the resulting unsaturated carbasugar (**116**) could be transformed to valienamine (**117**) applying a previously described protocol [71a].

The same starting material (**105**) was used by Kim, Jeon and coworkers in their approach to valienamine (**117**) [78]. Opening of the hemiacetal moiety with concomitant protection of the aldehydo



Reagents and conditions: (a) (**128a**) or (**128b**), Et_2BOTf, $(i\text{-}Pr)_2NEt$, cinnamaldehyde, CH_2Cl_2, (**129**) 88%, (**130**) 60%; (b) catalyst (**3b**), CH_2Cl_2, (**131**) 83%, (**132**) 74%; (c) K_2OsO_4, t-BuOH, NMO, DMF, 50%; (d) $NaBH_4$, EtOH, (**135**) 52%, (**136**) 95% .

Scheme 17. Perlmutter and Rose's approach to carbasugars.

function furnished dithiane (**118**). Oxidation of C5-OH yielded ketone (**119**) in 94% yield. Olefination and unveiling of the aldehydo moiety led to (**121**). The aldehyde, used without purification, was reacted with vinylmagnesium bromide to give diene (**122**) as a 7:3 epimeric mixture. These dienes were then submitted to RCM to yield cyclohexenes (**123**) and (**124**) in a 2.4:1 ratio. The major isomer (**123**) was subjected to reaction with diphenylphosphonylazide (DPPA) in the presence of NaN_3 to give allylic azide (**125**). Reduction of the azide moiety followed by debenzylation yielded valienamine (**117**) that was characterized as its pentaacetate (**127**).

3.3. Sequential Aldol Reaction-RCM

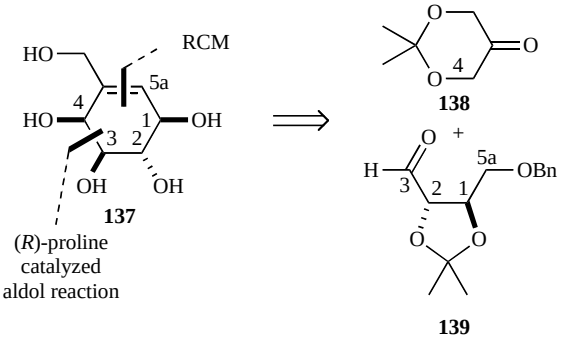
Two methodologies for the preparation of carbasugars have appeared recently. They share the use of an aldol reaction for the construction of the polyhydroxylated (open chain) backbone followed by RCM to generate the carbocyclic structure.

3.3.1. 2-epi-Validatol and 4a-carba-α-L-xylofuranose

Perlmutter and Rose described an interesting approach, common to carbapyranoses and carbafuranoses, that uses a *syn*-aldol reaction followed by RCM [79]. Their synthesis features the reaction of Oppolzer's acylsultams [80], differing on the chain length, (**128**) with *trans*-cinnamaldehyde. The size of the chain then, determines the nature of the final carbasugar (furanose or pyranose form) (Scheme **17**). Accordingly, reaction of the *Z*-boron enolate of the acylsultams (**128**) [81] with *trans*-cinnamaldehyde yielded *syn*-aldol adducts (**129**) (n=1, 88%) or (**130**) (n=2, 60%). The RCM reaction of both dienes furnished the expected unsaturated carbocycles (**131**) and (**132**), respectively. *Bis*-hydroxylation of these compounds yielded (**133**) and (**134**) [82], respectively. Reductive elimination of the sultam auxiliary led to 4a-carba-α-L-xylofuranose (**135**) [83] and carbasugar derivative (**136**). Compound (**136**) is epimeric at C-2 to validatol [84], the product of hydrolysis [85] of the aminoglycoside antibiotic validamycin A [86], and also known as the reduction product [87,88] of the important carba-oligotetrasaccharide acarbose [89].

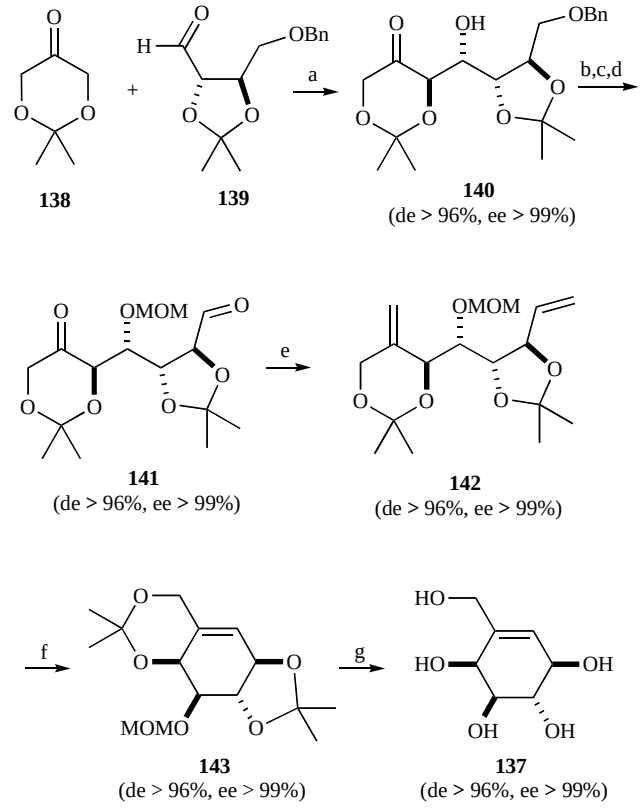
3.3.2. 1-epi-(+)-MK7607

Grondal and Enders described a concise approach to 1-*epi*-(+)-MK7607 (**137**) [90] based on a (*R*)-proline-catalyzed aldol reaction [91] between 2,2-dimethyl-1,3-dioxan-5-one (**138**) and the aldehyde (**139**), readily available from (*S*,*S*)-tartaric acid in four steps [92] (Scheme **18**).



Scheme 18. Retrosynthetic analysis of 1-*epi*-(+)-MK7607 (**137**).

Their synthetic route started with the above mentioned (*R*)-proline-catalyzed aldol reaction that proceeded to (**140**) with good yield (69%) and excellent stereocontrol (de ≥ 96%, ee >99%). The small MOM protecting group was then installed in (**140**) and subsequent hydrogenolytic debenzylation and Dess-Martin oxidation furnished aldehyde-ketone (**141**). The conversion of (**141**) to the bisolefin (**142**) was troublesome and the best results were obtained using Ph_3PCH_3Br and potassium *tert*-butoxide (KOt-Bu) as the base. The diene (**142**) was then submitted to RCM reaction in the presence of Grubbs' second generation catalyst (**3b**). The reaction took place smoothly and after five hours in refluxing CH_2Cl_2 led to cyclohexene (**143**) with 90% yield, a noteworthy result since (**143**) represents a penta-functionalized cyclohexene as part of a tricycle. The final step of the synthesis was the acidic deprotection of all acid sensitive protecting groups that led to (**137**) in 90% yield. Compound (**137**) is epimeric at C-2 to (+)-MK7607 [93] that has effective herbicidal activity.

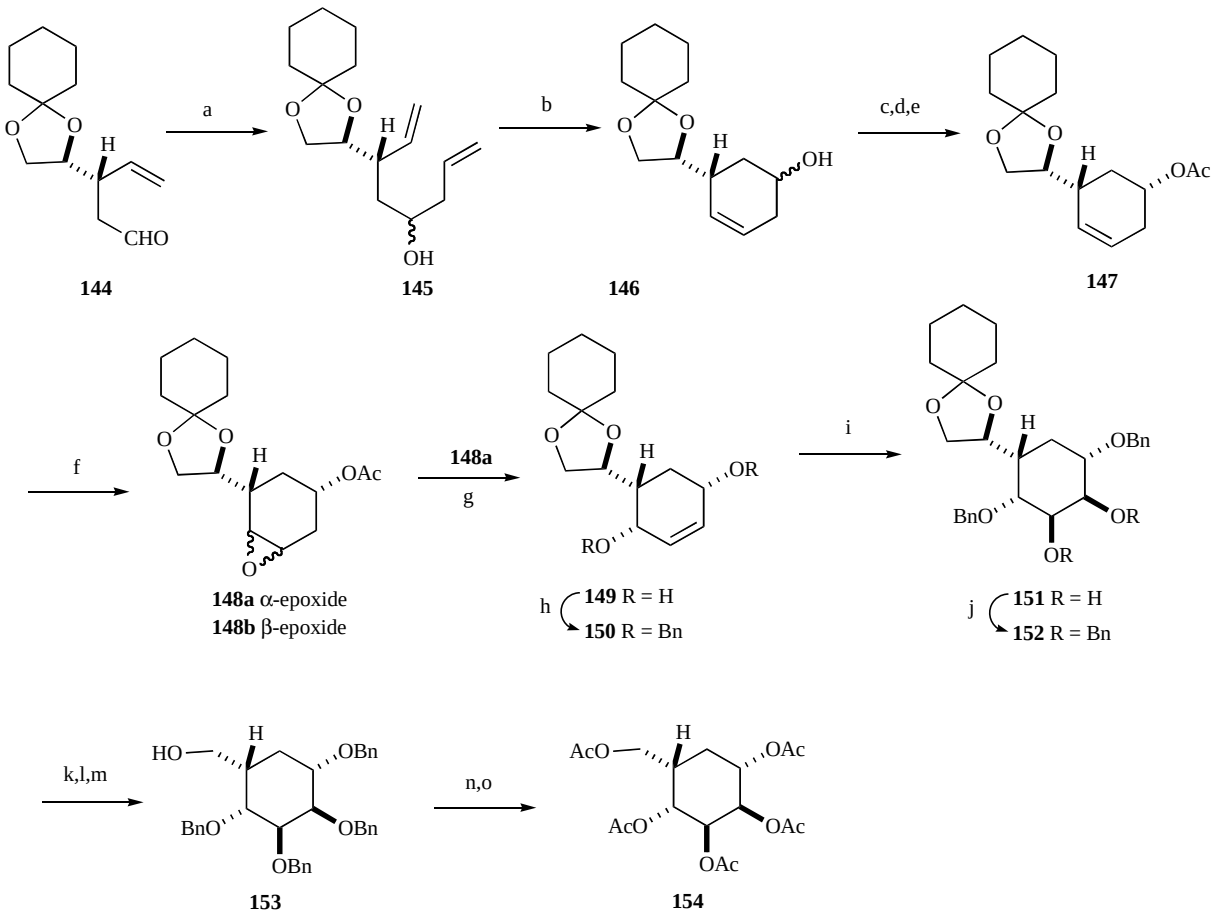


Reagents and conditions: (a) (R)-proline, DMF, 69%; (b) MOMCl, 2,6-lutidine, Bu_4NI, CH_2Cl_2, 99%; (c) Pd-C, H_2, 99%; (d) Dess-Martin oxdn, CH_2Cl_2, 90%; (e) PPh_3CH_3Br, KOt-Bu, THF, -78 °C, 43%; (f) catalyst (***3b***), CH_2Cl_2, reflux, 90% (g) DOWEX, MeOH, 70 °C, 90%.

Scheme 19. Grondal and Enders' synthesis of 1-*epi*-(+)-MK7607 (**137**).

3.4. 5a-carba-β-L-gulopyranose

The previously mentioned approach by Ghosh and coworkers (Scheme **4**) [45] was also implemented for the synthesis of 5a-carba-β-L-gulopyranose pentaacetate (**154**) as shown in Scheme **20**. Reaction of aldehyde (**144**) with allyl zinc afforded a diastereomeric mixture of alcohols (**145**). RCM of this dienol mixture with Grubb's first generation catalyst (**3a**) afforded the cyclohexenols (**146**). From this mixture one single acetate (**147**) could be obtained through an oxidation-reduction sequence followed by acetylation. Epoxidation of the homoallyl acetate (**147**) resulted in a 2:3 mixture of epoxides (**148a**) and (**148b**). Application of the procedure of Sharpless and Lauer [94] to this mixture led to the isolation of ene-diol (**149**) in 41% yield, as a result of the sole transformation of isomer (**148a**). The hydroxyl groups in the cyclohexenediol (**149**) were protected to provide benzyl ether (**150**). Dihydroxylation of the latter with OsO_4 led exclusively to *cis*-diol (**151**) that was benzylated to (**152**). Next, the ketal unit in the tetrabenzylated derivative (**152**) was converted to the hydroxymethyl group using their previously mentioned protocol. Finally, hydrogenolysis and acetylation yielded 5a-carba-β-L-gulopyranose pentaacetate (**154**).



Reagents and conditions: (a) Zn, allyl bromide, THF, 83%; (b) Grubbs' I catalyst (***3a***), CH_2Cl_2, 89%; (c) Swern oxdn, 82%; (d) LAH, Et_2O, -60 °C, 92%; (e) Ac_2O, DMAP, Et_3N, 92%; (f) MCPBA, CH_2Cl_2, 89%; (g) (i) $NaBH_4$-Ph_2Se_2, EtOH, then (ii) 30% H_2O_2, 0 °C -70 °C, 70%; (h) NaH, BnBr, THF, 69%; (i) OsO_4, NMO·H_2O, acetone:H_2O (4:1), 85%; (j) NaH, BnBr, THF, rt, 72%; (k) AcOH:H_2O (4:1), 82%; (l) $NaIO_4$, 60% aq MeOH, 81%; (m) $NaBH_4$, MeOH, 0 °C, 91%; (n) 10% Pd-C, H_2, MeOH, 95%; (o) Ac_2O, pyridine, 86%.

Scheme 20. Ghosh *et al*. synthesis of carbagulopyranose by RCM.

4. CONCLUSIONS AND PERSPECTIVES

Four decades have already elapsed since McCasland's group synthesized the first carbocyclic analog of a carbohydrate: a *carbasugar*. At that time, they could only postulate –and perhaps imagine- that these *pseudo*sugars, would enjoy enhanced chemical stability, could replace carbohydrates in their interaction with enzymes and therefore, be endowed with interesting biological properties. A few years later their prediction came true with the discovery of biologically active natural products containing *carbasugars*. Since then, many new interesting biological activities associated with carbasugars, aminocarbasugars, carba-oligosaccharides, and different carbasugar analogs have been discovered. On the other hand, the RCM has recently emerged as an impressive tool for the preparation of unsaturated carbocyclic rings. The unsaturation present in these systems is exceptionally well-suited for the incorporation of *bis*-hydroxyl functionalities present in carbohydrates. As a consequence, one can expect great promise for stereocontrolled strategies to carbasugars and analogs based on the sequential application of RCM reactions and stereocontrolled *bis*-hydroxylation (or epoxidation) of the ensuing double bond. This method will complement some well-established methods for the synthesis of carbasugars [95]. The Ferrier-II rearrangement [96] approach to carbasugars has been widely employed although it can not be applied to the preparation of carbafuranoses [97]. A recent modification of this method, the rearrangement of hex-5-enopyranosides catalyzed by TIBAL, the Ferrier-Sinaÿ carbocyclization [98], has been applied to the preparation of carbapyranoses [99]. Radical cyclization protocols have been described for the preparation of carbafuranoses [100], carbapyranoses [101], and higher carbasugar analogs [102]. A general approach based on a silylative cycloaldolyzation, described by Rassu, Casiraghi and co-workers, allows access to five-, six- and seven-membered carbasugars [103]. Compared to these methods, the RCM allows access to five- and six-membered ring precursors of carbafuranoses and carbapyranoses, and has recently been applied to the preparation of seven- and eight-membered carbasugar analogs [104]. In this context, the RCM is a simple, yet efficient approach to the preparation of carbasugars as well as carbasugar derivatives and carbasugar related compounds, such as the carbocyclic analogs of nucleosides [105], which will complement already existing synthetic methods [106].

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