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Synthetic Strategies for Converting Carbohydrates into Carbocycles by the Use of Olefin Metathesis

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This microreview covers recent advances in the use of ring-closing metathesis for the synthesis of carbocycles from carbohydrates. Various strategies for the synthesis of α,ω-dienes from carbohydrates are presented, which give rise to a large variety of dienes with different stereochemistries, protecting groups and substituents. Subsequent ring-closing metathesis with a ruthenium carbene complex affords highly functionalized carbocycles with ring sizes ranging from five- to eight-membered rings. The application of these methods for the synthesis of carbocyclic natural products from carbohydrates is also demonstrated.

1. Introduction

Carbohydrates are densely functionalized molecules which often require specially designed reactions in order to be used as chiral building blocks in organic synthesis. Some of these reactions involve methods for *O*-glycoside synthesis, *C*-glycoside synthesis, addition of nucleophiles to the anomeric center, and formation of heterocyclic and carbocyclic structures. The conversion of carbohydrates into carbocycles has been widely investigated because many natural products and other biologically active molecules contain polyhydroxylated carbocyclic rings.[1,2] One of the classical methods for carbocyclization of carbohydrates is the Ferrier reaction, where methyl hex-5-enopyranosides are converted into hydroxylated cyclohexanones in the presence of a mercury(II) catalyst.[1] Other procedures employ a radical cyclization, a carbanion cyclization, a Claisen rearrangement, or a nitrile oxide/nitrone cycloaddition reaction.[2] Although these methods have been widely applied in carbohydrate chemistry, they often have some limitations with regard to the types of products that can be generated.

About 15 years ago new carbene (pre)catalysts were developed for the olefin metathesis reaction, which made it possible to perform this reaction with functionalized substrates.[3] Since then, olefin metathesis has experienced a tremendous development in organic chemistry and many review articles have been published on various aspects of this transformation.[4] Olefin metathesis was also quickly adopted as a synthetic tool in carbohydrate chemistry, and two review articles were published in 2000 which described the application of olefin metathesis with carbohydrate substrates during the 1990s.[5] The purpose of this review is to survey the literature since the beginning of this century on the use of ring-closing metathesis for converting carbohydrates into carbocycles.

2. Catalysts and Mechanism for the Olefin Metathesis Reaction

In the early 1990s two new metal carbene complexes were shown to catalyze the olefin metathesis reaction with functionalized substrates.[3] The first catalyst, **A**, consisted of a

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molybdenum imido complex, originally prepared by Schrock, which showed very high activity (Figure 1).[3c–3e] Unfortunately, it turned out to be very sensitive to oxygen, moisture and some polar functional groups, and has therefore found limited use in complex synthesis[6] and only a few applications are known in carbohydrate chemistry.[5] The second catalyst, **B**, was developed by Grubbs, and is composed of a ruthenium carbene with two tricyclohexylphosphane ligands attached.[3b] This complex was not significantly affected by oxygen or moisture, and showed an excellent functional group tolerance. The ruthenium carbene catalysts were further developed during the 1990s in order to improve their activity. This led to the development of three catalysts, **C**, **D** and **E**, which are now commercially available and by far the most widely used metathesis catalysts today (Figure 1). Catalyst **C** was first described by Grubbs in 1995, and has a similar structure as catalyst **B**, but is easier to prepare and shows better activity due to a higher initiation rate.[7] Later it was shown that the catalyst performance could be improved by introducing an *N*-heterocyclic carbene ligand, which led to the development of the more reactive catalyst **D**.[8] In 2000, Hoveyda developed catalyst **E** which in some cases shows a higher reactivity than catalyst **D**.[9] In addition, complex **E** can be recovered by flash chromatography after the metathesis reaction, which is not the case with complex **C** and **D**. All three complexes are highly colored, and sometimes special workup procedures are necessary in order to remove catalyst residues after a metathesis reaction.[10]

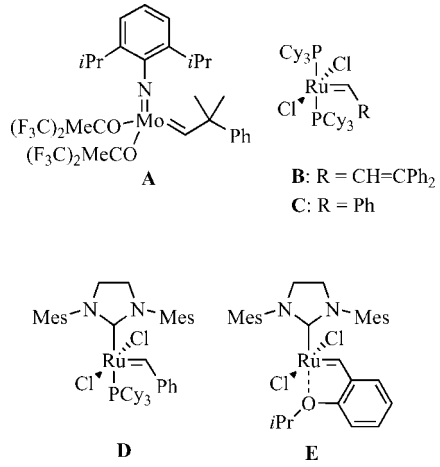


Figure 1. Structure of metathesis catalysts

The mechanism for the olefin metathesis reaction with ruthenium complexes **C** and **D** has been thoroughly studied both experimentally[11] and theoretically.[12] The results show that the reaction proceeds by initial dissociation of a phosphane ligand from the (pre)catalyst to form a 14-electron intermediate (Figure 2). In the following step, the olefin is coordinated to ruthenium to give a 16-electron complex. Migratory insertion of the olefin into the ruthenium-carbene bond then forms a ruthenacyclobutane, which has been observed experimentally by NMR spectroscopy.[13] Subsequent ring-opening generates a new 16-electron olefin complex which, after decomplexation of the olefin, regenerates the 14-electron carbene intermediate. There is still no general agreement on which of the individual steps constitutes the rate-limiting step of the reaction. The higher reactivity of complex **D** is attributed to the fact that the strongly σ-donating *N*-heterocyclic carbene ligand is better at stabilizing the intermediate 14-electron species than the corresponding phosphane ligand in complex **C**.[12] There are no mechanistic studies on the phosphane-free catalyst **E**. However, free phosphane in solution is known to inhibit metathesis reactions.[11a] After loss of the styrenyl ether ligand, complex **E** will generate the same catalytically active 14-electron species as complex **D**, but the styrenyl ether is a weaker ligand for ruthenium than the phosphane and therefore competes less effectively with olefin coordination.[14] Furthermore, free phosphane in solution has been shown to participate in the decomposition of the catalytically active 14-electron species by nucleophilic attack on the methylene carbon atom.[15]

The overall result of a catalytic cycle is a [2+2] cycloaddition between the ruthenium carbene and the olefin followed by a retrocycloaddition to produce a new carbene and a new olefin (Figure 3).[16] When the reaction is performed with α,ω-dienes, the catalytic cycle is repeated twice, and the products are cycloalkenes and ethylene. The release of a second molecule provides the necessary driving force for ring-closing olefin metathesis due to the gain in entropy.

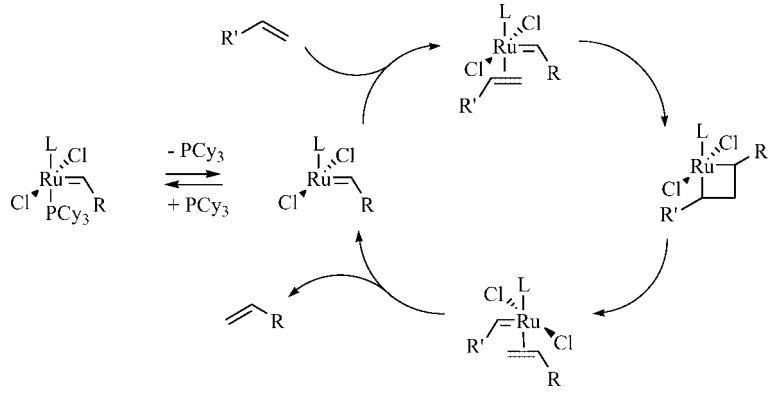


Figure 2. Mechanism of the olefin metathesis reaction.

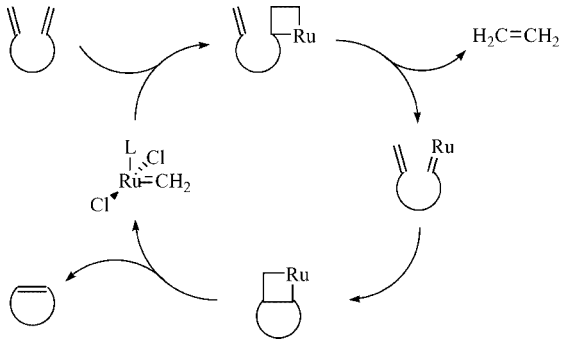


Figure 3. Cyclization of α,ω-dienes by olefin metathesis.

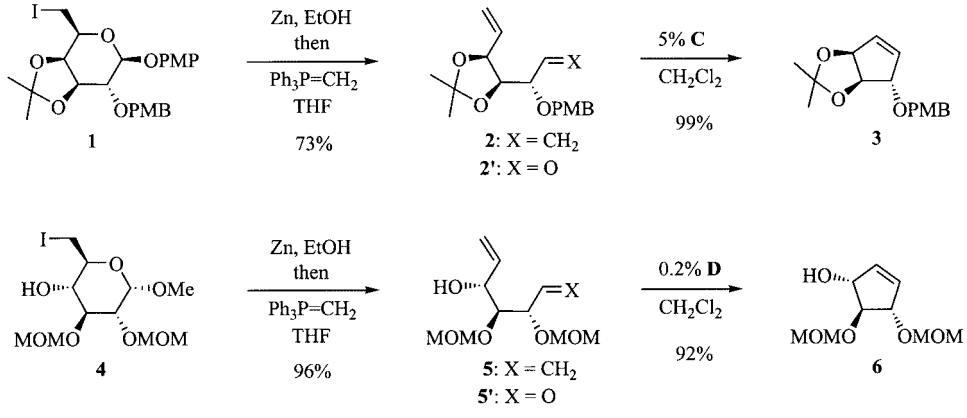
3. Diene Synthesis from Carbohydrates and Ring-Closing Metathesis

At first glance, carbohydrates are not obvious substrates for olefin metathesis. They contain no C–C double bonds and are not soluble in the most common aprotic solvents for metathesis, such as dichloromethane and toluene. As a result, the main challenge for using carbohydrates in ring-closing metathesis reactions is often to install the two terminal olefins in an effective manner. This is typically achieved by using two different reactions. A classical transformation in carbohydrate chemistry for introducing a terminal olefin is the zinc-mediated fragmentation of methyl 6-iodohexopyranosides or 5-iodopentofuranosides originally developed by Bernet and Vasella.[17] Other suitable reactions that install a terminal olefin include the Wittig methylenation, organometallic reactions for adding vinyl, allyl and butenyl groups, and various elimination reactions. Usually, the two olefins are introduced in two separate steps and only in a few cases has it been possible to assemble the α,ω-dienes in one step. The first olefin-forming reaction is in most cases a zinc-mediated fragmentation, a Wittig methylenation or a vinyl Grignard addition. In the following, different strategies for the synthesis of α,ω-dienes will be presented, and the syntheses are categorized after the first olefin-forming reaction. Furthermore, the ring-closing metathesis reactions will be discussed with particular emphasis on the protecting groups, the ring size and the catalyst.

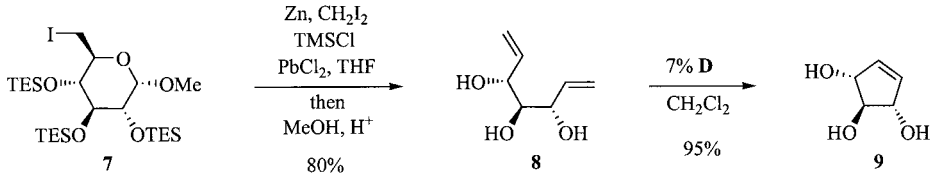
3.1. Diene Synthesis by Zinc-Mediated Fragmentation of Iodoglycosides

The zinc-mediated fragmentation of ω-iodoglycosides is a convenient method for introducing a terminal double bond in carbohydrates. Furthermore, the reaction liberates the aldehyde at the anomeric center and makes it ready for the next olefin-forming reaction without any further protecting group manipulations. van Boom and co-workers used this fragmentation reaction with galactose substrate **1** (Scheme 1).[18] The intermediate aldehyde **2′** was isolated by extraction, but otherwise it was not further purified. Instead, the crude aldehyde was submitted to a Wittig reaction to afford diene **2** in 73% overall yield. The subsequent metathesis reaction was carried out in a degassed dichloromethane solution with 5% of catalyst **C** to provide cyclopentene **3** in a near quantitative yield without affecting the acetal protecting group or the *p*-methoxybenzyl ether.[18] Hirama and co-workers utilized the same transformations with glucose substrate **4** (Scheme 1).[19] The zinc-mediated fragmentation was performed with 170 g of iodide **4** to afford the unsaturated aldehyde **5′** which was not purified, but subjected directly to a Wittig reaction to give diene **5** in 96% yield over the two steps. The subsequent metathesis reaction was first investigated with catalyst **C**, but in this case a cyclic enone was formed as a byproduct together with the desired cyclopentene **6**. It is well known that allylic alcohols can cause side reactions, especially if the metathesis reaction is slow.[20] The most common side reaction is an isomerization into the corresponding ketone, but alcohol oxidation and fragmentation reactions with loss of one carbon atom have also been observed.[20] In this case, the problem was solved by using the more reactive catalyst **D**, which performed the cyclization of **5** in high yield at room temperature. Notably, the metathesis reaction was carried out with 54.6 g of **5** and a low catalyst loading of 0.2%.[19] The catalyst residues were removed in the workup by simple treatment with activated carbon.[10a]

This strategy for generating 1,6-dienes requires two separate steps, since the zinc-mediated fragmentation is not compatible with the highly basic conditions for the Wittig reaction. Hyldtoft and Madsen developed a one-step pro-



Scheme 1.



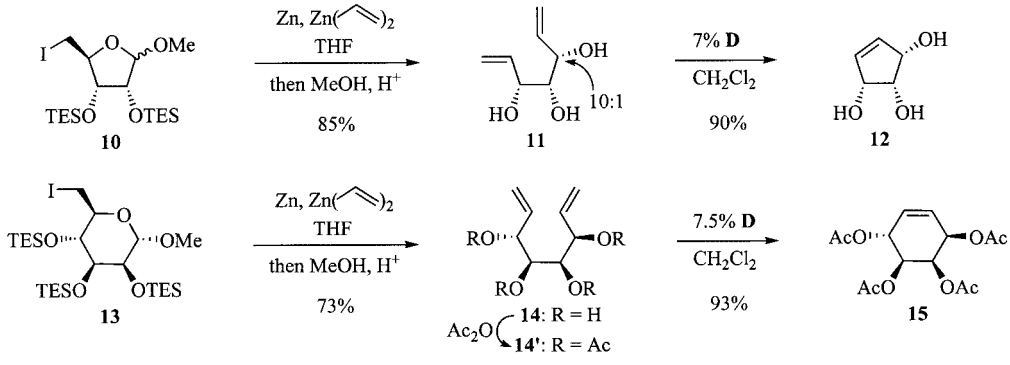
Scheme 2.

cedure by using a Takai methylenation instead of the Wittig reaction.[21] The Takai methylenation of carbonyl compounds is performed with zinc, diiodomethane and a Lewis acid in anhydrous THF. The Lewis acid is typically titanium tetrachloride, but trimethylsilyl chloride can also be used, and the reaction is accelerated by the addition of a catalytic amount of lead dichloride.[22] Thus, when iodoglycoside **7** was treated with zinc, diiodomethane, trimethylsilyl chloride and a small amount of lead dichloride, the fragmentation proceeded to give the corresponding aldehyde, which immediately reacted further to afford the 1,6-diene (Scheme 2).[21] Triol **8** was isolated in good yield after deprotection in the workup. Zinc serves a dual role in this tandem reaction by mediating both the reductive fragmentation of **7** and the subsequent Takai methylenation. The tandem reaction was performed with ultrasound in a sonic bath in order to maintain a high reactivity of the zinc metal. Triol **8** reacted sluggishly in the metathesis reaction with catalyst **C**, but underwent a smooth ring-closure with catalyst **D** to give cyclopentene **9**.[21]

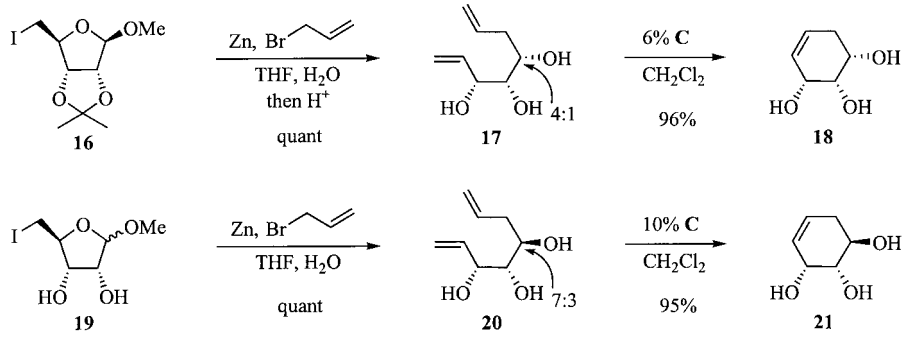
Hyldtoft and Madsen have further developed this zinc-mediated tandem reaction for preparation of dienes in one step from iodoglycosides.[21] 1,6-Dienes can also be generated from pentoses by the addition of a vinyl group after the fragmentation. It is not possible to form a vinylzinc reagent under the fragmentation conditions, since vinyl bromide is too unreactive and too volatile (b.p. 16 °C). Instead, a vinylmagnesium bromide solution is prepared in THF and transmetallated with 0.5 equiv. of a zinc halide (chloride or bromide). The precipitated magnesium halide is removed and the resulting divinylzinc solution is then added to a sonicated solution of the iodoglycoside and zinc in THF. Under these conditions, iodide **10** gave diene **11** in high yield and with a high diastereoselectivity after removing the silyl groups in the workup (Scheme 3).[21] Hexoses can also be reacted under these conditions, and compound **14** was obtained as the only diastereomer from iodide **13**.[21] The metathesis reaction with **11** proceeded readily to give cyclopentene **12**.[21] Tetrol **14**, on the other hand, reacted poorly with catalyst **D**, and in this case it was necessary to protect the four hydroxy groups as acetates before the metathesis reaction could be achieved.[21] The acetate is often the protecting group of choice if a hydroxy group has to be protected in a metathesis reaction because the acetate is easy to install/remove and is sufficiently small that it does not affect the ring-closure reaction.

The zinc-mediated tandem reaction is not limited to the addition of a one carbon methylene group or a two carbon vinyl group. In fact, the most promising applications have come from the addition of a three carbon allyl group. In this case, the fragmentation is performed in the presence of an allylic bromide, since zinc will mediate both the reductive fragmentation of the iodoglycoside and a subsequent Barbier-type allylation of the intermediate aldehyde. The tandem reaction was originally discovered when ribofuranoside **16** was exposed to zinc and allyl bromide (Scheme 4).[21] The product was obtained as a 4:1 mixture of diastereomers in a quantitative yield after deprotection in the workup. In this case, the heterogeneous reaction could be performed in an aqueous medium, which generally leads to a faster conversion. Triol **17** was cyclized into cyclohexene **18** with catalyst **C** in high yield. The metathesis reaction was facilitated by the fact that **18** crystallized from the reaction mixture during the course of the reaction. Unprotected ribofuranoside **19** also reacted very efficiently with zinc and allyl bromide. Notably, in this case the opposite diastereomer **20** was formed as the main product.[21]

Functionalized allylic bromides can also be employed in the zinc-mediated tandem reaction, e.g. reaction between **16** and 3-benzoyloxyallyl bromide gave **22** as a single dia-



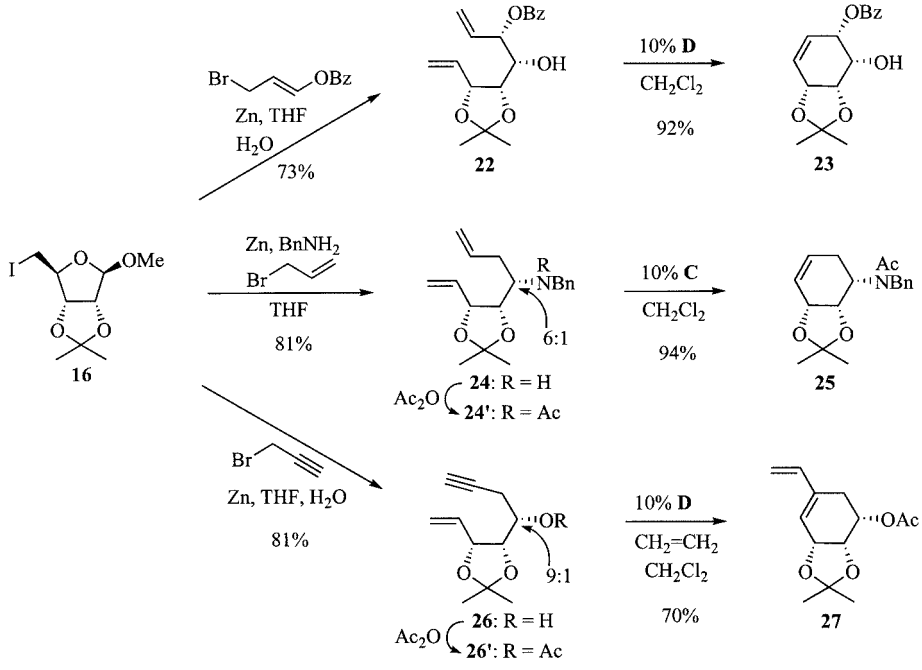
Scheme 3.



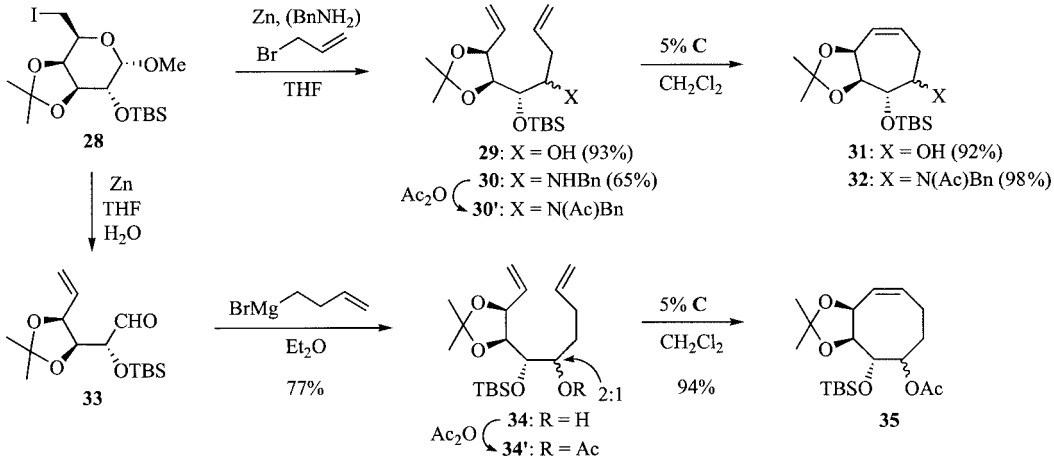
Scheme 4.

stereomer in 73% yield (Scheme 5).[23] Diene **22** was converted into cyclohexene **23** in 92% yield with catalyst **D**.[23] A very interesting development occurred when the tandem reaction was performed in the presence of a primary amine. It turned out that it was possible to intercept the intermediate aldehyde with an amine prior to the allylation. As a result, the allylation occurred with the formed imine, and gave rise to an amino group in the product. Thus, zinc-mediated reaction between **16**, benzylamine and allyl bromide gave rise to aminodiene **24** in 81% yield as a 6:1 mixture of diastereomers (Scheme 5).[21] Allyl bromide was added by syringe pump during the course of the reaction, which was carried out in a THF solution under sonication. Unfortunately, it was not possible to cyclize **24** directly by ring-closing metathesis with catalyst **C** or **D**. It appears that the secondary amine serves as a ligand for ruthenium, thereby hampering the metathesis reaction. Instead, amine **24** was converted into amide **24′**, which could be cyclized in high yield with catalyst **C**.[21] The zinc-mediated tandem reaction with allyl bromide and a primary amine is an efficient procedure for preparing a carbohydrate structure with an amino group. The tandem reaction with **16** has recently been used in the synthesis of several aminocyclitols,[24] aminoglycosides,[25] and heterocyclic structures.[26]

Another variation of the tandem reaction is achieved when allyl bromide is replaced with propargyl bromide. In this case, the product is an enyne that can also be cyclized by metathesis. Ring-closing enyne metathesis is a special metathesis reaction where the enyne undergoes a cycloisomerization into a cyclic 1,3-diene.[4f] The zinc-mediated reaction between **16** and propargyl bromide afforded enyne **26** in 81% yield with a high diastereoselectivity (Scheme 5).[27] Unlike the case of the olefin metathesis reaction, it was not possible to perform the enyne metathesis reaction in the presence of an alcohol, and the hydroxy group in **26** was therefore acetylated. The enyne metathesis reaction is often carried out under an atmosphere of ethylene in order to prevent the product from dimerizing by cross metathesis. Under these conditions, vinyl cyclohexene **27** was obtained in 70% yield from **26′** and used as a diene in a subsequent



Scheme 5.



Scheme 6.

Diels–Alder reaction.[27] Lièvre and co-workers have used the same metathesis conditions for cyclizing a number of other 1,7-enynes that were prepared from hexoses by a Corey–Fuchs reaction at C-1 and a Wittig methylenation at C-6.[28]

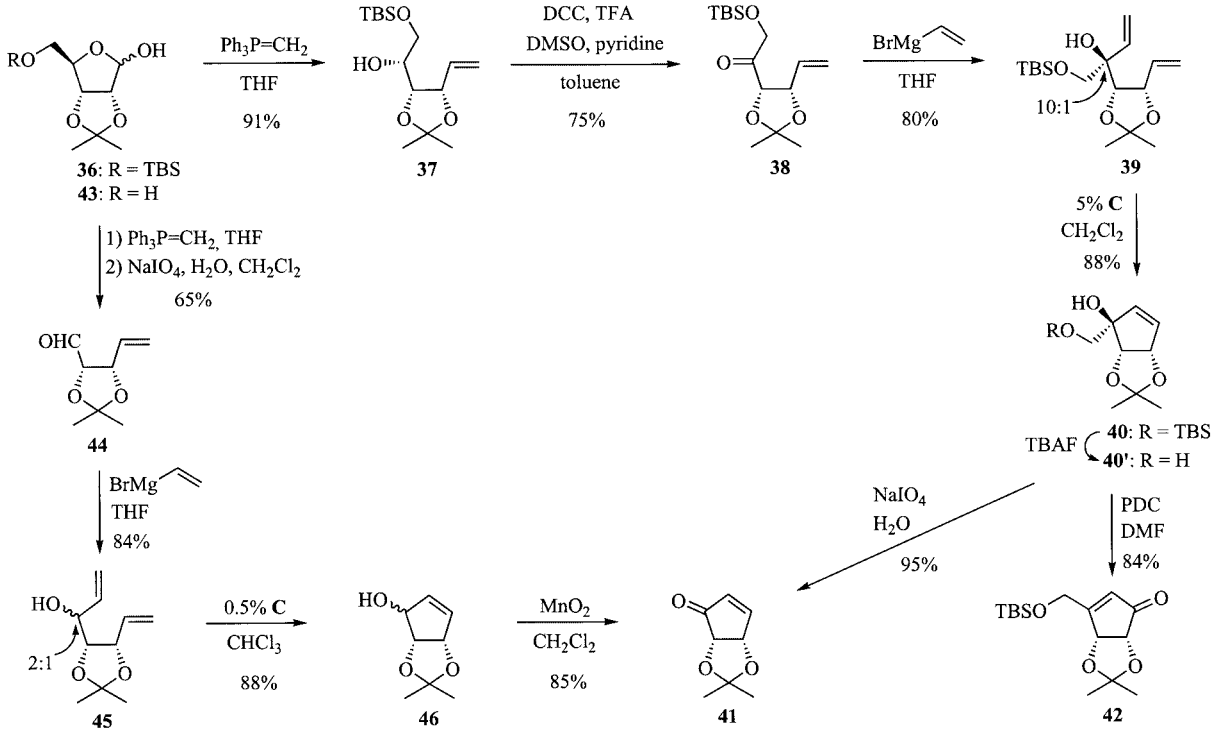
The tandem reaction with allyl bromide can easily be extended to hexoses. Zinc-mediated fragmentation and allylation of **28** gave diene **29** in high yield (Scheme 6).[29] The two diastereomers were obtained in a 1.2:1 ratio and were not separated. Instead, the mixture was submitted to the metathesis reaction with 5% of catalyst **C** to afford seven-membered cyclitol **31** in high yield.[29] The tandem reaction with **28** could also be carried out in the presence of benzylamine, which gave the corresponding aminodiene **30** in 65% yield as a 6:1 mixture of diastereomers.[29] Again, it was not possible to perform the cyclization in the presence of the secondary amine, and it was therefore protected to give amide **30′**. Ring-closing metathesis with 5% of **C** then gave aminocyclitol **32** in excellent yield.[29]

Eight-membered cyclitols can also be prepared from hexoses, but in this case it was not possible to use the zinc-mediated tandem reaction. Instead, a two-step procedure was employed, and **28** was first fragmented with zinc to give aldehyde **33** (Scheme 6). This aldehyde was then reacted with butenylmagnesium bromide to afford **34** in 77% yield from **28**.[29] Unlike the seven-membered ring formation, it was not possible to close the ring in the presence of the secondary alcohol. The metathesis reaction with **34** gave mainly homodimerization, and **34** was therefore converted into acetate **34′**. The subsequent cyclization of **34′** was achieved with 5% of **C** in a 0.006 M dichloromethane solution and gave eight-membered cyclitol **35** in 94% yield.[29]

3.2. Diene Synthesis by Wittig Reactions

The Wittig reaction is another classical procedure for introducing a C–C double bond into carbohydrates. Stabilized Wittig reagents will react with unprotected aldoses,[30] while non-stabilized Wittig reagents require the use of protecting groups. The Wittig reaction has especially been employed in the synthesis of several five-membered carbocycles that are useful for the synthesis of carbanucleosides. In this case, two different approaches have been developed starting from either a pentose or a hexose. In the first approach, a Wittig methylenation is performed at the anomeric center of a partly protected pentose, which is then followed by an alcohol oxidation and a vinyl Grignard addition. In the second approach, a Wittig methylenation is performed on a hexose, followed by an alcohol oxidation and another Wittig methylenation. The first approach has been studied by several research groups with D-ribose as the starting material. The groups of Chu[31] and Jeong[32] have developed a similar synthetic route from partly protected **36** (Scheme 7). Reaction with methylenetriphenylphosphorane was performed on a 60 g scale to give **37** in 91% yield.[31] A Moffatt oxidation of the secondary alcohol provided ketone **38**, which was then reacted with vinylmagnesium bromide to afford **39** as a 10:1 mixture of diastereomers.[31] The bulky silyl group turned out to be important for the diastereoselectivity. When a smaller benzyl ether was employed for protection of the primary alcohol, the diastereoselectivity fell to 5:1, while the more sterically demanding trityl or *tert*-butyldiphenylsilyl ethers furnished only one diastereomer in the Grignard reaction.[32] The ensuing metathesis reaction gave 88% yield with 5% of catalyst **C**[31] and 83% yield with 1% of catalyst **D**.[32] Desilylation/oxidative cleavage or oxidative rearrangement of cyclopentene **40** then yielded cyclopentenones **41**[31] or **42**[32], respectively.

A shorter route to **41** was also reported from ribofuranose **43** (Scheme 7).[33] Again, a Wittig reaction installed the terminal olefin, but the product was contaminated with triphenylphosphane oxide. As a result, the oxidative cleavage with periodate was performed on the crude product to afford aldehyde **44** in 65% yield over two steps.[33] Reaction with vinylmagnesium bromide introduced the second double bond, which was followed by ring-closing metathesis with 0.5% of catalyst **C** to give cyclopentene **46**. Allylic oxidation then afforded cyclopentenone **41** in 85% yield from



Scheme 7.

46 and 38% overall yield from ribose.[33] All the steps in the synthesis of **41** and **42** have been performed on a large gram scale.[31–33]

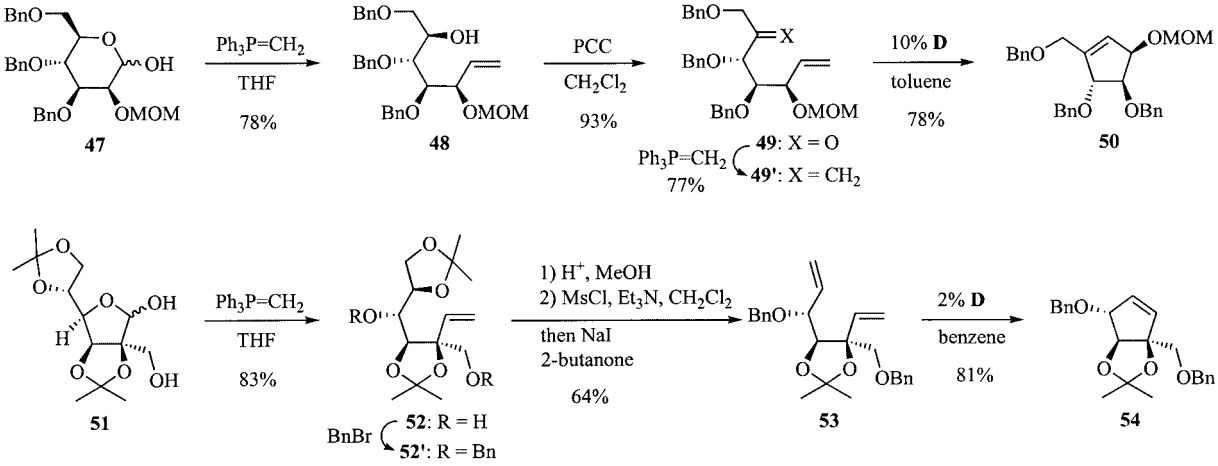
A different route to **42** has been reported by the groups of Jacobson[34] and Rodriguez.[35] In their synthesis, ribofuranose **43** was protected at C-5 and reduced to the corresponding ribitol, which was protected at C-1. An oxidation and a Wittig methylenation were then performed at C-4, followed by another oxidation and a vinyl Grignard reaction at C-1. Subsequent metathesis and oxidation then gave **42**, but in a lower overall yield than in Scheme 7 due to the additional steps for oxidation/reduction and protection/deprotection.[34,35]

A second approach to cyclopentenes uses the Wittig reaction on hexoses to install the double bonds. Callam and Lowary described the synthesis of carba-arabinofuranose from the protected mannopyranose **47** (Scheme 8).[36] The Wittig methylenation was performed at the anomeric center to furnish **48**, which was oxidized and submitted to another Wittig olefination to give diene **49′**. The subsequent metathesis reaction gave a good yield with catalyst **D**, while the yield with catalyst **C** was only 19%. 2-Substituted α,ω-dienes are known to be less reactive in ring-closing metathesis reactions, which often makes it necessary to use the more reactive catalyst **D** with these substrates.[8] Agrofoglio and co-workers reported a similar cyclopentene synthesis from a protected galactopyranose by the use of two Wittig methylenations at C-1 and C-5 followed by ring-closing metathesis with catalyst **D**.[37]

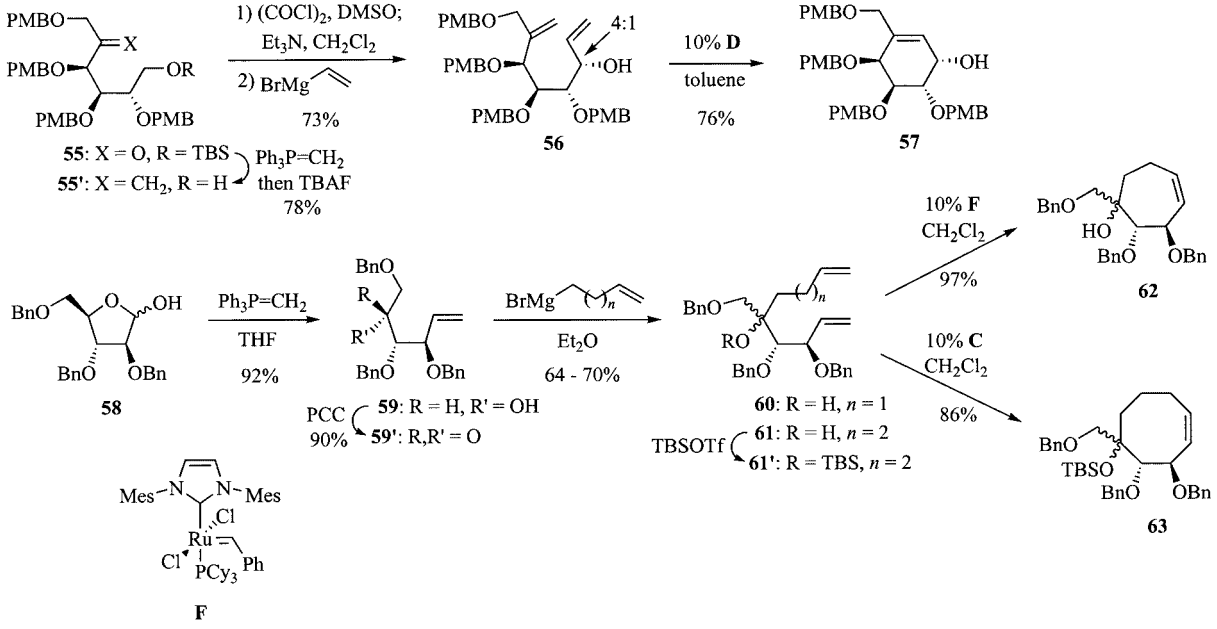
A slightly different cyclopentene synthesis was described by Ramana and co-workers by using mannose as the starting material (Scheme 8).[38] Branched furanose **51** is available by an aldol condensation between formaldehyde and diisopropylidene mannofuranose. A Wittig methylenation introduced the first double bond at the anomeric center to afford **52**. The second double bond was installed by an iodide-mediated elimination of a bis-mesylate, which was prepared after selective hydrolysis of the more labile 5,6-isopropylidene acetal. The ring-closing metathesis reaction failed with catalyst **C**, but could be affected in good yield with catalyst **D**.[38]

The Wittig reaction has also been used in the synthesis of larger rings where the second olefin is introduced by a Grignard reaction. Whalen and Halcomb used this approach for the synthesis of α-carba-galactopyranose from galactose (Scheme 9).[39] Ketone **55** was obtained by a Swern oxidation of the corresponding alcohol and exposed to methylenetriphenylphosphorane and tetrabutylammonium fluoride to give olefin **55′**. Swern oxidation and addition of vinylmagnesium bromide then yielded diene **56** as a 4:1 mixture of diastereomers. The ring-closure was carried out with catalyst **D** to give cyclohexene **57**, which was used in the synthesis of a small glycopeptide containing a carba-sugar.[39]

Sinaÿ and co-workers used the same combination of a Wittig reaction and a Grignard reaction to prepare seven- and eight-membered rings (Scheme 9).[40] Protected arabinofuranose **58** was converted into olefin **59**, which was then oxidized to the corresponding ketone **59′**. Subsequent reaction with butenyl- or pentenylmagnesium bromide gave diene **60** or **61**, respectively, as a 1:1 mixture of diastereomers in both cases.[40] The subsequent metathesis re-



Scheme 8.



Scheme 9.

action was studied with catalysts **C** and **F**,[41] where the latter is an unsaturated analogue of **D** with a similar reactivity. Dienes **60** and **61** could both be cyclized with catalyst **C**, but the yields of the seven- and the eight-membered ring were only 60% and 29%, respectively. Instead, the metathesis reaction was performed with catalyst **F**, which gave a very high yield of the cycloheptene **62** (from **60**), while **61** failed to react with **F**. It appears that the tertiary alcohol possesses a problem in the formation of the eight-membered ring, which is presumably due to chelation. Therefore, it was decided to protect the hydroxy group in **61** as the *tert*-butyldimethylsilyl ether. Ring-closing metathesis with protected **61′** proceeded effectively with catalyst **C** to give cyclooctene **63**.[40]

3.3. Diene Synthesis by Vinyl Grignard Reactions

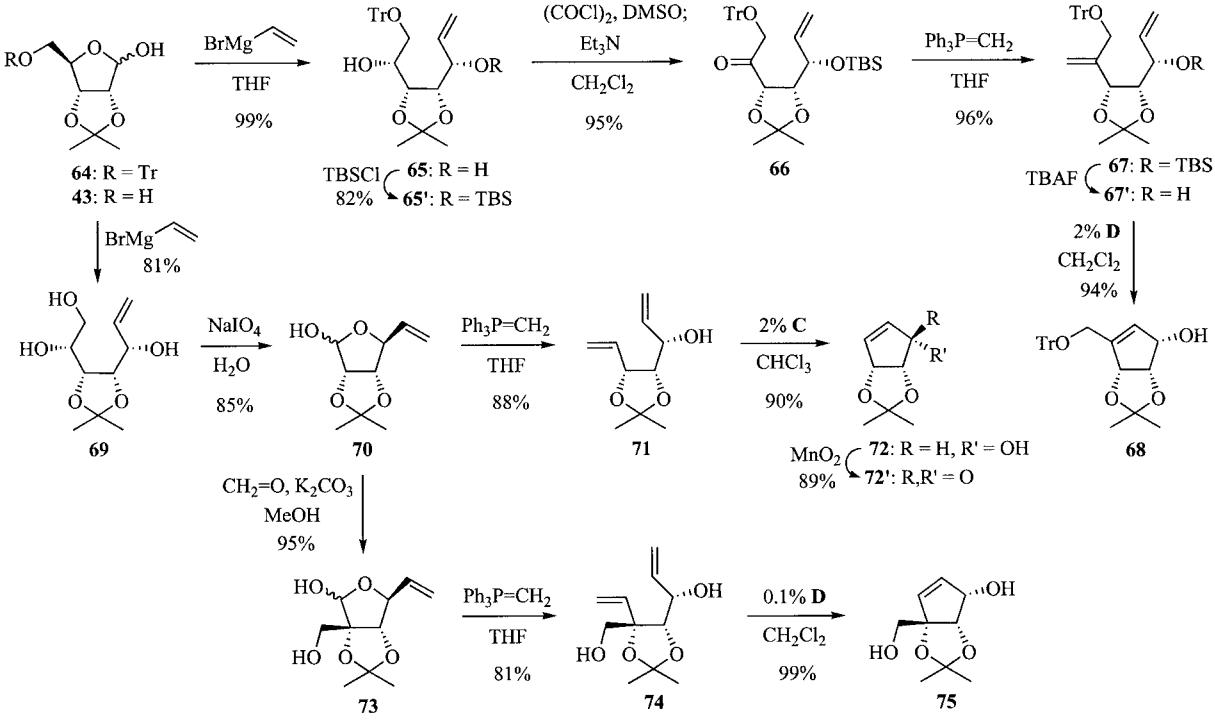
The Grignard reaction with vinylmagnesium bromide is a widely employed protocol for installing a C–C double bond. As shown above, this transformation is often used in combination with the Wittig reaction. An example is illustrated in the cyclopentene syntheses by Chu[31] and Jeong[32,33] in Scheme 7, where a Wittig reaction was performed at the anomeric center of D-ribose followed by an oxidation and a Grignard reaction at C-4. The same groups have developed an alternative cyclopentene synthesis by using the two olefin-forming reactions in the opposite order. Chu and co-workers reacted trityl-protected ribofuranoside **64** with vinylmagnesium bromide to afford olefin

65 as a single diastereomer (Scheme 10).[42] The allylic alcohol was selectively protected with a silyl ether, followed by a Swern oxidation of the other hydroxy group and a Wittig methylenation to give diene **67**. Unfortunately, it turned out to be impossible to perform the ring-closing metathesis reaction on **67** with catalysts **C** and **D**. The reason seemed to be the bulky protecting groups, and it was therefore decided to remove the silyl ether. The resulting alcohol **67′** cyclized very well with 2% of catalyst **D** to afford cyclopentene **68**. The metathesis reaction proceeded less efficiently with catalyst **C**, where substoichiometric amounts of catalyst were required in order to produce a good yield of **68**. All the steps in the synthesis of **68** were performed on a multigram scale (10 g or more).[42] A similar synthetic route was reported by Seepersaud and Al-Abed, where a protected arabinofuranose served as the starting material and was submitted to a vinyl Grignard reaction at C-1 and a Wittig methylenation at C-4 followed by ring-closing metathesis.[43]

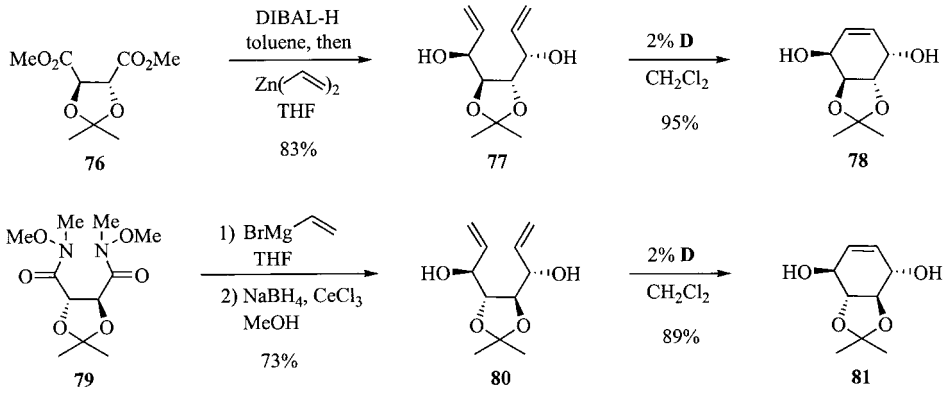
Another cyclopentene synthesis was developed by Jeong and co-workers from ribofuranose **43** (Scheme 10).[33] Again, the reaction with vinylmagnesium bromide produced the desired product as a single diastereomer. Periodate cleavage gave lactol **70** which, after a Wittig methylenation and ring-closing metathesis, afforded cyclopentene **72**. Allylic oxidation then gave cyclopentenone **72′** in a total of 6 steps and 45% overall yield from D-ribose.[33] It should be noted that **72′** is the enantiomer of **41** in Scheme 7, and that both compounds have been prepared from the same starting material. Thus, depending on the order of the Grignard reaction and the Wittig reaction, either enantiomer of **72′** can be obtained in five steps from ribofuranose **43**.[33]

A branched cyclopentene can also be prepared by the same route. Isopropylidene-protected lactol **70** was submitted to an aldol condensation with formaldehyde to produce **73** as a single diastereomer (Scheme 10).[44] The diastereoselectivity is dictated by the isopropylidene group, since the aldol condensation is reversible and only the product with a *cis* acetonide will cyclize to form the lactol. Compound **73** was then converted into diene **74**, which was cyclized in a highly efficient metathesis reaction to afford branched cyclitol **75**. Cyclopentenes **68**, **72** and **75** have all been used in the synthesis of a range of diverse carbanucleosides.[31,42,44]

Cyclohexenes have been prepared by a very short route from tartaric acid by introducing vinyl groups at C-1 and C-4. Madsen and co-workers reacted methyl tartrate **76** with 2 equiv. of DIBAL-H followed by an excess of divinylzinc in the same pot to afford diene **77** as a pure stereoisomer (Scheme 11).[45] The same transformation has previously been described with DIBAL-H and vinylmagnesium bromide, but in a lower yield due to the formation of other diastereomers.[46] Diene **77** is a useful chiral building block, and has been used as the starting material in two recent total syntheses.[47] Bertozzi and co-workers prepared another diastereomer by using the Weinreb amide of tartaric acid (Scheme 11).[48] Reaction between **79** and vinylmagnesium bromide furnished the corresponding diketone, which upon Luche reduction, gave diastereomerically pure diene **80**. The subsequent metathesis reaction was performed with catalyst **D** in both cases to give the acetonides of conduritol E (**78**)[49] and conduritol B (**81**).[48] Attempts to use catalyst **C** for the cyclization of **77** failed due to isomerization of one allylic alcohol into the ethyl ketone.[50] The excellent



Scheme 10.



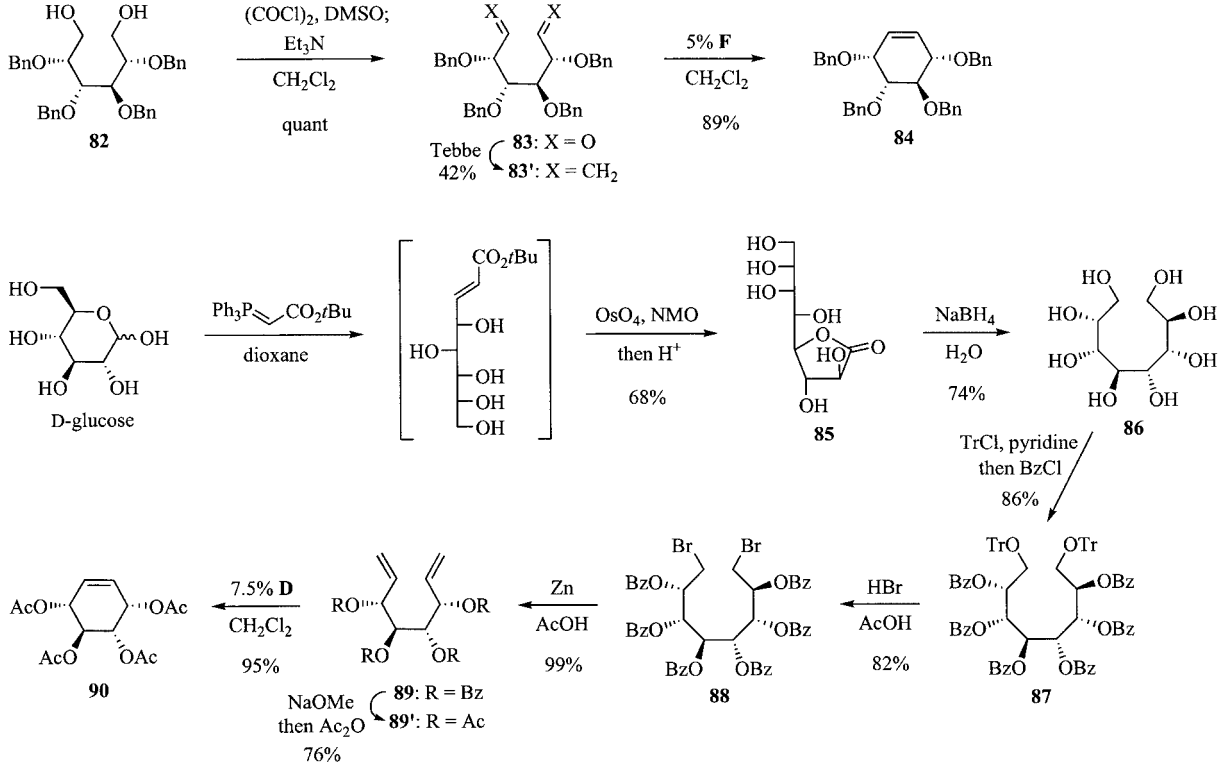
Scheme 11.

stereocontrol in the syntheses of **77** and **80** should be noticed, and this stereocontrol makes it possible to prepare two different cyclitols from the same tartaric acid.

3.4. Miscellaneous Methods for Synthesis of Dienes

Terminal olefins can also be introduced into carbohydrates by other methods than the three transformations described above. Fürstner and co-workers prepared benzyl-protected D-glucitol **82** from the parent polyol and oxidized the two primary hydroxy groups by a Swern oxidation (Scheme 12).[50] It was attempted to perform a double Wittig or Takai methylenation on the resulting dialdehyde, but both reactions failed due to the instability of the dialdehyde. Instead the two olefins were installed under mild conditions with the Tebbe reagent [$Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$] to afford diene **83′**. The subsequent metathesis reaction gave benzyl-protected (–)-conduritol F (**84**) in 89% yield with catalyst **F**, whereas the yield with catalyst **C** was only 32%.[50]

Madsen and co-workers prepared the enantiomer of **84** from D-glucose by using a different strategy.[30,45] Glucose was submitted to a Wittig reaction in dioxane with a stabilized phosphorane (Scheme 12).[30] The resulting unsaturated ester was not isolated, but subjected to a dihydroxylation in the same pot to afford octonolactone **85** in 68% overall yield after an acidic workup. The dihydroxylation occurred with a 5:1 diastereoselectivity, and the minor isomer was not isolated.[30] Reduction of the lactone gave octitol **86**, which was protected with trityl ethers on the primary



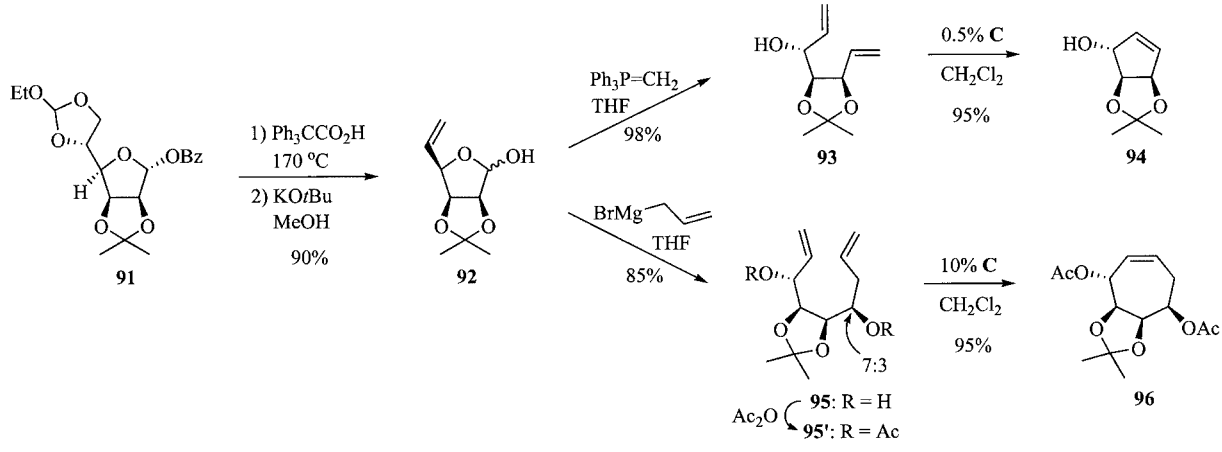
Scheme 12.

hydroxy groups and benzoate esters at the secondary positions.[45] Fully protected **87** was then exposed to a saturated solution of hydrogen bromide in acetic acid. The trityl ethers were cleaved immediately under these conditions followed by introduction of bromine at the terminal positions, presumably through the formation and ring-opening of 1,2-benzoxonium ions.[45] Subsequent reductive elimination with zinc then gave diene **89**. Unfortunately, the ensuing metathesis reaction proceeded poorly with catalyst **D**, and it was therefore decided to replace the four benzoate esters with smaller acetates. This had a significant impact on the cyclization, which could now be achieved with catalyst **D** in 95% yield to give peracetylated (+)-conduritol F (**90**). A slightly lower yield in the metathesis reaction was observed when catalyst **C** was used.[45]

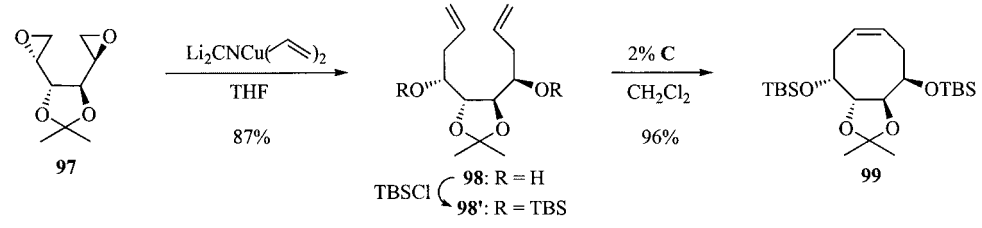
An elimination reaction can also be achieved by thermal rearrangement of an orthoester. This transformation has been applied in several cases to introduce a 5,6-double bond in mannose from the corresponding isopropylidene mannofuranose. van Boom and co-workers performed the thermal rearrangement of orthoester **91** in high yield to give olefin **92**, which was then subjected to a Wittig methylenation followed by ring-closing metathesis to afford cyclopentene **94** (Scheme 13).[18] Vonlanthen and Leumann used the same sequence to prepare **94** on a large gram scale, e.g. the metathesis reaction was carried out with 88 g of **93** and 0.05% of catalyst **C**.[51] Marco-Contelles and de Opazo employed the orthoester rearrangement of **91** in the preparation of seven-membered cyclitols (Scheme 13).[52] In this case, a Grignard reaction was performed on **92** with allylmagnesium bromide to give diene **95** as a 7:3 mixture of diastereomers. The major diastereomer reacted sluggishly with metathesis catalyst **C** and gave only 45% yield of the desired product after 7 d. The minor diastereomer, on the other hand, showed a much higher reactivity and could be cyclized in 85% yield after 6 h. The reactivity difference disappeared after converting **95** into diacetate **95′**, where both diastereomers cyclized in a very high yield after 1 h with catalyst **C**.[52]

A special method for installing two olefins in carbohydrates was exploited by Le Merrer and co-workers in a synthesis of eight-membered cyclitols.[53] Bis-epoxide **97**, which is available from D-mannitol, was treated with an excess of lithium divinylcyanocuprate to effect a clean opening of both epoxides (Scheme 14). The resulting diene was submitted to ring-closing metathesis with catalyst **C**, but the cyclization gave only 62% yield. Again, the secondary hydroxy groups seemed to be responsible for the moderate yield, and **98** was therefore protected with two *tert*-butyldimethylsilyl ethers. The cyclization of silyl-protected **98′** proceeded readily and gave cyclooctene **99** in high yield.[53] Marco-Contelles and de Opazo made the same observation in the synthesis of a similar cyclooctene where the metathesis reaction could only be achieved in good yield when all the hydroxy groups were protected.[54]

All in all, the synthetic methodologies for converting carbohydrates into carbocycles by metathesis are very diverse. Although three olefin-forming reactions clearly dominate, the combination of these methods and others allow for the synthesis of a wide range of α,ω-dienes with different lengths, stereochemistries, protecting groups and substituents. A number of these diene syntheses can be achieved



Scheme 13.



Scheme 14.

in only 3–5 steps from commercially available, unprotected carbohydrates. The ring-closing metathesis reactions are particularly successful with catalyst **D**, and ring-sizes from five- to eight-membered rings can be formed in good to excellent yields.

4. Application of Ring-Closing Metathesis in Natural Product Synthesis from Carbohydrates

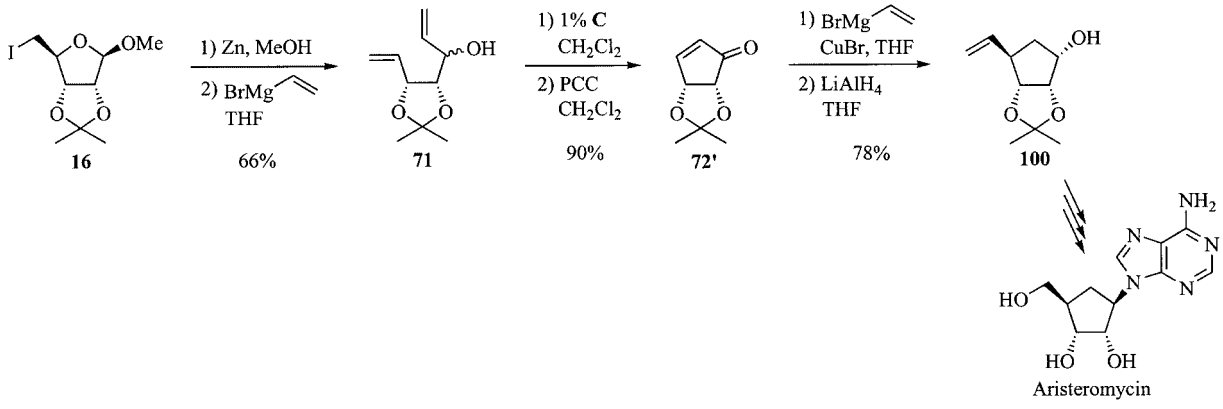
Many natural products contain a polyhydroxylated carbocyclic ring which can be either a five-, six- or seven-membered ring. Some of these natural products have been prepared from carbohydrates by using the metathesis strategies described above. The purpose of this chapter is to illustrate these syntheses, which are organized by ring-size.

Aristeromycin: The carbanucleosides are an important class of natural products containing a five-membered carbocycle. Many analogues of naturally occurring carbanucleosides have been prepared from D-ribose by using the strategies described in Scheme 7 and Scheme 10.[31,34,37,42,44] A slightly modified approach was used by Schneller and co-workers in their synthesis of the antiviral agent aristeromycin.[55] Ribofuranoside **16**, which is available in two steps from ribose, was fragmented with zinc metal (Scheme 15). The resulting aldehyde was isolated and reacted with vinylmagnesium bromide to provide diene **71** as a 4.5:1 mixture of diastereomers. Metathesis and oxidation then gave cyclopentenone **72′**, which was submitted to a 1,4-addition with vinylmagnesium bromide followed by a ketone reduction with lithium aluminum hydride. The obtained alcohol **100** was converted into aristeromycin in 5 steps.[55]

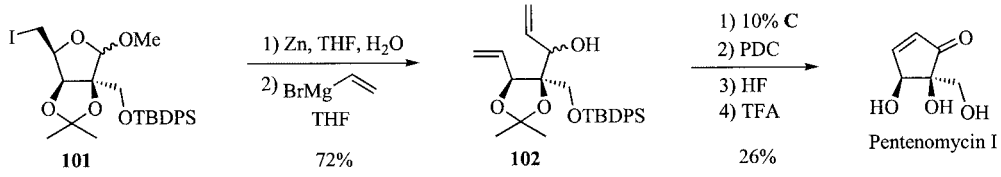
Pentenomycin I: A similar route was employed by Ramana and Rao in their synthesis of the antibiotic pentenomycin I.[56] Iodofuranoside **101** was prepared in 7 steps from diisopropylidene mannofuranose and subjected to a fragmentation with zinc (Scheme 16). The aldehyde thus formed was treated with vinylmagnesium bromide to afford diene **102**. The ensuing metathesis reaction occurred in 84% yield with catalyst **C** and was followed by an oxidation and a deprotection to furnish the natural product.[56]

***myo*-Inositol Phosphates:** *myo*-Inositol is one of the most abundant six-membered cyclitols in nature. *myo*-Inositol forms the major component of inositol phosphates and phosphatidylinositols which play important roles as secondary messengers in intracellular signal transduction. Shirai and co-workers developed a synthesis of D-*myo*-inositol 3,4,5,6-tetrakisphosphate (**107**) from D-glucose by the use of ring-closing metathesis.[57] Furanose aldehyde **103** was prepared in 3 steps from diisopropylidene glucofuranose and subjected to a completely diastereoselective Grignard reaction with vinylmagnesium bromide (Scheme 17). Protecting group manipulations and a Wittig reaction then gave diene **104**, which was cyclized with catalyst **C** to afford cyclohexene **105**. Further protecting group transformations and dihydroxylation gave protected *myo*-inositol **106′**, which was converted into **107** in 3 steps.[57]

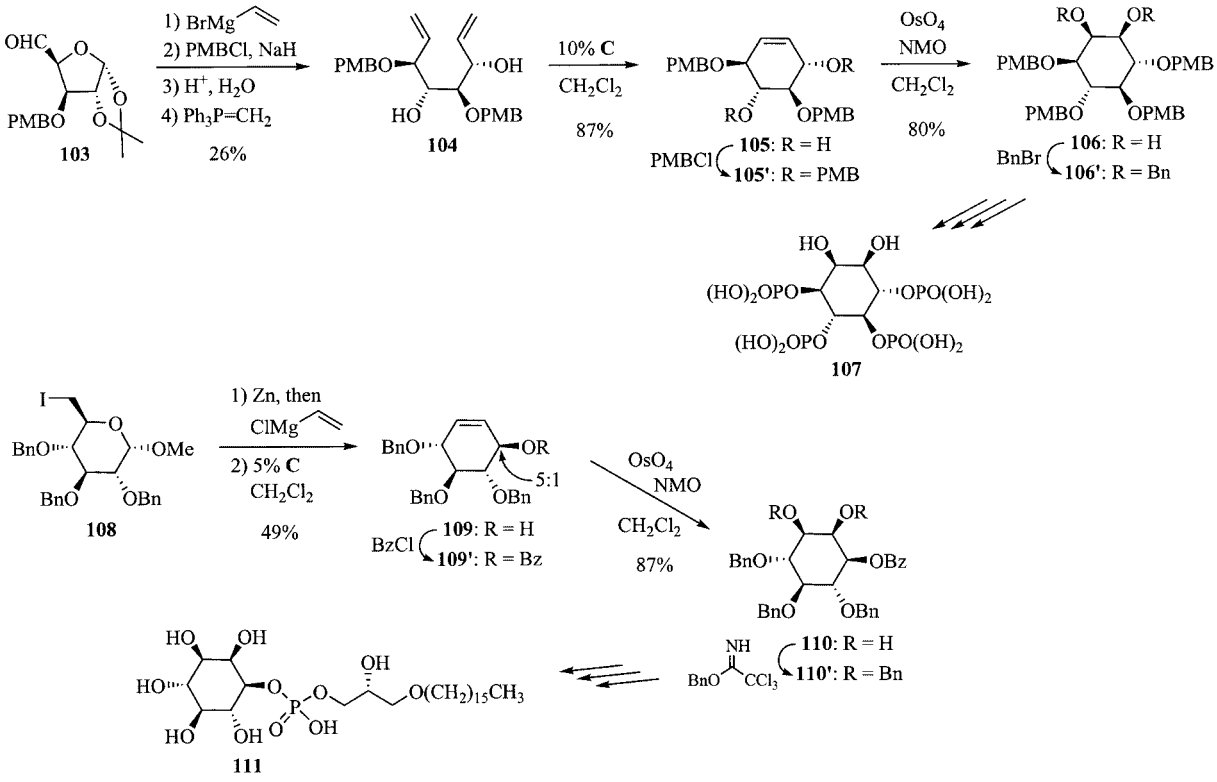
Madsen and co-workers described a synthesis of lysophospholipid **111**, which is an antitumor agent.[58] The synthesis commenced with iodopyranoside **108**, which is available from D-glucose in 3 steps (Scheme 17). A zinc-mediated fragmentation was performed to give the corresponding aldehyde, which was isolated by extraction and reacted with vinylmagnesium chloride to give the diene as a 5:1 mixture of diastereomers. The two isomers were separated after the metathesis reaction with catalyst **C**. It was attempted to add divinylzinc during the zinc-mediated fragmentation as described in Scheme 3, but unfortunately this protocol gave



Scheme 15.



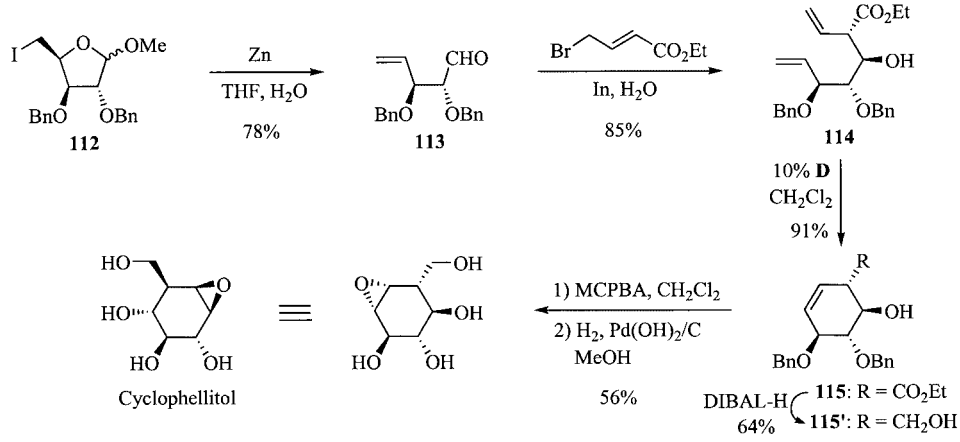
Scheme 16.



Scheme 17.

the two diastereomeric dienes in a 1:1 ratio. Next, the cyclohexene was protected with a benzoate and submitted to a highly diastereoselective dihydroxylation to give **110**. Protecting group manipulations and phosphorylation then gave **111** in 4 steps from **110**.[58]

Cyclophellitol: A number of glycosidase inhibitors consist of a six-membered cyclitol. Cyclophellitol is a carbocyclic analogue of D-glucopyranose with an epoxide on the β-face of the molecule. It is an irreversible β-glucosidase inhibitor whose activity is presumably due to protonation and opening of the epoxide by a carboxylate in the active site of the enzyme. Recently, Madsen and co-workers reported a short synthesis of cyclophellitol from D-xylose.[59] Iodofuranoside **112** was prepared in 3 steps from xylose and reacted with zinc to afford unsaturated aldehyde **113** (Scheme 18). This was followed by a diastereoselective indium-mediated coupling with ethyl 4-bromocrotonate to give **114** as the only isolated diastereomer. It was not possible to perform the zinc-mediated fragmentation and the indium-mediated coupling as a one-pot tandem sequence. Diene **114** was then converted into cyclophellitol by metathesis, reduction, epoxidation and deprotection to give the natural product in a total of 9 steps and 14% overall yield from D-xylose.[59] Another cyclophellitol synthesis from xylose was also recently reported from the group of Kornienko, where the target molecule was assembled in 13 steps by the use of a



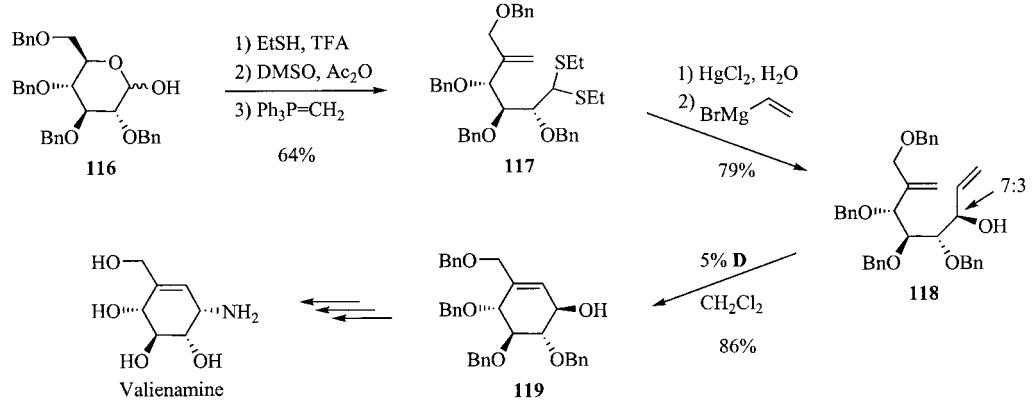
Scheme 18.

Wittig methylenation and a 1,4-addition of a vinylcopper reagent to install the two double bonds.[60]

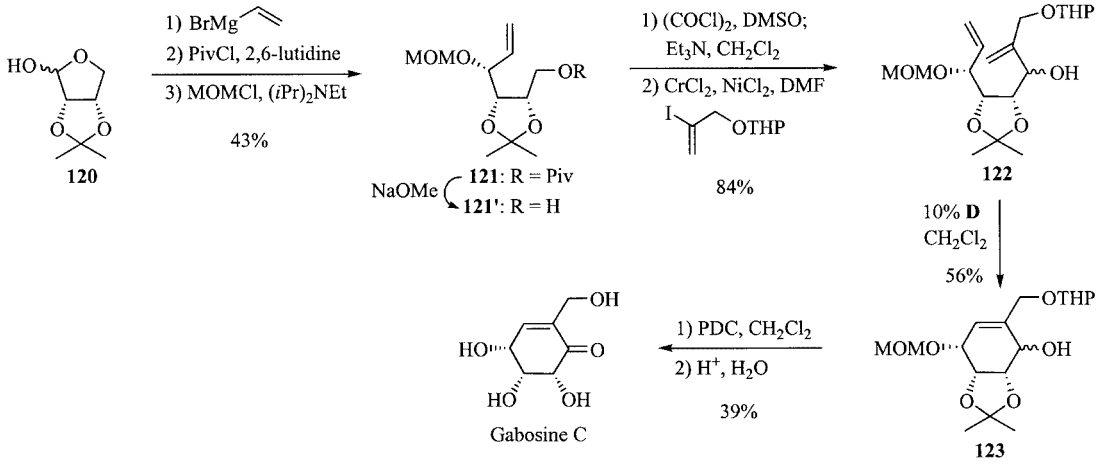
Valienamine: Another potent glycosidase inhibitor with a six-membered ring is the reversible α-glucosidase inhibitor valienamine. Like cyclophellitol, valienamine also has a structural resemblance with D-glucose, which was used by Kim and co-workers in their synthesis from protected glucopyranose **116** (Scheme 19).[61] Thioacetalization with ethanethiol liberated the alcohol at C-5, which was oxidized and reacted with methylenetriphenylphosphorane to afford **117**. Hydrolysis of the thioacetal and exposure to vinylmagnesium bromide then gave diene **118** as a 7:3 mixture of diastereomers that were separated after the metathesis reaction with catalyst **D**. Cyclohexene **119** was then converted into valienamine in 4 steps by substitution with azide followed by a Staudinger reaction and a Birch reduction.[61] Recently, Cumpstey published an alternative synthesis where the Grignard reaction was performed directly on pyranose **116**, followed by an oxidation and a Wittig methylenation at C-5.[62] However, due to some additional protecting group manipulations this route required 8 steps from pyranose **116** to cyclohexene **119**.[62]

Gabosine C: The gabosines are a class of natural products where a majority contain a cyclohexenone ring system. Gabosine C is an antibiotic and was recently prepared by Ramana and Rao by the use of metathesis.[63] Lactol **120** was obtained in 3 steps from ribose and submitted to a highly diastereoselective reaction with vinylmagnesium bromide (Scheme 20). Subsequent protecting group manipulations gave alcohol **121′**, which was subjected to a Swern oxidation and a Nozaki–Hiyama–Kishi reaction to afford diene **122** as a 1:1 mixture of diastereomers. The subsequent metathesis reaction gave 56% yield together with some unreacted **122** after 2 d at 80 °C. Oxidation and protecting group removal then gave gabosine C in a somewhat moderate yield from **123**.[63]

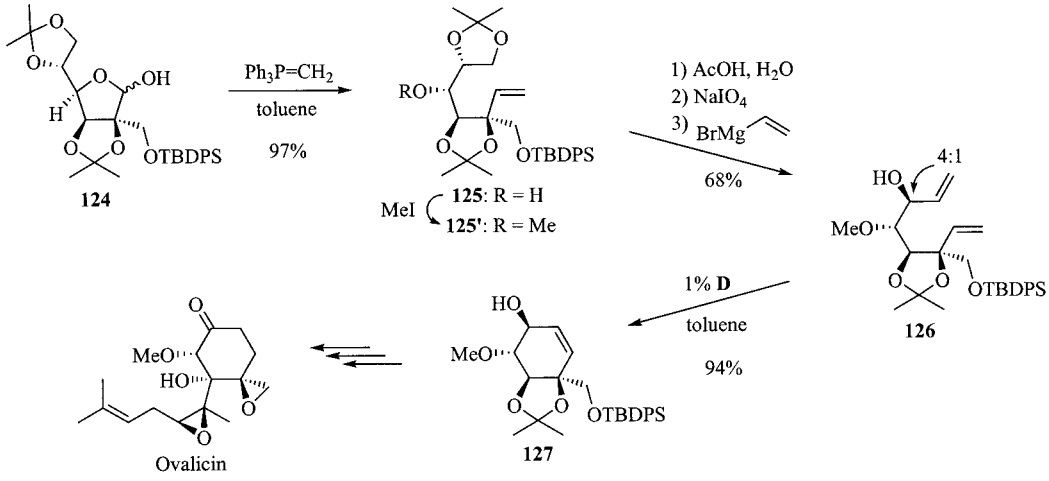
Ovalicin: The angiogenetic inhibitor ovalicin contains a more substituted cyclohexanone ring system. Takahashi and co-workers developed a synthesis of ovalicin by starting from D-mannose.[64] Branched mannofuranose **124** was exposed to methylenetriphenylphosphorane to afford **125**, which after protecting group transformations, periodate cleavage and a Grignard reaction, was converted into diene **126** as a 4:1 mixture of diastereomers (Scheme 21). The me-



Scheme 19.



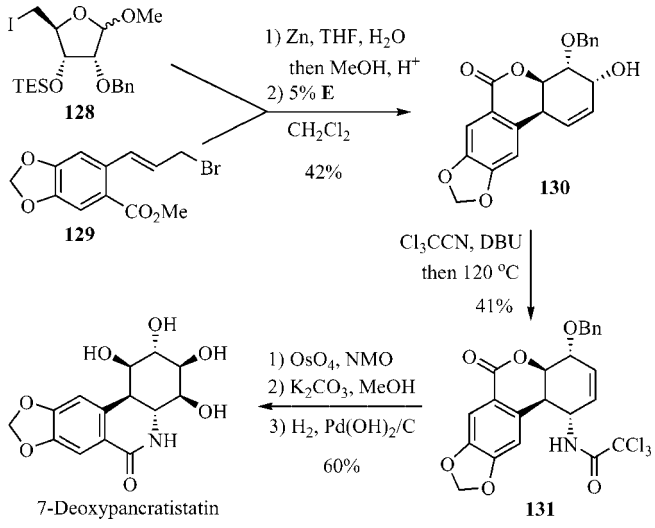
Scheme 20.



Scheme 21.

tathesis reaction proceeded efficiently with catalyst **D** to give **127**, which was then reacted in 12 additional steps to install the other functional groups in ovalicin.[64]

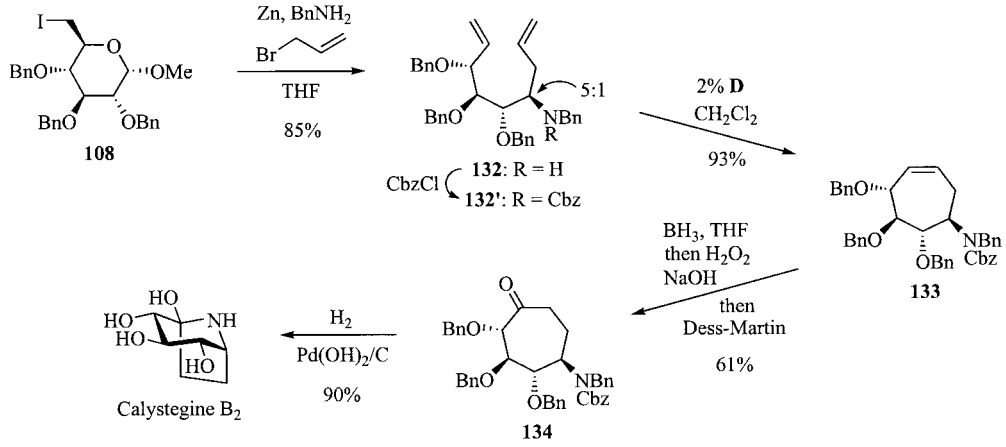
7-Deoxypancratistatin: A complicated cyclohexane ring system is also found in the antitumor agent 7-deoxypancratistatin. Very recently, Madsen and co-workers reported a synthesis of 7-deoxypancratistatin by using the zinc-mediated tandem reaction as the key step.[65] Bromide **129** was chosen as the allylic bromide and prepared from piperonal in 5 steps (Scheme 22). Ribose was required as the carbohydrate component in the tandem reaction in order to obtain the correct stereochemistry in the coupling product. After some experimentation, furanoside **128** was found to be the best substrate, particularly because a benzyl group was necessary at position 2. Furanoside **128** was prepared in 7 steps from D-xylose and then reacted with **129** and zinc. The tandem reaction afforded two diastereomeric dienes in a 2:1 ratio which could not be separated. The crude product was therefore treated with acid to remove the silyl group



Scheme 22.

and then submitted to metathesis with catalyst **E** to afford the major diastereomer **130** in 42% overall yield. The metathesis reaction could also be achieved with catalysts **C** and **D**, but the yield of **130** was lower. This is one of the few applications in carbohydrate chemistry with catalyst **E** which seems to give a slightly faster and cleaner conversion than catalyst **D**.[23] Cyclohexene **130** was then transformed into **131** by an Overman rearrangement where the benzyl group in **130** conveniently protected the homoallylic alcohol. The amide **131** was obtained in moderate yield and converted into 7-deoxypancratistatin by dihydroxylation and removal of the protecting groups. This synthesis gives rise to the natural product in 13 linear steps and 4.3% overall yield from D-xylose.[65]

Calystegine B_2: Natural products containing a seven-membered cyclitol are relatively rare in nature. One of the exceptions is the calystegine alkaloids, which are a general class of glycosidase inhibitors consisting of a polyhydroxylated nortropane ring system. Skaanderup and Madsen,[66] as well as Boyer and Hanna,[67] have developed virtually identical syntheses of calystegine B_2 by using the zinc-mediated tandem reaction as the key transformation. Calystegine B_2 is a β-glucosidase inhibitor with a structure resembling D-glucose. Therefore, glucopyranside **108** was chosen as the starting material and reacted with zinc, benzylamine and allyl bromide to give diene **132** as a 5:1 mixture of diastereomers (Scheme 23). The secondary amine was protected with a benzyloxycarbonyl group followed by ring-closing metathesis to afford cycloheptene **133**. A ketone was then introduced by hydroboration of the alkene followed by oxidative workup and further oxidation with the Dess–Martin periodinane. The regioselectivity in the hydroboration/oxidation was 3:1, and the major isomer **134** was isolated in 61% yield. Final deprotection by hydrogenolysis furnished the natural product in a total of 9 steps and 19% overall yield from D-glucose.[66,67] Skaanderup and Madsen have applied the same route for the preparation of two other calystegines by starting from D-galactose and D-mannose, respectively.[68]



Scheme 23.

5. Conclusions

Ring-closing olefin metathesis is a very versatile method for converting carbohydrates into carbocycles. A large variety of α,ω-dienes can be prepared from carbohydrate starting materials by the use of different olefin-forming reactions, especially the zinc-mediated fragmentation of iodoglycosides, the Wittig methylenation and the alkenyl Grignard reaction. The most efficient routes install the two double bonds in the same pot, e.g. by combining the zinc-mediated fragmentation with another zinc reaction in a tandem sequence. The ring-closing metathesis reaction makes it possible to form ring sizes from five- to eight-membered rings in good to excellent yields. Catalyst **D** is the preferred catalyst for the metathesis reaction, and performs better than catalyst **C** in virtually all cases. More recently developed catalyst **E** is a promising new discovery, since it seems to give a slightly faster and cleaner conversion than catalyst **D** with carbohydrate substrates. The catalyst loading is still a matter of concern in some metathesis reactions, which makes it important to continue the search for better catalysts. Hydroxy groups sometimes hamper a metathesis reaction, particularly when forming eight-membered rings. These difficulties can usually be solved by simple acetylation prior to the metathesis reaction. The carbocyclization strategy has been applied in the synthesis of a number of natural products and other biologically active molecules. In some cases, very efficient syntheses have been developed which require less than 10 steps for assembling the target molecule from a commercially available, unprotected carbohydrate. In other cases, the total number of steps is still relatively high, which shows that new and more effective synthetic transformations are still needed in carbohydrate chemistry.

Acknowledgments

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