Synthesis and Conformational and Biological Aspects of Carbasugars†

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1. Introduction

Carbohydrate chemistry constitutes today a "multifaceted" discipline strongly connected with organic, pharmaceutical, and medicinal chemistry.[1] Carbohydrates are important biomolecules whose role is not only limited to energy storage, since they are constituents of glycoproteins, glycolipids, and other conjugates. They are therefore key elements in a variety of processes such as signaling, cell−cell communication, and molecular and cellular targeting.[2] Many biological processes, ranging from blood clotting to fertilization, all involve carbohydrates, and the biological implications of these compounds are strongly related with diseases such as cancer, diabetes, or inflammatory processes. In addition, some intriguing compounds such as sialyl Lewis X (sLe^x)[3] or glycosylphosphatidylinositols (GPIs)[4,5] are now known to play a pivotal role in numerous biological functions.[6]

On the basis of these considerations, the search for new derivatives with analogous or even improved biological properties compared to those of the parent structures (the *carbohydrate mimetics*) appears to be a logical matter of research.[7,8] The term "*carbohydrate mimetic*" is frequently used to refer to any carbohydrate derivative or other compound that has multiple hydroxy groups and thus resembles a sugar or a saccharide. However, some authors prefer to reserve this term for compounds that have been demonstrated to truly mimic the structural and functional aspects of a known target.[9] In our opinion, ***carbasugars*** (*vide infra*) fall within this category, since they are endowed with important biological properties.

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Professor G. E. McCasland's group prepared a series of derivatives in which the ring oxygen of a monosaccharide had been replaced by a methylene group,[10−12] and they coined the term *pseudosugars* for this family of compounds, although they are currently known as ***carbasugars***.[13,14] 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.

They synthesized 5a-carba-α-DL-talopyranose (**1**)[10] (the first reported carbasugar), 5a-carba-α-DL-galactopyranose (**3**),[11] and 5a-carba-*β*-DL-gulopyranose (**5**)[12] (Figure 1). It is noteworthy that, 7 years later, 5a-carba-α-D-galactopyranose was isolated as a *true* natural product from a fermentation broth of *Streptomyces* sp. MA-4145.[15] In the following four decades, the chemistry, biology, and conformational aspects of carbasugars have been extensively studied. For instance, of the 32 isomers of 5a-carba-aldopyranoses theoretically possible, all 16 of the racemic forms have already been synthesized, as well as 25 of the possible 32 pure enantiomers. On the other hand, an important number of analogues

† Dedicated to Prof. Seiichiro Ogawa for his contribution to the development of this field.

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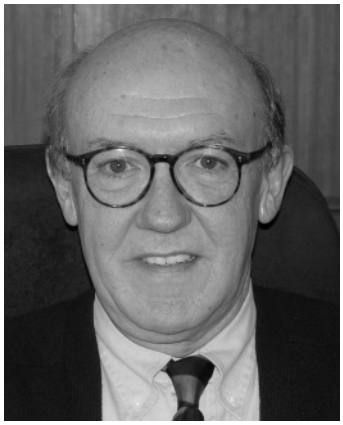


Odón Arjona studied Chemistry at the University Complutense of Madrid (UCM), where he obtained his Diploma in 1975 and his Ph.D. in 1981 at the Department of Organic Chemistry. In 1985 he became Associate Professor of Organic Chemistry at the UCM, and in 2004 he was promoted to full Professor of Organic Chemistry at the same University (UCM). He was a Visiting Fellow at the University of Durham (U.K.) in 1989. His current research interests focus on the development of new synthetic methodologies and the total synthesis of natural products.

Ana M. Gómez was born in Madrid, Spain. She received her Ph.D. degree, under the direction of Dr. S. Valverde, from the University Complutense of Madrid (UCM) in 1991. She was a posdoctoral associate at the Chemistry Department of Duke University with Prof. B. Fraser-Reid (1992–1994). Since 1998 she has been a Tenured Researcher at the Instituto de Química Orgánica General (CSIC) in Madrid. Her research interests involve several aspects of chemical transformations on carbohydrates, including glycosylation, radical reactions, and natural product synthesis.

J. Cristóbal López was born in Madrid, Spain. He graduated from the University Complutense of Madrid (UCM) in 1980 and obtained his Ph.D. degree from the same university with Dr. S. Valverde in 1986. He was a posdoctoral associate at the Institut de Chimie des Substances Naturelles (CNRS, Gif sur Yvette, France) with Dr. G. Lukacs (1986–1987) and at the Chemistry Department of Duke University with Prof. B. Fraser-Reid (1988–1990). He has been a Visiting Professor at Duke University (1992–1994), the University of Buenos Aires (2004), and the Natural Products and Glycotechnology Research Institute, Inc., North Carolina State University (2006). In 1990 he was appointed a Tenured Researcher at the Instituto de Química Orgánica General (CSIC) in Madrid, where he was promoted to Research Scientist in 2003. His research interests involve several aspects of chemical transformations on carbohydrates, including glycosylation, radical reactions, and natural product synthesis.

Joaquín Plumet received his Diploma in 1968 and his Ph.D. in 1973 from the University Complutense of Madrid (UCM). He continued his scientific education, as an Alexander von Humboldt Postdoctoral Fellow, at the Institute of Organic Chemistry University in Munich with Prof. Rolf Huisgen. In 1986 he joined the Department of Organic Chemistry in the University of Extremadura in Badajoz (Spain) and in 1988 was promoted to full Professor at the UCM. His current research interests focus on the use of bicyclic compounds as chiral building blocks in organic synthesis and on the development of new organocatalysts.

have also been prepared in the search for improved biological (especially enzymatic inhibitory) activities. In this context, the impressive contribution of Prof. Seiichiro Ogawa must be recognized. Without his seminal contribution, the development of this research field, from both the synthetic and biological points of view, would be inconceivable.

The aim of this review is to give coverage on the progress made in the chemistry, synthesis, and biology of carbasugars until May 2004. This review includes the extensively studied carbapyranoses[16] as well as the scarcely considered carbafuranoses (to the best of our knowledge, no account on their chemistry and biology has been published to date), and it focuses on their synthesis, biosynthetic aspects, biological properties, and conformational analysis. Important compounds related to carbasugars, such as cyclohexane epoxides[17,18] and aminocarbasugars[19] (*valienamine* and derivatives), have been the subject of recent reviews and, therefore, will not be extensively covered here. Natural products containing carbasugar subunits, such as carbanucleosides,[20] fall beyond the scope of this review and will not be treated here. Aminocyclopolyols, which are constituents of several broad-spectrum antibiotics[21] (e.g., streptomycin, gentamicin, or tobramycin) or glycosidase inhibitors[20c,22] (e.g., mannostatin, allosamidine, or trehazolin), are not conceived as analogues and will not be touched upon either.

The chemical synthesis of carbasugars and derivatives constitutes a significant part of this review. The different approaches to these compounds have been broadly classified into two groups: synthetic methods which use non-carbohydrates as starting materials and protocols which utilize carbohydrates as precursors. Some other strategies starting from natural products other than carbohydrates have also been examined.

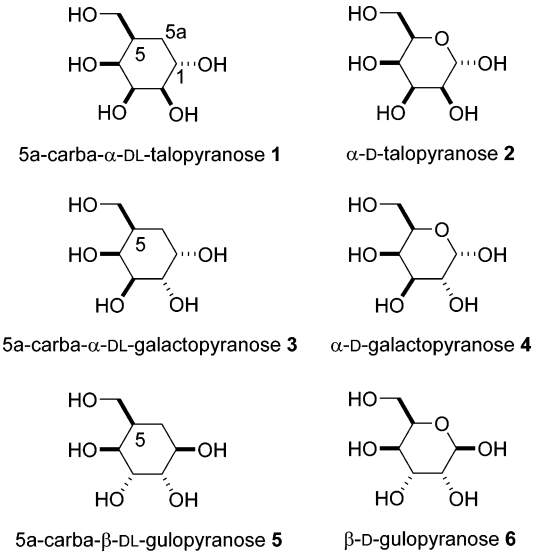


Figure 1. Racemic carbasugars prepared by McCasland et al. (only D-enantiomers are shown) and the corresponding "*true*" sugars.

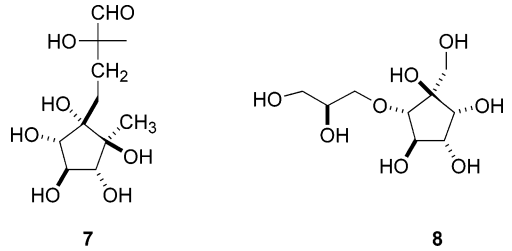


Figure 2. Naturally occurring carbafuranoses.

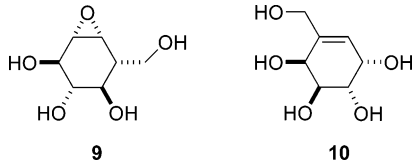


Figure 3. Naturally occurring carbapyranose derivatives.

2. Natural Occurrence of Carbasugars

2.1. Natural Carbafuranoses

Carbafuranoses have not been found free in Nature but are subunits of products isolated from natural sources, in particular carbanucleosides. These compounds have been the subject of several recent reviews[20] and will not be considered here.

It should be pointed out, however, that five-membered cyclitols, such as caryose (**7**)[23] or calditol (**8**)[24] (Figure 2), have been isolated as natural products. No other examples of five-membered carbocyclic carbohydrate analogues from natural sources have been reported.

2.2. Natural Carbapyranoses

Carbapyranoses have been scarcely found in Nature; however, they are abundant as subunits of other natural products. Compounds such as carba-α-D-galactopyranose (**3**) (isolated from *Streptomyces* sp. MA-4145),[15] cyclophellitol (**9**) (isolated from *Phellinus* sp.),[25,26] or MK7607 (**10**) (isolated from *Curvularia eragestrides*)[27] (Figure 3) were isolated directly from natural sources, whereas aminocarbasugars such as valienamine (**11**) (Figure 4) have been mainly

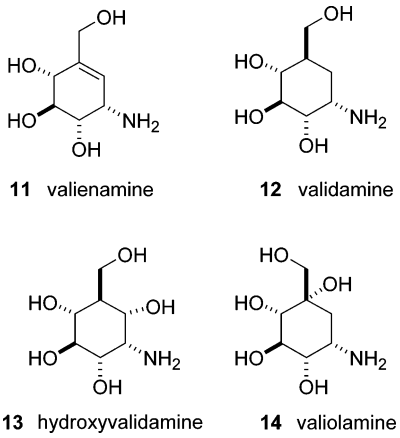
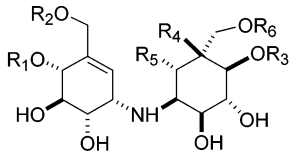


Figure 4. Naturally ocurring aminocarbapyranoses.



Validamycin A, **15**	R_1, R_2, R_4, R_5, R_6 = H, R_3 = β-D-Glc
Validamycin B, **16**	R_1, R_2, R_4, R_6 = H, R_3 = β-D-Glc, R_5 = OH
Validamycin C, **17**	R_1, R_4, R_5, R_6 = H, R_3 = β-D-Glc, R_2 = α-D-Glc
Validamycin D, **18**	R_1, R_2, R_3, R_4, R_5 = H, R_6 = α-D-Glc
Validamycin E, **19**	R_1, R_2, R_4, R_5, R_6 = H, R_3 = α-D-Glc-(1-4)-β-D-Glc
Validamycin F, **20**	R_1 = α-D-Glc, R_2, R_4, R_5, R_6 = H, R_3 = β-D-Glc
Validamycin G, **21**	R_1, R_2, R_4, R_5 = H, R_3 = β-D-Glc, R_4 = OH
Validamycin H, **22**	R_1, R_2, R_4, R_5, R_6 = H, R_3 = α-D-Glc-(1-6)-β-D-Glc

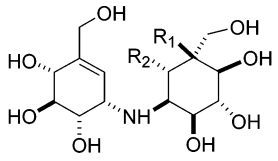
Figure 5. Validamycin-type compounds.

found as subunits of several, more complex, molecules (*vide infra*).

From a formal standpoint, carba-α-D-galactopyranose (**3**) is the only "*genuine*" carbasugar isolated from natural sources.[15] There are, however, a large number of highly oxygenated cyclohexane and cyclohexene derivatives, closely related to carbasugars, which have been isolated from Nature. These include epoxides[17] and carbonyl compounds (e.g., the important family of Gabosines is a case in point[28]).

Aminocarbasugar derivatives, such as valienamine (**11**),[29−31] validamine (**12**),[32] hydroxyvalidamine (**13**),[32] and valiolamine (**14**)[32] (see Figure 4), are secondary metabolites exclusively produced by microorganisms. They have been detected only as minor components in the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus*.[33] They are mainly found in validamycins, acarbose, and related carbaoligosaccharides.

In 1970, during the screening for new antibiotics from the fermentation culture of *Streptomyces hygroscopicus* subsp. *limoneus*, researchers at Takeda Chemical Company discovered a family of antibiotics named validamycins.[34,35] Validamycin A (**15**) (Figure 5), the main component of the complex, is a pseudotrisaccharide consisting of a core moiety, validoxylamine A (**23**), and D-glucopyranose. The core consists of two aminocyclitols, valienamine (**11**), and validamine (**12**), which are connected through a single nitrogen atom. Validamycin B (**16**) differs from validamycin A in the second aminocyclitol unit, which, in validamycin B (**16**),



Validoxylamine A, **23** R_1, R_2 = H

Validoxylamine B, **24** R_1 = H, R_2 = OH

Validoxylamine G, **25** R_1 = OH, R_2 = H

Figure 6. Validoxylamines.

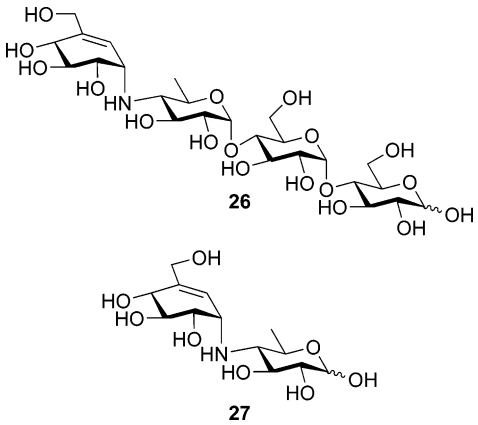


Figure 7. Acarbose (**26**) and acarviosine (**27**).

is hydroxyvalidamine (**13**). The minor components of the validamycins complex, validamycins C−F (**17**−**20**) and validamycin H (**22**), contain validoxylamine A (**23**) (Figure 6), as the core unit, but they differ in at least one of the following features: (a) the position of the glucosidic linkage, (b) the number of D-glucopyranose residues, or (c) the anomeric configuration of the D-glucopyranose unit.[36−39] Validamycin G (**21**) contains validoxylamine G (**25**) as its core unit.

The α-amylase inhibitor acarbose (**26**)[40] was found in a screening of strains of various *Actinomycete* genera. Acarbose is considered as one of the most clinically important compounds containing carbasugar units, since it is currently used for the treatment of type II insulin-independent diabetes (Figure 7). Structurally, acarbose is a carbatrisaccharide consisting of valienamine, a deoxyhexose, and maltose. The structure of acarbose (**26**) was determined by degradation reactions, derivatization, and spectroscopic analysis. The carbadisaccharic core of acarbose, known as acarviosine (**27**), is postulated to be essential for its biological activity. The core unit, **27**, is also linked to a variable number of glucose residues, resulting in several other components of the complex mixture of acarbose. The formation of these components is highly dependent on the composition of the carbon source available in the culture medium. Media containing glucose and maltose will result in a specifically high yield of acarbose and the lower components, while media with high concentrations of starch will yield longer oligosaccharide species. The transglycosylation involved in this process was proposed to be catalyzed by an extracellular enzyme, acarviosyl transferase, found in the culture of the acarbose producer.[41] The biochemistry and molecular biology of acarbose have been reviewed.[42,43]

Amylostatins, of general formula **28** (Figure 8), were isolated from several strains of *Streptomyces diastaticus* subsp. *Amilostaticus*.[44] The chemical structures of amylostatins are very close to that of acarbose analogues containing the acarviosine core.

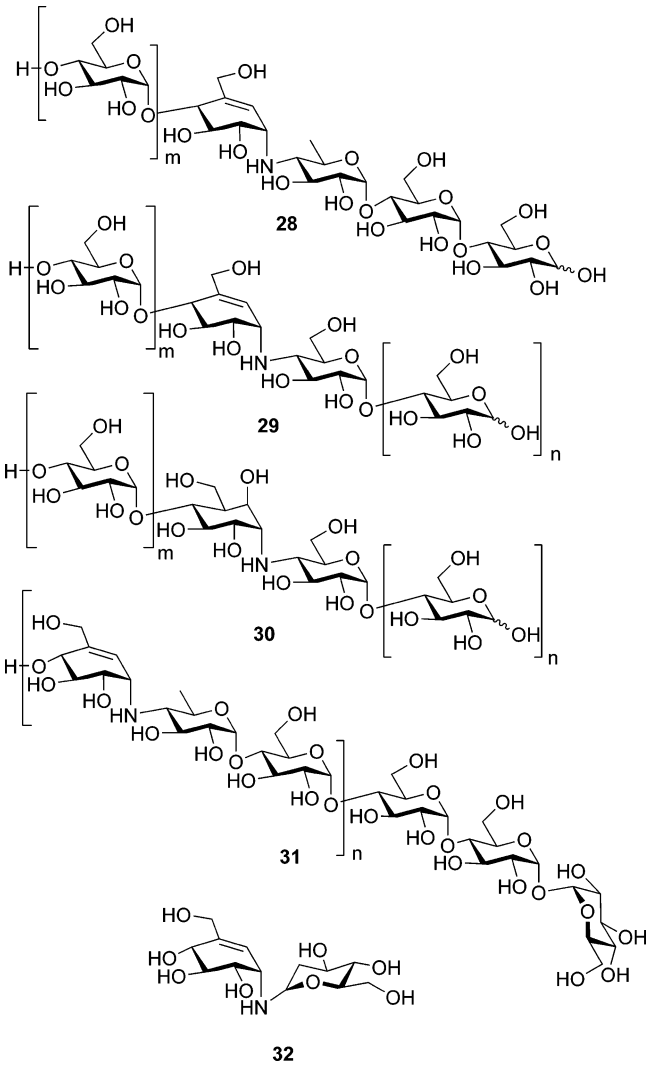


Figure 8. Carbaoligosaccharide-type compounds.

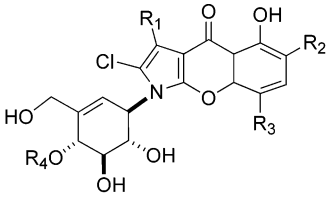
Adiposins (**29**) contain the same aminocarbasugar (valienamine (**11**)) that acarbose (**26**) and amylostatins (**28**), but they differ in the nature of the deoxy sugar (4-amino-4-deoxyglucose in adiposins and 4-amino-4,6-dideoxyglucose in acarbose). They have been isolated from *Streptomyces calvus*.[45]

Oligostatins (**30**) are carbaoligosaccharide antibiotics isolated from *Streptomyces myxogenes*.[46] Structurally, they consist of penta-, hexa-, and heptasaccharides containing hydroxyvalidamine rather than valienamine.

Trestatins (**31**) are a family of carbaoligosaccharides containing valienamine. They were isolated from fermentation cultures of *Streptomyces dimorphogenes*.[47] Structurally, they differ from acarbose mainly in its nonreducing nature, which is defined by the presence of a terminal trehalose unit.

Salbostatin (**32**) is a basic nonreducing carbadisaccharide consisting of valienamine linked to 2-amino-1,5-anhydro-2-deoxyglucitol. It was isolated from the fermentation culture of *Streptomyces albus*.[48]

Pyralomicins **33**−**36** (Figure 9) are a family of antibiotics isolated from the culture broth of *Actinomadura spiralis*,[49] which was later renamed *Microtetraspora spiralis*.[50] They possess unique chemical structures, which consist of benzopyranopyrrole chromophores containing a nitrogen atom



Pyralomicin 1a, **33** R_1 = H, R_2 = Cl, R_3, R_4 = CH_3
Pyralomicin 1b, **34** R_1 = H, R_2, R_4 = CH_3, R_3 = Cl
Pyralomicin 1c, **35** R_1, R_4 = H, R_2 = Cl, R_3= CH_3
Pyralomicin 1d, **36** R_1, R_2 = Cl, R_3 = CH_3, R_4= H

Figure 9. Pyralomicin-type compounds.

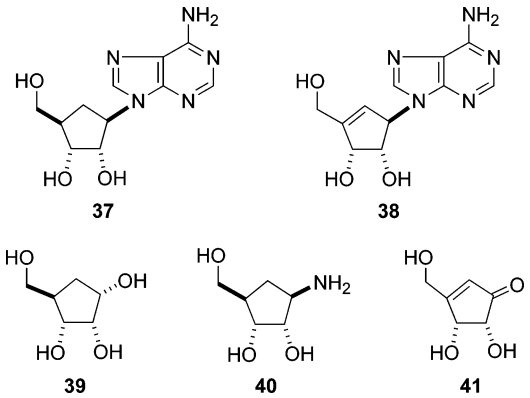


Figure 10. Aristeromycin (**37**), Neplanocin A (**38**), and some proposed intermediates in their biosynthesis, **39**−**41**.

which is also shared with 1-epi-valienamine.[51] Pyralomicins are, thus far, the only examples of natural products having an aminocarbasugar unit, acting as the glycone, attached to a polyketide-derived core structure.

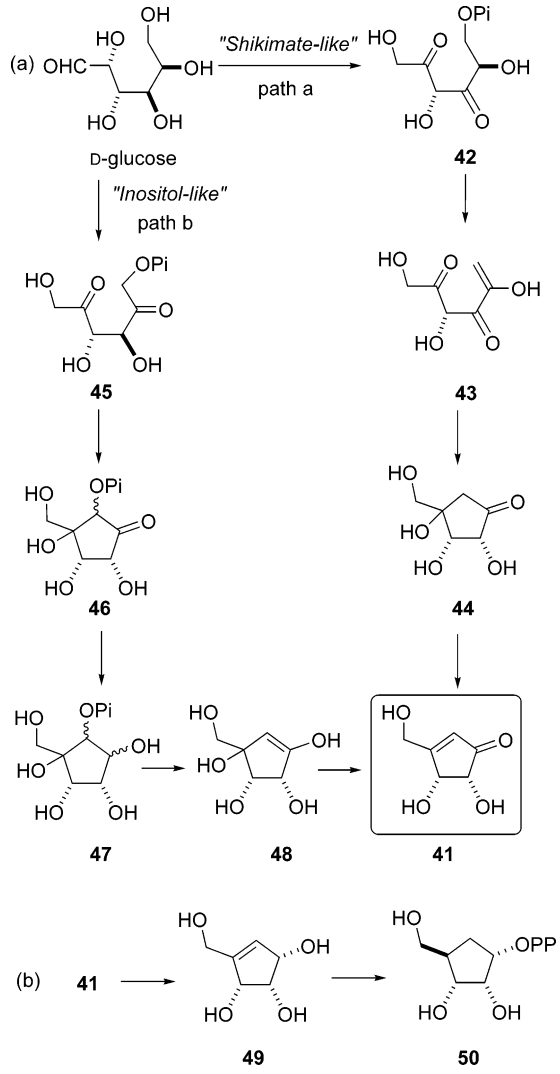
3. Biosynthesis of Carbasugars

3.1. Biosynthesis of Carbafuranoses

The biosynthesis of carbapentofuranoses has only been considered in the literature in connection with the more biologically relevant carbocyclic nucleosides.[52] Early biosynthetic studies on aristeromycin (**37**) and neplanocin A (**38**) (Figure 10) had established that the carbocyclic ribose ring was derived from D-glucose. On the basis of isotopically labeled precursors incorporation experiments, Parry et al.[53] were able to demonstrate that cyclization occurs between C_2 and C_6. Subsequent isotope dilution experiments identified the saturated tetrol **39**[54] and aminotriol **40**[55] as putative intermediates produced by *Steptromyces citricolor*. More recent work[56] suggests that, contrary to this previous proposal, the saturated carbocycles **39** and **40** do not lie on the central biosynthetic pathway of the carbocyclic nucleosides, and instead enone **41** is postulated as the first-formed carbocyclic intermediate from D-glucose.

Two plausible mechanisms were postulated for the formation of the cyclopentane ring,[57] and in both the cyclization reaction was presumed to proceed via a fructose derivative (Scheme 1a). In the first proposed mechanism, a "shikimate-like" pathway (Scheme 1, path a), isomerization to fructose-6-phosphate is followed by oxidation at C_4 to yield compound **42**. Elimination of the phosphate group then leads to enol **43** followed by a 5-[enol-*endo*]-[*exo*-*trig*] cyclization. Reduction of the keto group would yield the carbocycle **44**,

Scheme 1. Proposed Biosynthetic Pathways to Carbapentofuranoses



which could undergo dehydration, with stereospecific removal of the 6-pro*S*-hydrogen atom, to introduce the double bond, thus generating the enone **41**.

The alternative "inositol-like" process (Scheme 1, path b) begins with the oxidation of the C_5 hydroxyl group to give the diketone **45**. Cyclization can then proceed by stereospecific loss of the 6-pro*S*-hydrogen atom followed by an aldol-type ring closure. Subsequent epimerization at C_4 would yield the carbocycle **46**. Reduction of **46** followed by elimination of the phosphate moiety in **47** would lead to **48**, which could undergo an extended elimination reaction to give enone **41**.

Reduction of the ketone function in **41** will then give the unsaturated carbocyclic derivative **49** (Scheme 1b), whose double bond could be reduced in an *anti* fashion with subsequent reduction of the carbonyl group and phosphorylation to produce the carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate, **50**.

Many issues related to the cyclization mechanism still remain to be solved. All the studies reported have been carried out using intact cells, and thus far, there is no data concerning the enzymes that are responsible for the conversions. A more complete understanding of the mechanism of cyclopentane ring formation will require access to cell-free extracts that catalyze the cyclization reaction. On the other hand, very little evidence has been obtained on the identity

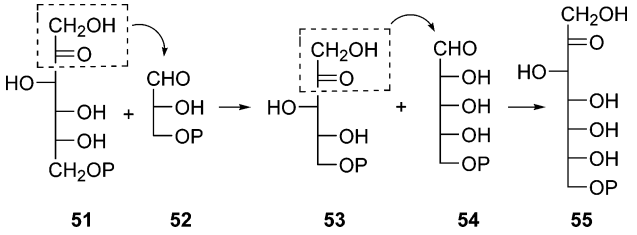


Figure 11. Biosynthetic pathway of sedoheptulose 7-phosphate (**55**).

of the intermediates between D-glucose and the carbocyclic analogue of ribose **50**. The determination of the structure of such compounds will allow firm conclusions to be drawn regarding the biosynthesis of these five-membered rings.

3.2. Biosynthesis of Carbapyranoses

The biosynthetic pathway leading to carbapyranoses[58] has been investigated in connection with secondary metabolites such as validamycins **15**−**22**, acarbose (**26**), or pyralomycin 1a (**33**).[19b,59] The valienamine moiety of these compounds was initially regarded as an aliphatic version of the mC_7N units found in a variety of natural products, particularly the ansamycin and mitomycin antibiotics.[60] The mC_7N units in the latter compounds are specifically originated from an unusual aromatic amino acid, 3-amino-5-hydroxybenzoic acid, which is derived from a branch of the shikimate pathway.[61] However, feeding experiments with uniformly and positionally ^{13}C-labeled glucose[62] or glycerol[63] and analysis of the labeling and coupling patterns in the products demonstrated that the carbon skeleton of the cyclitol moieties in validamycin A (**15**), acarbose (**26**), or pyralomycin 1a (**33**) is not derived from the shikimate pathway, but from the pentose phosphate pathway.

Specifically, the seven carbon atoms are derived from a 3-carbon piece (presumably a triose phosphate **52**) and a successive transfer of two 2-carbon fragments, each derived intact from glucose or glycerol. This suggests the assembly of a seven-carbon sugar phosphate, such as sedo-heptulose 7-phosphate (**55**), which is a key intermediate in the biosynthetic pathway (Figure 11). A similar origin has recently been demonstrated by Zeeck and co-workers for the gabosines A, B, and C from *Streptomyces cellulosae*.[64]

The cyclization process of sedo-heptulose 7-phosphate (**55**) to a six membered carbocyclic intermediate was examined by two approaches: (i) the synthesis of various candidate cyclitols in isotopically labeled form and evaluation of their incorporation into acarbose (**26**),[65,66] validamicine A (**15**),[65] and pyralomicin 1a (**33**),[67] and (ii) the cloning and expression of the cyclase gene from the acarbose producer and characterization of the substrate and the product of the recombinant enzyme.[68] Both approaches led to the conclusion that the cyclization process is catalyzed by a dehydroquinate (DHQ) synthase-like enzyme, involving transient dehydrogenation of C_5 to a ketone (**A**) by NAD^+, which sets the stage for the elimination of phosphate to generate the enol of a 6,7-methyl ketone (**B**). The latter then undergoes an intramolecular aldol condensation to give 2-epi-5-epi-valiolone (**56**), as the initial cyclitol precursor for valienamine (**11**) (Figure 12).

In the biosynthesis of validamycin A,[65] it is accepted that 2-epi-5-epi-valiolone (**56**) is later epimerized at C_2 to give 5-epi-valiolone (**57**) and dehydrated via a *syn* elimination, possibly involving a type I DHQase-like mechanism,[69] between C_5 and C_6 to yield valienone (**58**) (Figure 13).

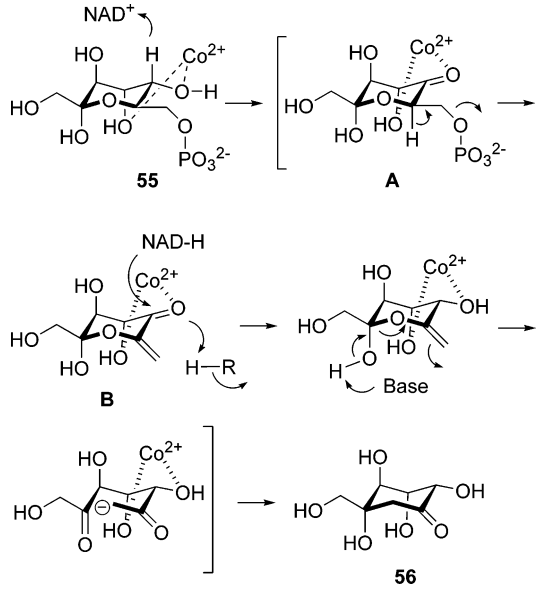


Figure 12. Proposed reaction mechanism of the cyclase converting sedoheptulose-7-phosphate (**55**) to 2-epi-5-epi-valiolone (**56**).

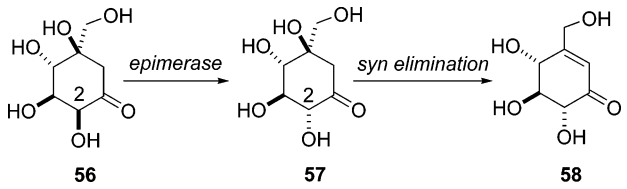


Figure 13. Biosynthesis of valienone (**58**).

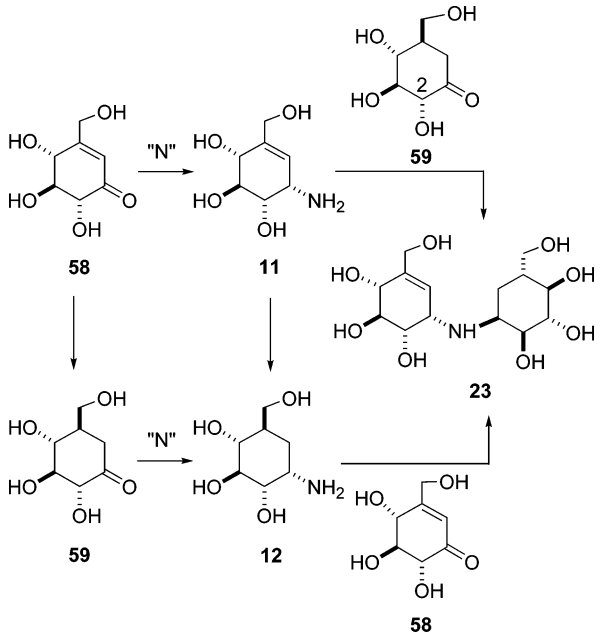


Figure 14. Proposed biosynthetic pathway to validoxylamine A (**23**).

The final question in the synthesis concerns, then, the source of nitrogen and the mode of introduction of the bridging nitrogen atom. Studies on *Actinoplanes* sp. have identified glutamate, a typical substrate of transaminases, as the most efficient nitrogen donor in the biosynthesis of acarbose.[70] In view of the similarity of the two systems, the most plausible mechanism[58] of the validamycin A biosynthesis (Figure 14) is the introduction of nitrogen into one ketocyclitol, **58** or **59**, by transamination to give either valienamine (**11**) or validamine (**12**), followed by a reductive

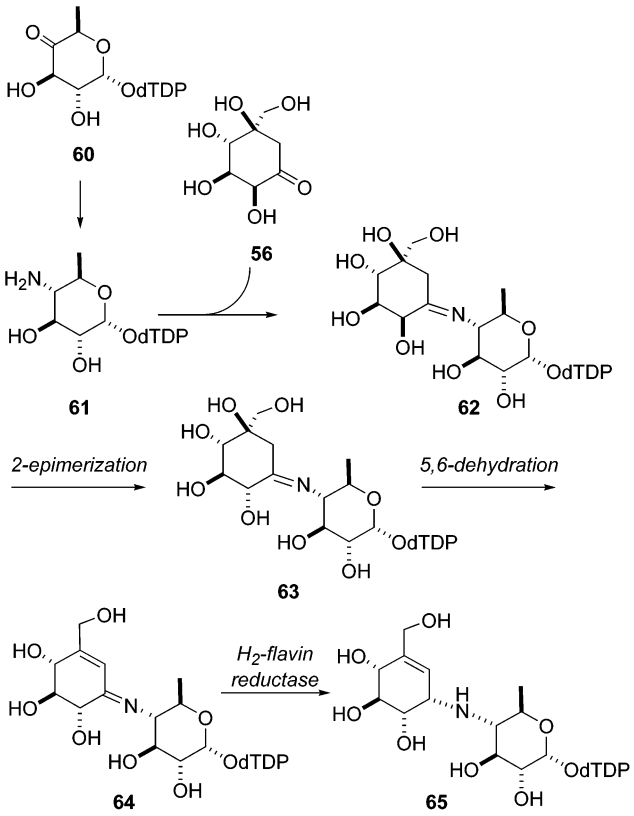


Figure 15. Proposed biosynthetic pathway to dTDP-acarbiose (**65**).

coupling with a second ketocyclitol, **59** or **58**. The coupling reaction could involve either formation of an imine and its subsequent reduction, or reduction of the ketocyclitol followed by a S_N2 displacement of the ensuing activated OH group by the amino moiety.[66]

Whereas, in the synthesis of validamycin A, several discrete cyclitol intermediates have been identified, the mechanism of formation of acarbose, despite the identical origin of the aminocyclitol moieties, still remains obscure. The pathways in the formation of both metabolites seem to be substantially different. Rather unpredictably, none of the ketocyclitols fed, except 2-epi-5-epi-valiolone (**56**), were incorporated into the valienamine moiety of acarbose.[59b,65] This includes 5-epi-valiolone (**57**), valienone (**58**), and validone (**59**). One suggested explanation to these findings is that the transformation of 2-epi-5-epi-valiolone (**56**), to the valienamine moiety involves a substrate channeling mechanism in which enzyme-bound intermediates are directly transferred from one enzyme active site to the next in a multienzyme complex.[71] The nonincorporation of plausible cyclitols leaves the pathway from 2-epi-5-epi-valiolone (**56**) to the valienamine moiety of acarbose highly speculative. It is assumed[58] that the biosynthesis first generates deoxythymidine diphosphate (dTDP) acarviose (**65**), as an intermediate, which then transfers the acarviosyl moiety, either directly or via an intermediate carrier, to $C_{6'}$ of maltose. In the most reasonable route for the formation of dTDP-acarviose (**65**), the nitrogen atom may be introduced first into the deoxy sugar moiety by transamination of dTDP-4-keto-6-deoxy-D-glucose (**60**) to dTDP-4-amino-4,6-dideoxy-D-glucose (**61**). The amino sugar nucleotide then forms a Schiff's base with 2-epi-5-epi-valiolone (**56**), which undergoes successive 2-epimerization and 5,6-dehydration before reduction of the imine double bond (Figure 15).

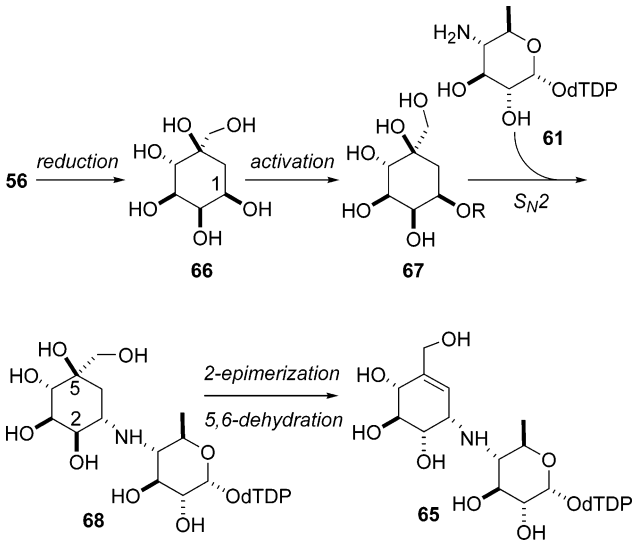


Figure 16. Alternative biosynthetic pathway to dTDP-acarbiose (**65**).

An alternative hypothetical pathway involves the reduction of the keto-sugar **56** to 1-epi-valiol (**66**), followed by activation of the C_1 hydroxyl group as a phosphate and subsequent nucleophilic displacement by the nitrogen of amino sugar **61** to give pseudosaccharide **68**, which after epimerization at C_2 and 5,6-dehydration would give dTDP-acarviose (**65**) (Figure 16).[59c,65]

Recently, Piepersberg's group carried out combined genetic and biochemical studies. According to them, during the biosynthesis of acarbose in *Actinoplanes* sp. *SE50/110*, the cyclitol precursor, 2-epi-5-epi-valiolone (**56**), is phosphorylated,[72] forming the intermediate 2-epi-5-epi-valiolone-7-phosphate (**69**), by the enzyme 2-epi-5-epi-valiolone 7-kinase as the first step in its transformation to the valienol moiety. The product is then epimerized at C_2 to give 5-epi-valiolone-7-phosphate (**70**).[73] These results suggest that the intermediates involved are phosphorylated cyclitols which, except for 2-epi-5-epi-valiolone (**56**), cannot be generated directly from their unphosphorylated counterparts. These findings have led to a revised proposal for the biosynthetic pathway of the acarviosyl moiety of acarbose (Figure 17).[43a] Such a pathway resembles those for activation (by phosphorylation and subsequent nucleotidylation) and modification of hexoses to be incorporated into oligo- or polysaccharides by glycosyl transfer (Figure 17).

In contrast to validamycin acarbose and other related compounds, the cyclitol structure in pyralomycin 1a (**33**) was shown to be 1-epi-valienamine. Initial incorporation experiments suggested that 1-epi-valienamine is also derived from the pentose phosphate pathway.[59a] However, the (opposite) stereochemistry at C_1 suggests an essential biosynthetic divergence between the cyclitol moiety in **33** and that in **15** or **26**. This could take place most likely during the condensation of the cyclitol and the core benzopyranopyrrole. The condensation occurs at a late stage in the biosynthesis and presumably via a nucleophilic displacement of an activated alcohol at C_1 (e.g., as phosphate or nucleosidyl diphosphate), which in turn had to be formed by reduction of ketocyclitol (**56**) (Figure 18). However, potential biosynthetic intermediates of this 1-OH activated compound in isotopically labeled form (valiolone, valienol, 1-epi-valienol, valiol, 1-epi-5-epi-valiol) were not incorporated into pyralomicin 1a (**33**).[67] To account for this observation, it was proposed either that 2-epi-

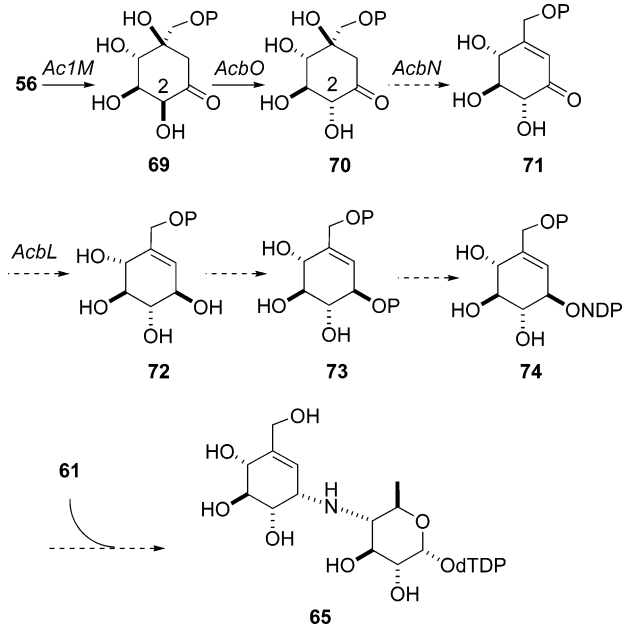


Figure 17. Revised proposal of the biosynthetic pathway to dTDP-acarbiose (**65**).

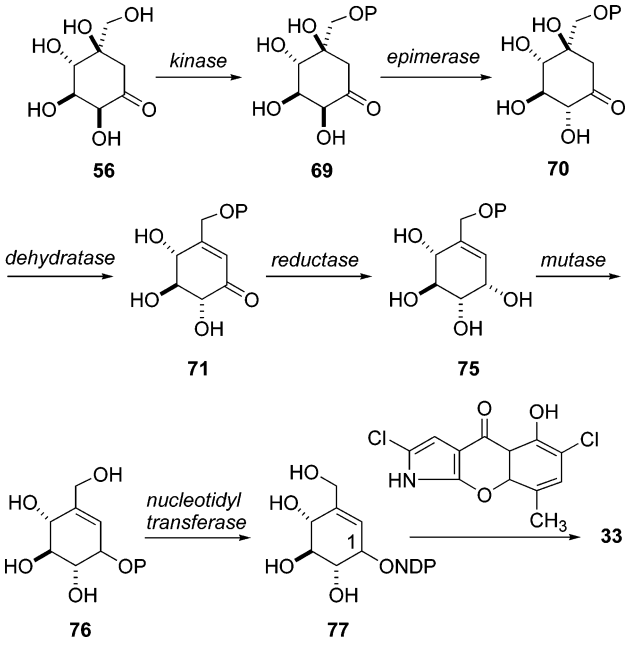


Figure 18. Proposed biosynthetic pathway to pyralomicin 1a (**33**).

5-epi-valiolone (**56**) is specifically activated (e.g., to its phosphate **69**) and then further transformations (from **69** to **75**) occur on activated intermediates which cannot take place from their unactivated counterparts or, alternatively, that the transformation of **56** into **33** involves a substrate-channeling mechanism[67] similar to that proposed by Piepersberg and co-workers in the biosynthesis of acarbose.[43a] Accordingly, Piepersberg proposed that phosphorylation might take place twice during the conversion of 2-epi-5-epi-valiolone (**56**) into the activated nucleotidyl diphosphoderivative **73**, whereas Naganawa et al. suggested the involvement of an enzyme similar to phosphoglucomutase that would transfer the phosphate from C_7 to C_1 of valienol, setting the stage for the activation of the cyclitol to a nucleotidyl diphosphovalienol **77**.

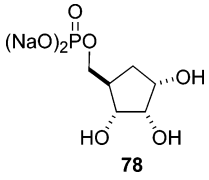


Figure 19. Carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate (cPRPP).

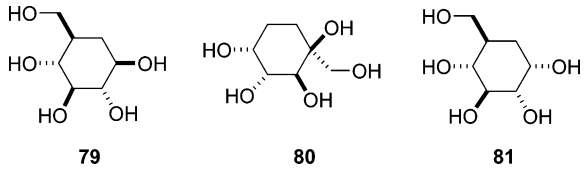


Figure 20. Racemic carbasugars (only D-enantiomers are shown).

4. Biological Activity of Carbasugars

4.1. Biological Activity of Carbafuranoses

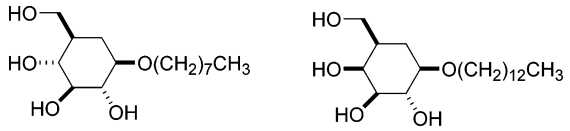
To the best of our knowledge, the only report[74] regarding the biological activity of carbafuranoses was devoted to evaluating the enzymatic inhibitory activity of the carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate (cPRPP **78**, Figure 19) against the enzyme 5-phosphoribosyl-α-1-pyrophosphate (PRPP) synthetase.

This enzyme reacts with ATP in the presence of Mg ion to give PRPP, a compound involved in the biosynthesis of histidine and tryptophan. From a biological point of view, there is evidence that the activity of PRPP synthetase is elevated in tumors. Then, inhibitors of this enzyme show antineoplastic activity. Compound **78** inhibits PRPP synthetase with a K_i of 186 μM (human type PRPP synthetase) and a K_i of 3811 mM (*Bacillus subtilis* PRPP synthetase).

4.2. Biological Activity of Carbapyranoses

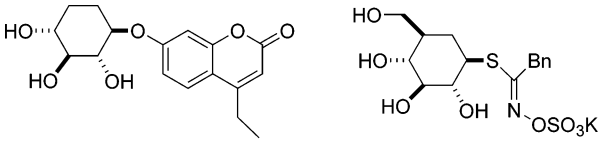
In 1966, McCasland anticipated that "pseudo-sugars may be found acceptable in place of corresponding true sugars to some but not all enzymes or biological systems, and thus might serve to inhibit growth of malignant or pathogenic cells". In this context, human beings are not able to distinguish between synthetic carba-β-DL-glucopyranose ((±)-**79**) and D-glucose by taste,[75] and synthetic 6a-carba-β-DL-fructopyranose ((±)-**80**) was found to be almost as sweet as D-fructose (Figure 20).[76] Additionally, compounds related to carbasugars such as (+)-cyclophellitol (**9**) and (+)-MK7067 (**10**) have relevant biological activities. (+)-Cyclophellitol (**9**) is a potent inhibitor of β-glucosidases with potential inhibition of the human immunodeficiency virus (HIV) and with possible antimetastatic therapeutic activity.[77] Its unnatural diastereomer, (1*R*,6*S*)-cyclophellitol, inhibits α-glucosidases (Figure 3).[78] The unsaturated carbapyranose **10** was found to have an effective herbicidal activity.[79] Carba-α-D-galactopyranose (D-**3**) exhibited a low antibiotic activity against *Klebsiella pneumonia* MB-1264,[15] whereas the racemic mixture, (±)-**3**, was about half as potent as the natural product in the same assay system, thus indicating that the L-enantiomer is inactive.[16c]

Inhibition of D-glucose-stimulated release of insulin has been studied by using synthetic 5a-carba-α-DL-glucopyranose ((±)-**81**) as a glucokinase inhibitor.[80] Compound (±)-**81** was used as an analogue in the investigation of the mechanism of D-glucose-stimulated release of insulin by the pancreatic islets. It was found that carbasugar (±)-**81** inhibited both



82 **83**

Figure 21. Alkyl 5a-carba-β-D-glycopyranosides.



(+)- or (-)-**84** (±) -**85**

Figure 22. Synthetic carbasugar analogues of coumarins, **84**, and glucotetropaeolin, **85**.

glucose-stimulated insulin release and islet glucokinase activity whereas the β-anomer (±)-**79** showed no activity. On the other hand, (±)-**79** is a substrate of the cellobioside phosphorilase of *Cellvibrio gilvuse*.[81]

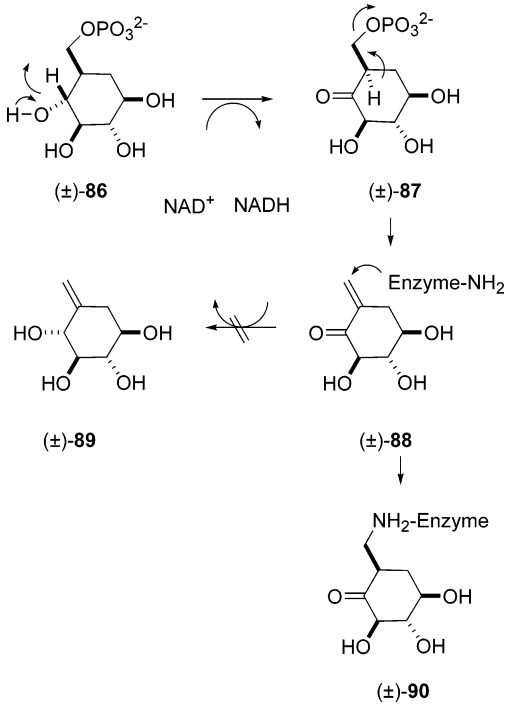
Very recently, *O*-linked alkyl carba-β-D-glycosides **82** and **83** (Figure 21) have been shown to be useful as primers for biocombinatorial glycosylation involving efficient uptake in B16 mouse melanoma cells.[82] Uptake of the carbaglycosides resulted in β-galactosylation and subsequent sialylation of the galactose residues incorporated, to give rise to glycosylated products having a glycan similar to that in ganglioside GM3, thus indicating that carbasugars can be versatile building blocks in biocombinatorial synthesis. In addition, a strong and specific inhibition of β-galactosidase (bovine liver) was found for dodecyl 5a-carba-β-D-galactopyranoside (**83**).

More complex carbaglycosides have been shown to possess interesting biological activities. Synthetic carbaxylosides of coumarins, i.e., (+)-**84** or (−)-**84**, have significant potential as oral antithrombotic agents,[83] and a 5a-carba analogue of glucotropaeolin, (±)-**85**, was shown[84] to display a good inhibition power against myrosinase, the only enzyme able to hydrolyze glucosinolates (Figure 22).

In addition, 5a-carba-β-D-glucopyranose-6-phosphate ((±)-**86**) is an inhibitor of 2-deoxy-scyllo-synthase (DOIS), a key enzyme in the biosynthesis of 2-deoxystreptamine-containing aminoglycoside antibiotics. 5a-Carba-DL-glucose-6-phosphate ((±)-**86**) is indeed a mechanism-based irreversible inhibitor, and its proposed reaction with DOIS is shown in Scheme 2. Thus, after the initial oxidation at C_4 and subsequent elimination of a phosphate, compound (±)-**86** was converted within the enzyme into an α,β-unsaturated methylene cyclohexanone (±)-**88**, which is attacked by a nucleophilic residue in the active site (Lys-141), resulting in the formation of a covalent bond.[85]

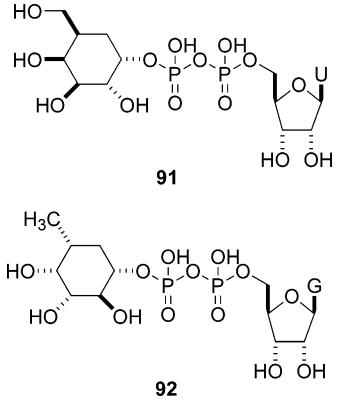
Some synthetic carbasugar-nucleotide analogues have displayed biological activity as glycosyltransferase inhibitors. The carbocyclic analogue of UDP-galactose **91** exhibits inhibitory activity of β-(1→4)-galactosyltransferase from bovine milk (Figure 23).[86] The carbasugar analogue of GDP-fucose **92**[87] was found to be a competitive inhibitor of fucosyltransferases, key enzymes in the biosynthesis of the Lewis-x determinant. Compound **92** showed a K_i value similar to the K_m value for the GDP-fucose, indicating that the ring oxygen of Fuc is not critical for the recognition of GDP-Fuc by the enzyme. However, it is essential for the transfer to occur.[88]

Scheme 2. Proposed Inhibition Mechanism of C_6−P (Only D-Enantiomers Are Shown)



(±)-**86** (±)-**87** (±)-**89** (±)-**88** (±)-**90**

The most important and appealing carbapyranose derivatives from a biological standpoint are the amino carbasugars. A number of them have become clinically successful to combat diseases in humans and plants. Validamycins **15**−**22** and salbostatin (**32**) have been reported to be mechanistically unique antifungal agents. Validamycin A (**15**) is the most active compound of the complex and is widely used in Japan and other rice-producing countries in Asia to control sheath blight disease of the rice plants caused by the fungus *Rhizoctonia solani*. Validamycin A is neither fungicidal nor fungistatic, but is able to control the spread of the patogen by inhibiting specifically the hyphal extension without affecting the specific growth rate. Further extensive studies on the mechanism of action of validamycin in controlling the hyphal extension have been carried out by several research groups,[89−93] and it seems to be related to the anti-trehalase activity[94−96] of the carba-disaccharide validoxylamine (**23**).[97] Efforts in developing more potent trehalase inhibitors have been carried out by Ogawa and co-workers, who synthesized several pseudo-trehalosamines, **93** and **94**, as well as dicarba analogues of trehalose, **95**−**97**, composed of valienamine, validamine, and valiolamine moieties (Figure 24).[98]



91 **92**

Figure 23. Carbapyranose nucleotide analogues.

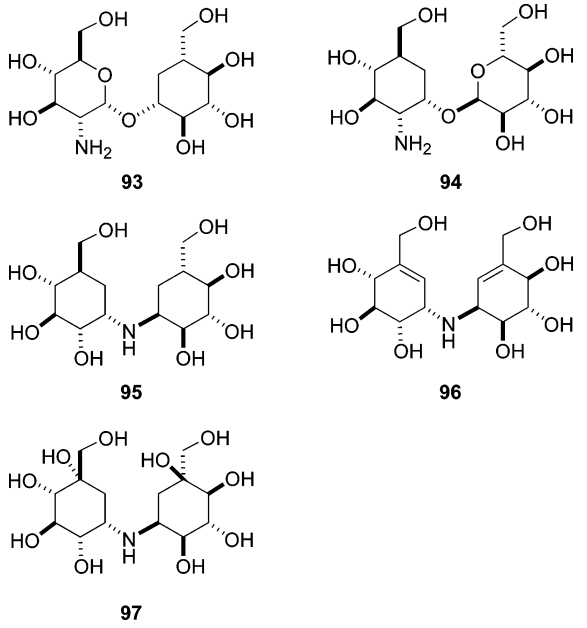


Figure 24. Carbatrehalosamines and dicarbatrehaloses.

Many members of the carba-oligosaccharidic group, e.g., acarbose (**26**), adiposins (**29**), amylostatins (**28**), oligostatins (**30**), and trestatins (**31**), are known to display potent α-glucosidase inhibitory effects. Among these active metabolites, acarbose is of considerable pharmacological interest. In addition to its α-glucosidase activity, acarbose also displays potent inhibitory activity against sucrase, maltase, dextrinase, and glucoamilase. This pronounced inhibitory effect has resulted in its use as a clinical drug for the treatment of type II non-insulin-dependent diabetes, in order to enable patients to better control blood sugar contents while living with starch-containing diets. Interestingly, individual members of different series of carba-oligosaccharides deactivate α-amylase and sucrase quite differently. Thus, whereas amylase inhibition is maximum with homologues of four and five glucose units, the greatest sucrase inhibition is caused by acarbose containing two glucose residues.[44b]

Adiposins (**29**) have shown potent inhibitory activities against disaccharidases, such as sucrase, maltase, and isomaltase.[99] They have also displayed antibacterial activity against some Gram positive bacteria, Gram negative bacteria, some anaerobic bacteria, and phytopathogenic fungi.[100]

Oligostatins (**30**) exhibited strong inhibitory activity against α-amylase and are active against Gram negative bacteria, while Gram positive bacteria are not affected.[46]

The glycosidase inhibitory activities of acarbose and related carba-oligosaccharides have been ascribed to their acarviosine moiety, in which the valienamine portion mimics the glucopyranosyl cation intermediate at the active site for hydrolysis of α-glucosides. Therefore, several chemically modified acarviosin analogues, **98**−**103** (Figure 25), were prepared and evaluated by Ogawa et al.,[101] who found that the 4-amino-4,6-dideoxy moiety could be replaced by other simple structures, such as 1,6-anhydrohexoses, without losing its inhibitory power against α-glucosidase. However, modification of the valienamine portion, in order to mimic each substrate structure, did not result in any inhibitory activity against the targeted enzyme; see, for example, compounds **102** and **103** for *β*-glucosidase and α-mannosidase activities, respectively.

Simple aminocarbasugars such as valienamine (**11**), validamine (**12**), hydroxyvalidamine (**13**), and valiolamine (**14**)

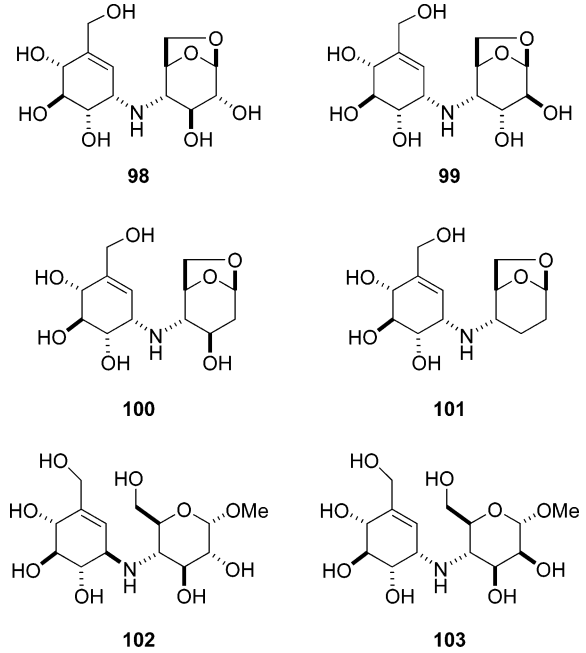


Figure 25. Chemically modified acarviosin analogues.

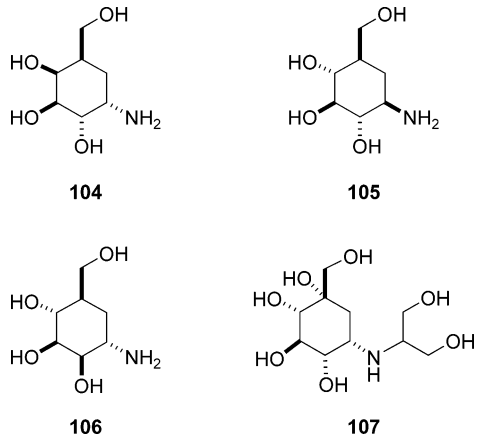
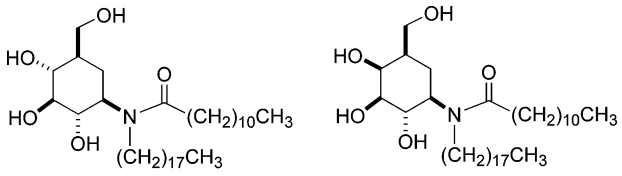


Figure 26. α-Galacto-, *β*-gluco-, and α-mannovalidamine analogues **104**, **105**, and **106** and voglibose (**107**).

appeared to be active against several sugar hydrolases. The α-galacto-, *β*-gluco-, and α-mannovalidamine analogues **104**−**106** have been synthesized and their glycosidase activity tested (Figure 26).[102,103] These analogues, however, displayed only a weak or moderate activity as glycosidase inhibitors when compared with (α-gluco-) validamine.

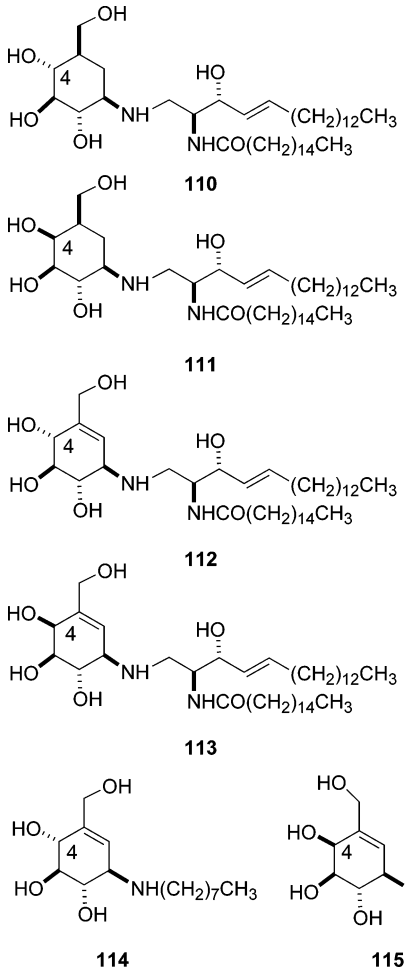
Rather surprisingly, valiolamine (**14**) was found to be a more potent α-glucosidase inhibitor against porcine intestinal sucrase, maltase, and isomaltase than the rest of the aminocarbasugars.[33] This information stimulated the synthesis and screening of a series of *N*-substituted valiolamines, resulting in the preparation of the glycohydrolase inhibitor voglibose (**107**),[104] which is used as a therapeutic agent to control diabetes. Voglibose inhibits disaccharidases competitively, suppressing the elevation of the blood glucose concentration after oral sucrose, maltose, or starch administration, but not after oral glucose, fructose, or lactose intake. Voglibose was launched as an antidiabetic agent in 1994.

In addition, carbocyclic analogues of glycosylamides,[105] which contain the 5a-carba-D-hexopyranose residues, have been synthesized and their biological activities examined. 5a-Carba-*β*-glucopyranosyl- and 5a-carba-*β*-galactopyranosyl-amides **108** and **109** (Figure 27) have been shown to



108 **109**

Figure 27. Carbocyclic analogues of glycosylamides.



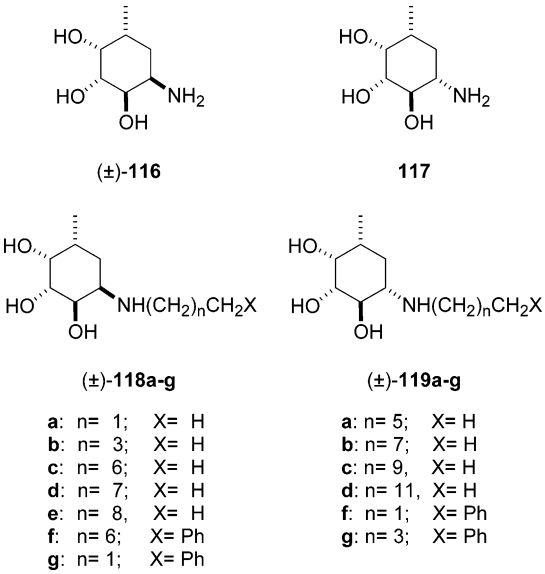
110 **111** **112** **113**

114 **115**

Figure 28. Carbocyclic analogues of glycosylceramides.

possess similar potencies as immunomodulators to those displayed by the corresponding *true* sugars.[106] This suggests that the glycolipid analogues may be useful models for understanding the biological roles and functions of glycolipids.

Novel, *N*-linked, carbocyclic analogues of glycosylceramides, structurally related to glycosphingolipids and glycoglycerolipids, have also been synthesized by replacing the sugar residue with either saturated[107] (**110**, **111**) or unsaturated[108] (**112**, **113**) 5a-carba-D-gluco- or 5a-carba-D-galactopyranoses, respectively (Figure 28). The unsaturated gluco-**112** and galacto-**113** analogues were found to be very potent and specific inhibitors of gluco- and galactocerebrosidase, respectively, thus showing the critical role played by the C_4 configuration for specificity in inhibition. These compounds were then modified by replacing their ceramide chains, and various *N*-alkyl- and *N*,*N*-dialkyl-β-valienamines were prepared.[109−111] Among these substances, *N*-octyl-β-valienamine derivative **114** was found to possess a 10-fold inhibitory activity ($IC_{50} = 3 \times 10^{-8}$ M) against rat liver β-glucocerebrosidase compared to the parent derivative. On the



(±)-**116** **117**

(±)-**118a-g**

a: n= 1; X= H
b: n= 3; X= H
c: n= 6; X= H
d: n= 7; X= H
e: n= 8, X= H
f: n= 6; X= Ph
g: n= 1; X= Ph

(±)-**119a-g**

a: n= 5; X= H
b: n= 7; X= H
c: n= 9, X= H
d: n= 11, X= H
f: n= 1; X= Ph
g: n= 3; X= Ph

Figure 29. Carbafucopyranosylamines as hydrolase inhibitors (when racemic, only L-enantiomers are shown).

contrary, galacto derivative **115** did not show any improvement in potency. Additionally, it was later demonstrated that **114** and **115** are strong competitive inhibitors of human β-glucosidase and human β-galactosidase, respectively. These activities suggest that carbasugar derivatives **114** and **115** work as chemical chaperones to accelerate transport and maturation of mutant forms of enzyme proteins and therefore may be considered as novel therapeutic agents for human genetic diseases related to lysosomal storage disorders.[112,113]

5a-Carba-α-DL-fucopyranosyl amine ((±)-**116**)[114] and 5a-carba-β-L-fucopyranosylamine (**117**)[115] were prepared and evaluated (Figure 29) in the search for different sugar hydrolase inhibitors. They have displayed a very potent and specific inhibition of α-L-fucosidase (bovine kidney), with the effect of (±)-**116** being essentially comparable to that of deoxyfuconojirimicin, the most powerful mammalian α-L-fucosidase inhibitor identified. α-Fucosidase inhibitors are considered to be potential candidates for cancer and HIV drugs, due to their inhibitory effect on the extracellular matrix secreted fucosidases.[116] The inhibitory activity was increased by incorporation of alkyl and phenylalkyl groups into the amino function of the parent (±)-**116**. The change of the *N*-alkyl substituents, from ethyl on **118a** to nonyl on **118e**, improved the inhibitory power, reaching a maximum with an *n*-octyl chain at the nitrogen (**118d**).[117] In a similar manner, compounds (±)-**119a**−**g**, prepared by chemical modification of (±)-**117**, showed very strong inhibitory activity toward both β-galactosidase and β-glucosidase enzymes with no specificity associated with the 4-epimeric structures. This activity appeared to be associated with the D-enantiomers exclusively, that is, *N*-alkyl-6-deoxy-5a-carba-β-D-galactopyranosylamines (D-**119**).[118]

Carbasugar derivatives have also been envisaged to play roles in elucidating and controlling other biological events that involve sugar moieties. This includes the synthesis of analogues of enzyme substrates, which were modified by replacing part of their structures with carbasugar units and which were expected to be used in the elucidation of the mode of action of sugar transferases. These analogues have been recognized as good substrates, thus showing that the ring oxygen in the acceptor is not involved in the specific recognition by the enzyme.

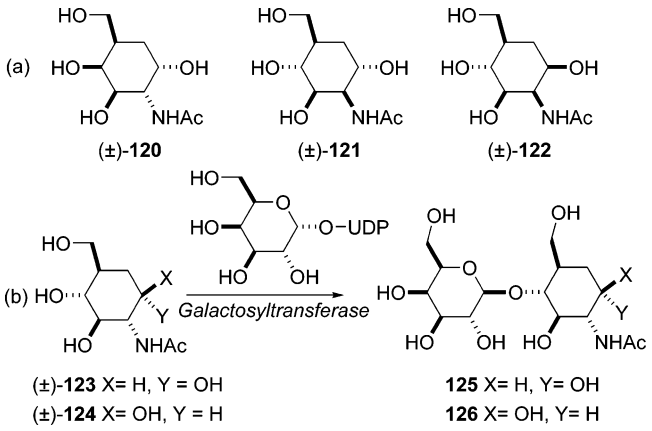


Figure 30. Carbasugars as substrates for glycosyltransferases (when racemic, only D-enantiomers are shown).

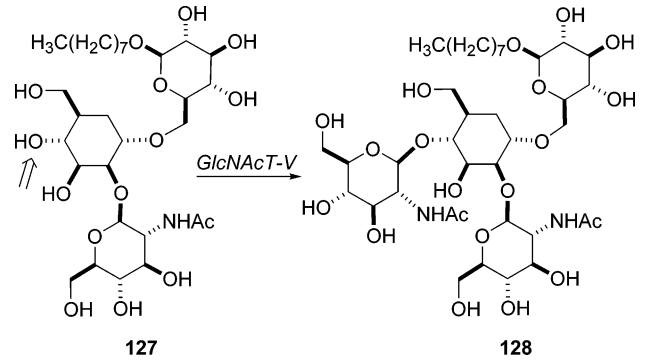


Figure 31. Carbatrisaccharide **127**, a substrate for *N*-acetylglucosaminyltransferase-V.

Bovine β-(1→4)-galactosyltransferase was assayed with α-galacto- (**120**), α- and β-manno- (**121** and **122**), and α- and β-gluco- (**123** and **124**) 2-acetamido-2-deoxy-5a-carba-DL-hexopyranoses (Figure 30).[119] In enzymatic assays, only **123** and **124** acted as galactosyl acceptors. The reactions afforded disaccharides **125** and **126**, but half of the material remained unreacted, suggesting that only the D-enantiomers behaved as acceptors.

Carbatrisaccharide **127** (Figure 31), an analogue of the "trimannosyl core" which frequently occurs in biologically important glycoconjugates,[120,121] was found[122] to be fully active as an acceptor for *N*-acetylglucosaminyltransferase-V, both with the enzyme isolated from hamster kidney and with the one cloned from rat kidney; the kinetic parameters were compatible with those of the *true* trisaccharide.

An area of recent interest is the design of potential substrates and inhibitors of fucosyl and sialyl transferases involved in the assembly of the Sialyl Lewis-x structure (a tumor-associated structure and ligand of E-selectin-mediated inflammatory processes).[123] These enzymes are involved in the last steps of the biosynthesis of Lewis oligosaccharide antigens by transferring α-fucopyranosyl residues.[124] In this context, Ogawa et al. have carried out studies aimed at finding inhibitors of the biosynthesis of Lewis oligosaccharide antigens.[125,126] They reported the synthesis of carbasugar analogues of the disaccharide fragment highlighted in Figure 32. They prepared ether- and imino-linked *N*-acetyl-5a′-carba-β-lactosaminides and -isolactiminides, and tested them against fucosyltransferases. Compounds **129a**[125] and **129b** (Figure 32) were shown to be acceptor substrates for human milk α-(1→3/4)-fucosyltransferase with kinetic parameters

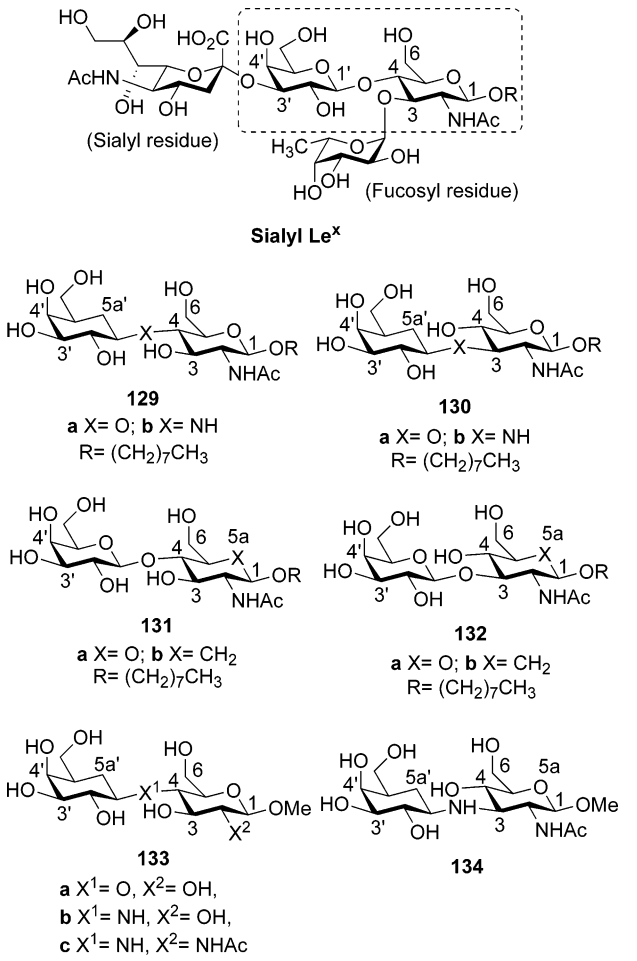


Figure 32. Carbasugar analogues of *N*-acetyl-5a′- and *N*-acetyl-5a-carba-β-lactosaminides and -isolactiminides.

comparable to those observed for standard *true* disaccharides.[126] Small-scale reaction of **129a** and **129b** with GDP-fucose and milk fucosyltransferase resulted in the conversion to the corresponding trisaccharides (by fucosylation at O3). Surprisingly, compounds **130a**[125] and **130b** were neither acceptors nor inhibitors for milk fucosyltransferase, suggesting that α-(1→4) transfer is not possible. The milk preparation contains a mixture of two different [α-(1→3/4)- and α-(1→3)-] fucosyl transferase enzymes. These enzymes were separated, and it was shown that both forms utilized compounds **129a** and **129b** as acceptor substrates, whereas **130a** and **130b** were neither substrates nor inhibitors for the enzyme. This was the first demonstration of a specific substrate for an α-(1→3)-fucosyltransferase.[126]

In contrast with these results, screening carried out on isomeric octyl 5a-carba-β-lactosaminide (**131b**) and isolactosaminide (**132b**) (where the carbasugar unit is at the reducing end, Figure 32) showed that both compounds were good substrates for α-(1→3)-fucosyltransferase V (human recombinant, *Spodoptera frugiperda*) as well as α-(2→3)-(N) sialyltransferase (rat, recombinant, *Spodoptera frugiperda*) when compared to the parent compounds **131a** and **132a**.[127]

More recently,[128] Kajihara, Ogawa, and co-workers have evaluated the inhibitory activity of four new carbadisaccharides (ether-linked methyl 5a′-carba-β-lactoside (**133a**) and imino-linked methyl 5a′-carba-β-lactoside (**133b**), methyl *N*-acetyl-5a′-carba-β-lactosaminide (**133c**), and methyl

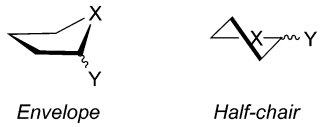


Figure 33. Conformations of the cyclopentane ring.

N-acetyl-5a′-carba-β-isolactosaminide (**134**)) toward rat recombinant α-(2→3)-sialyl and rat liver α-(2→6)-sialyl transferases with the presence of 4-methylumbellipheryl-labeled Lac-NAc as an acceptor substrate. Their enzyme-inhibition assays led to the following results: (a) compounds **133a**, **133b**, and **134** showed more inhibition for α-(2→3)-sialyltransferase than for α-(2→6)-sialyltransferase; (b) compounds **133b** (K_m = 185 μM) and **134** (K_m = 245 μM) presented IC_{50} values similar to that for the acceptor (K_m = 264 μM) toward α-(2→3)-sialyltransferases, whereas compound **133c** displayed less inhibition (K_m = 419 μM); (c) compound **133c**, which was expected to inhibit both enzymes, did not show any appreciable inhibition toward any of them. The authors concluded from this study that the imino function enhances affinity for sialyltransferases but that when two nitrogen atoms exist, the enzymes maintain an equilibrium of interaction between them. They also established that a carbagalactose residue in carbadisaccharides may bind to sialyltransferases, but without the transfer of sialic acid.

5. Conformational Analysis of Carbasugars

Since carbohydrate-based ligands are an object of hydrolytic cleavage, carbaglycosyl compounds have been developed in the search for improved chemical and biochemical stability. However, the methylene analogues do not simply behave as noncleavable glycosides, and carbocyclic analogues of oligosaccharides in which the endocyclic oxygen atom is replaced with a methylene group may have conformational properties different from those of the natural oligosaccharides. Apart from the logical variations in bond lengths (C−O 1.42 Å vs C−C 1.55 Å) and bond angles (C−O−C 114°, C−C−C 115°), the conformational similarity of the intersaccharide linkages differs. Indeed, the substitution of an oxygen by a methylene group results in a change in the electronic properties of the glycosidic linkage, with concomitant changes upon the flexibility and the energy barriers to rotation around the glycosidic torsion angles. Thus, the *exo*-anomeric effect present in glycosides, due to the presence of the interglycosidic oxygen atom, disappears in the carba analogue, along with a consequent variation of the steric interactions between both residues.

5.1. Conformational Analysis of Carbafuranoses

For the cyclopentane ring, the more stable conformers are the envelope and the twist conformation's half-chair (Figure 33). Because the barriers between these conformations are very low, five-membered rings can adopt different half-chair or envelope conformations as well as intermediate ones.[129] This conformational change is originated by oscillatory motions of the five carbon atoms in a direction perpendicular to the plane of the ring, creating a "swelling" (out-of-the-plane atom) which appears to rotate around the ring even though there is no motion of the atoms in this direction. This process is called "pseudorotation", and the conformers generated in this way can be visualized using the "pseudorotational wheel".[130]

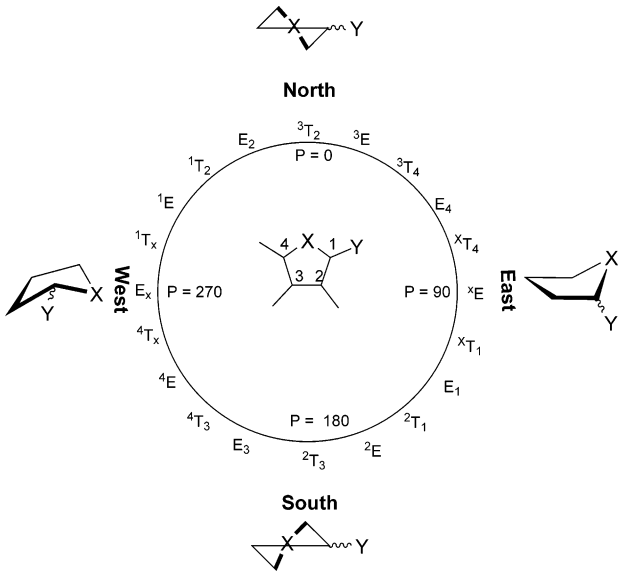
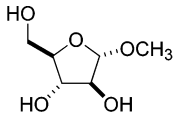


Figure 34. Pseudorotational wheel for a five-membered ring.

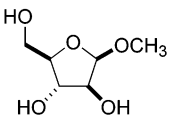
In the case of the furanose ring (Figure 34, X = O, Y = OMe), an equilibrium between two low-energy conformations is assumed in solution, with one of these conformers being located in the northern hemisphere of the pseudorotational wheel and the other in the southern hemisphere. Through the measurement of the $^3J_{H,H}$ (an average of the coupling constants arising from both conformers in solution), the contribution of each individual conformer can be determined. This may be done using the program PSEUROT,[131] which provides the populations of both conformers that best fit the experimental NMR data. The method, which can be applied to any five-membered ring,[132] has been used for the conformational analysis of furanose rings.[133] In this case, the relative populations of both conformers are determined by the steric demands of the substituents and by the stereoelectronic effects, in particular the anomeric effect,[134] together with the presence of favorable gauche interactions.[135] However, in the case of carbafuranoses (Figure 34, X = CH_2, Y = OMe), the substitution of an endocyclic oxygen by a methylene group may alter the equilibrium between both conformers.

Despite the synthetic efforts devoted to the preparation of carbocyclic nucleoside analogues, to the best of our knowledge,[136] only one report[137] has focused on the study of the conformation of carbafuranoses compared to the analogous furanose rings. For this purpose, the PSEUROT program has been applied to the carbafuranoses **137** and **138** and the results where contrasted with those obtained for the methyl glycosides **135**[138] and **136**[139] (see Figure 35). Comparison of the α isomers (compounds **135** and **137**) indicates that the conformational equilibrium in the carbasugar is biased to the northern conformer with regard to the analogous sugar. In the glycoside, both $^0T_4$ and $^2T_3$ conformers are stabilized by the anomeric effect. Indeed, in the case of the S conformer, an attractive gauche interaction between the ring oxygen and the OH groups at C_2 and C_3 is also present. In the carbasugar, these stereoelectronic effects have been eliminated and then only steric effects as well as gauche interactions between exocyclic hydroxy groups are present. Then, northern conformers are favored and the conformational preferences of glycosides and carbasugars are clearly different.

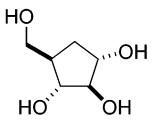
In the case of β isomers (compounds **136** and **138**), the conformer distributions are more similar. The glycoside and



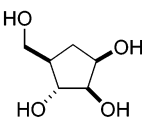
135[a]



136[b]



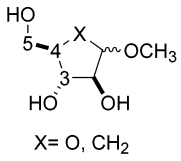
137



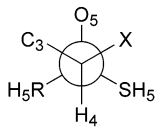
N conformer	$^0T_4$	E_2	^3E	$^3T_2$
X_N	56	99	86(83)[c]	75 (77)[c]
S conformer	$^2T_3$	^2E	^2E	^2E
X_S	41	1	14 (17)c	25 (23)c

a) Taken from reference 138.
b) Taken from reference 139.
c) Coupling constants for simulated spectra were used.

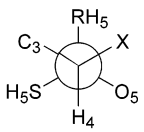
Figure 35. Ring conformers of compounds **135**−**138**.



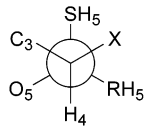
X= O, CH_2



gg



gt



tg

	Compound (population %)			
Conformer	**135**	**136**	**137**	**138**
X_{gg}	48	34	49	34
X_{gt}	38	55	39	45
X_{tg}	14	11	12	21

Figure 36. Rotamer populations about the C_4-C_5 bond in compounds **135**−**138**.

the carbasugar adopt the same S conformation, and both northern conformations (E_2 for the glycoside and $^3T_2$ for the carbasugars) are immediately adjacent on the pseudorotational wheel. In this case, the E_2 conformation of **136** is especially stabilized because the methoxy group is pseudoaxially oriented and, hence, stabilized by the anomeric effect.

Of additional interest are the rotameric equilibria about the C_4-C_5 and C_1-O_1 bonds because, in furanose rings, the rotamer populations about these bonds are influenced by the ring oxygen. For the C_4-C_5 bond, a gauche interaction between 5-OH and the endocyclic oxygen stabilizes the *gt* and *gg* rotamers relative to the *tg* counterpart, where such a stabilizing interaction is absent (see Figure 36 for rotamer definitions). The populations of rotamers about the C_4-C_5 bond in the case of carbafuranoses **137** and **138** was deduced from the analysis of $^3J_{4,5R}$ and $^3J_{4,5S}$, directly measured from the ^1H NMR spectra. In the case of compound **137**, the rotamer populations are essentially unchanged relative to those of the analogous glycoside **135**. In both compounds, the *gg* rotamer is stabilized by a hyperconjugative interaction, $\sigma_{(C4-H4)}-\sigma^*_{(C5-O5)}$,[140] whereas the predominance of *gt* over *tg* conformers can be ascribed to the stabilizing *gauche* effect involving O_4 and O_5 atoms which is not present in the *tg* conformer. On the other hand, a second factor may be considered in **137**: that is, that, in the *tg* rotamer of the major ring conformer (^3E), a "1,3-diaxial" interaction between O_5 and O_3 is present.

Comparison of the C_4-C_5 rotamer populations in compounds **136** and **138** shows that the *gg* rotamer population remains unchanged whereas the amount of the *tg* rotamer in **138** increases at the expense of *gt*. This observation may be a consequence of the fact that the southern ring conformer (^2E) is more populated at equilibrium. For this ring conformer, the *tg* rotamer does not show a "1,3-diaxial" interaction between O_3 and O_5.

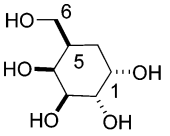
Considering the rotameric equilibrium between the C_1-O_1 bond, the staggered rotamers for glycosides and carbasugars are represented in Figure 37. For glycosides **135** and **136**, both an *exo*-anomeric effect and steric effects dictate that the preferred conformations should be those in which the methyl group is antiperiplanar to C_2 (conformer *tg*). For carbasugars **137** and **138**, NOE measurements indicate that this is also the major conformer. However, in these cases, it was not possible to confirm this preference from the consideration of the $^3J_{C-C}$ coupling constants.

cyclohexane ***oxane***

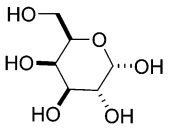
Figure 37. Cyclohexane and oxane.

5.2. Conformational Analysis of Carbapyranoses

Although the inversion barriers for cyclohexane and oxane are almost identical[141] [$\Delta G^*_{cyclohexane} = 42.9$ kJ·mol^{-1} (−60 °C) and $\Delta G^*_{oxane} = 43.1$ kJ·mol^{-1} (−61 °C)], in the corresponding 2-substituted derivatives, the oxygenated heterocycle displays a larger $\Delta G°$ for the corresponding methyl-substituted compound ($\Delta G°_{methylcyclohexane} = 7.28$ kJ·mol^{-1} and $\Delta G°_{2-methyloxane} = 12.0$ kJ·mol^{-1}). This appears to be a consequence of a change in molecular dimensions. Because the C−O bond length is shorter than the C−C length, the distance between an axial methyl group at C_2 and the *syn*-axial H at C_6 increases as one passes from oxane to cyclohexane. Consequently, the value of $\Delta H°$ decreases. This fact, together with the consideration of the anomeric



3

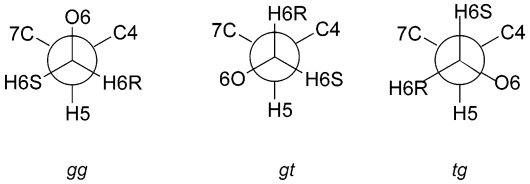


139

Compound	C1	C2	C3	C4	C5	C6	C7
3[a]	147.8	143.0	142.5	148	126	143	129
139[b]	170.2	145.8	144.0	146	142	145	–

a) Taken from ref 132.
b) Taken from ref 143.

Figure 38. ^{13}C NMR chemical shifts for compounds **3** and **139**.



gg *gt* *tg*

Figure 39. Rotamers around the C_5-C_6 bond. For definitions of the rotamers, see ref 143.

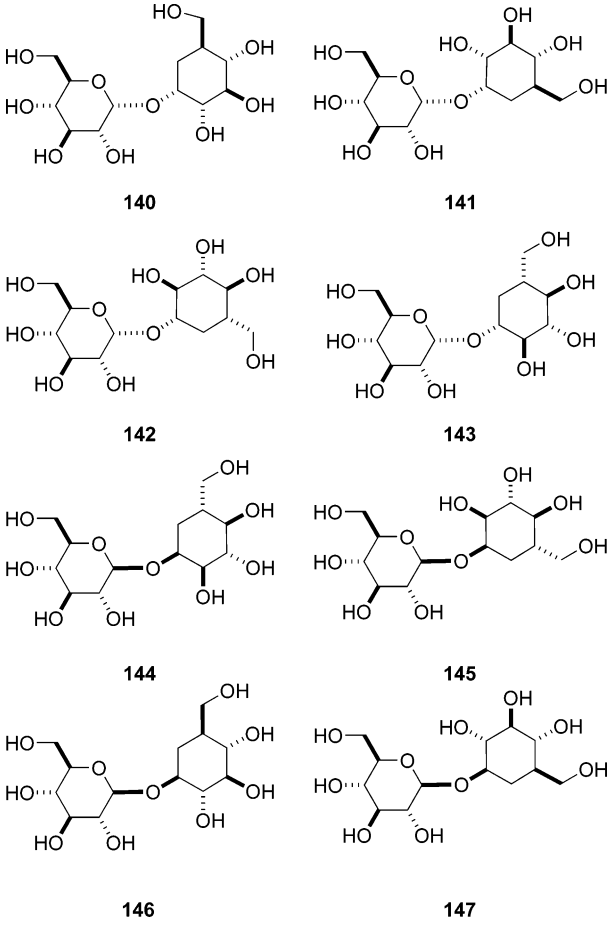
effect, should govern the conformational preferences of carbapyranoses relative to the parent pyranoses.

However, the analysis of the NMR parameters of six carbapyranoses[142] compared to those for the corresponding methyl hexosides strongly supports the conclusion that each compound adopts an almost unperturbed $^4C_1$ chair conformation. For instance, comparison of the ^{13}C NMR chemical shifts of carba-α-DL-galactopyranose (**3**) with those of the related methylhexoside **139**[143] shows significant differences only for C_1 and C_5, as may be expected. Observation of the rest of the chemical shifts does not suggest any major conformational differences between both types of compounds (Figure 38).

The *J* values for H-5, 6(*R*), and 6(*S*) in carbasugars are somewhat different depending on the axial or equatorial orientation of the hydroxy group at C_4. Thus, carbasugars of the galacto series show $J_{H5-H6(R)}$ between 7.8 and 8.0 Hz. These data, together with the more similar values of $J_{H5-H6(S)}$ for both series, indicate that the *gt* rotamer[144] (Figure 39) prevails in the galacto- series and that an appreciable amount of the *gg* rotamer is present in the gluco- and manno- series. The population of the *tg* rotamer is low for all compounds, as was also found for the hexosides. Similar results were obtained in the carbocyclic analogues of 2-acetamido-2-deoxy-DL-hexopyranoses[145] having the α- and *β*-DL-galacto-, gluco-, and manno- configurations.

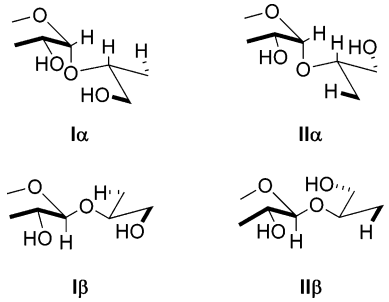
In the search for a relationship between conformational preferences and biological activity, mainly enzymatic inhibition, the conformational analysis of several carbadisaccharides has been carried out by several groups by combination of NMR studies and theoretical calculations. For instance, Bock and Ogawa estimated[146] the conformational preferences for eight carba-trehaloses, **140**−**147**, using the analysis of chemical shifts together with NOE measurements in association with empirical force field calculations (Figure 40).

Defining the angles Φ and Ψ as $H_1-C_1-O_1-C_{1'}$ and $C_1-O_1-C_{1'}-H_{1'}$, respectively, a greater flexibility in terms of Ψ regarding Φ was observed for all compounds, in accordance with the presence of the *exo*-anomeric effect. On



140 **141** **142** **143** **144** **145** **146** **147**

Figure 40. Carbatrehaloses studied by Duus, Bock, and Ogawa.



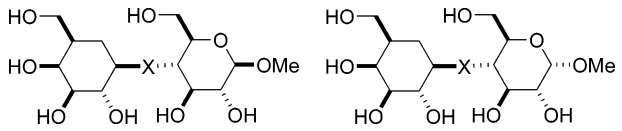
Iα **IIα** **Iβ** **IIβ**

Figure 41. Definition of structure types **I** and **II**, involved in the conformational preferences for compounds **140**−**147**.

the other hand, and considering the relative arrangements of atoms around the glycosidic linkage as Iα, IIα, I*β*, II*β* (Figure 41), compounds **140** and **142** show conformation type Iα and compounds **144** and **146** show conformation type I*β*. Also, for compounds **141** and **143**, the conformational arrangement is IIα, and for compounds **145** and **147**, it is II*β*.

Recently, Jiménez-Barbero's group has addressed the study of the conformation of a variety of carbaglycosides using a combination of molecular mechanics and dynamics calculations, with experimental data from NMR spectroscopic techniques, using a similar approach to that described by them for the *C*-glycosyl analogues (the *C*-analogue at the interglycosidic oxygen).[147]

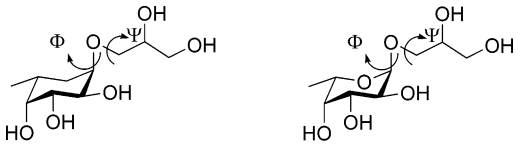
The conformation of the carba analogues of *β*-lactosides[148] **148** and **149** (Figure 42) has been analyzed using this methodology. In these cases, the glycosidic torsion angles which define the conformation around the glycosidic linkage



148 X = O
149 X = NH

150

Figure 42. Carbasugar analogues of lactosides.



151 **152**

Figure 43. Carbasugar analogues of fucosides.

are defined as Φ ($H_{1'}-C_{1'}-X-C_4$) and ψ ($C_{1'}-X-C_4-H_4$). In contrast with the regular *O*-glycosides, for which three different conformational families are found in all cases, four families are found for these types of compounds.

The global minimum of **148** is located in the *syn*-Φ/*syn*-Ψ population, as in the natural product. A higher flexibility with respect to lactose was deduced, since minor populations were detected for the *anti*-Φ and *anti*-Ψ local minima. In addition, a small contribution of the non-*exo* anomeric orientation was also inferred from the MM/NMR analysis. Obviously, this conformation cannot take place for the natural analogue, due to the additional stabilization of the *exo*-anomeric *syn*-Φ conformer provided by the stereoelectronic effect. This value amounts to ∼1.8−2.0 kcal/mol, as deduced from the comparison between a variety of gluco- and manno-glycosides and their *C*-glycosyl analogues.[149] A similar conformational behavior was observed for the carba-imino analogue **149**, for which the interglycosidic oxygen was replaced by a NH group. Also in this case, a conformational equilibrium among four different conformers was also shown to take place in water solution.

In a similar manner, lactose mimetic **150**, without *exo*-anomeric stabilization, presents a 90:10 proportion of *exo*/non-*exo* conformers around Φ, while natural lactose shows an almost exclusive predominance of *exo*-conformers. Nevertheless, in binding studies with a plant lectin, only the regular *exo*-anomeric type of conformation is bound, and so this compound, in fact, behaves as a true glycomimetic.[150]

The conformational behavior of carbafucopyranosyl glycosides (Figure 43) has also been evaluated.[151] In contrast to the *O*-glycosyl parent compound **152**, for which a population of *exo*-anomeric conformers above 95% was deduced, the carbafucosyl mimetic bearing a glycerol aglycon, **151**, shows a mixture of *exo*-anomeric and non-*exo*-anomeric populations at the glycosidic μ angle (ca. 4:1). Using TR-NOE experiments,[152] the authors demonstrated that the bound conformation was the same for the glycoside and the carba analogue, thus showing that, in this case, the synthetic analogue indeed mimics the behavior of the regular glycoside

Thus, generally speaking, it can be stated that the carba analogues may indeed access those conformational regions populated by the natural compounds, but that they are more flexible, especially around the Φ angle, due to the lack of the stereoelectronic stabilization provided by the *exo*-anomeric effect. This fact indicates that an entropy penalty has to be paid, and minima other than the global one may be bound by biological receptors, although without a major enthalpy conflict, since the energy barriers between the different regions are small. Similar situations occur for the *C*-glycosyl analogues.[153]

This enhanced conformational flexibility of the carbaglycosides is general as it was also deduced from the NMR/MM analysis of the conformation of carbaglycosides derived from β-D-Gal(1→1)-α-D-Man.[154] Also in this case, the glycomimetic presents an enhanced flexibility with respect to the natural analogue, but interestingly, it is not as flexible as the corresponding *C*-glycosyl compound.[155] Therefore, for a given ligand, and depending on the chosen biological target, and its intrinsic binding site architecture, it seems that a range of conformational flexibility may be tuned when passing from natural *O*-glycosides to carbaglycosides and, finally, to the most flexible *C*-glycosyl compounds.[156]

6. Synthesis of Carbasugars

Even prior to the knowledge of their existence in Nature, chemical routes to both carbafuranoses and carbapyranoses had already been studied and developed. In fact, a racemic synthesis[157] of arysteromycin, the first natural carbafuranose-related compound reported, preceded its isolation, and likewise, 5a-carba-α-D-galactopyranose (**3**) was discovered as a naturally occurring compound 7 years after McCasland's first synthesis.[10−12] Since then, the synthesis of such compounds has attracted considerable interest and a plethora of synthetic approaches have been developed. The endeavors of chemists have been motivated as much by the challenges posed by the syntheses of the title compounds as by an interest in their biological properties or their utility as biochemical tools in glycobiology.

The strategies adopted to obtain carbafuranoses and carbapyranoses can be broadly classified into two groups: (i) synthetic methods which employ non-carbohydrates as starting materials and (ii) protocols which utilize carbohydrates as precursors. Some other strategies which make use of natural products other than carbohydrates as starting materials have also been examined.

6.1. Synthesis of Carbafuranoses

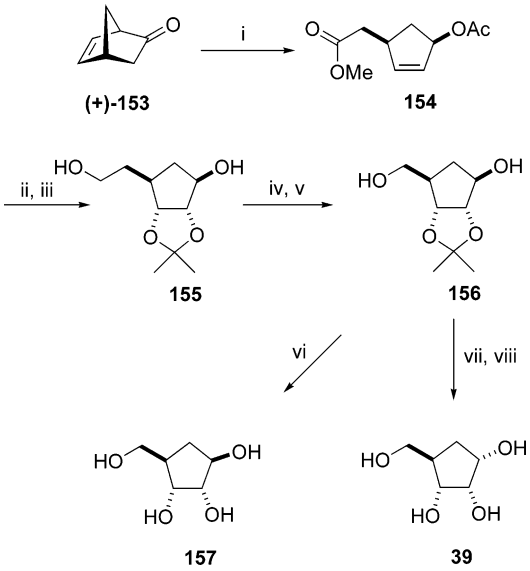
6.1.1. Synthesis from Non-carbohydrate Precursors

In this section, the different synthetic strategies will be classified according to the type of compounds employed as starting materials: (i) from bicyclic compounds; (ii) from furan derivatives; and (iii) from cyclopentadiene.

6.1.1.1. From Bicyclic Compounds. Griengl and coworkers described, in 1990,[158] the first synthesis of carbapentofuranoses from non-carbohydrate precursors, employing norborn-5-en-2-one (**153**) as the starting material (Scheme 3).[159]

Thus, 4a-carba-β- and -α-D-ribofuranoses (**157** and **39**), respectively, were obtained from (+)-**153**. Alkaline Baeyer−Villiger reaction of the latter followed by esterification and acetylation provided the unsaturated carbahexofuranuronic acid derivative **154**. Stereoselective dihydroxylation of **154** with OsO_4/NMO and protection of the ensuing diol as a dioxolane was followed by reduction with LAH to give compound **155**. Side-chain degradation was performed by a sequence of elimination, degradative oxidation, and reduction to the protected 4a-carba-β-D-ribofuranose (**156**). Deprotection of the latter with BCl_3 paved the way to 4a-carba-β-D-ribofuranose (**157**). In order to obtain the α-anomer from

Scheme 3. Synthesis of 4a-Carba-α- and -β-D-ribofuranoses (39 and 157) by Griengl's Group[a]



[a] Reagents: (i) (a) H_2O_2, NaOH, H_2O, Et_2O; (b) MeI, DMF; (c) Ac_2O, py, DMAP, CH_2Cl_2, 71%; (ii) (a) OsO_4, NMMO, acetone; (b) 2,2-dimethoxypropane, p-TsOH, 77%; (iii) LAH, Et_2O, 0 °C, 97%; (iv) (a) Ph_3P, Br_2, Et_3N; (b) 2-nitrophenylselenocyanate, $NaBH_4$, EtOH; (c) H_2O_2, THF; (d) Ac_2O, py, DMAP, CH_2Cl_2, 61%; (v) (a) OsO_4, $NaIO_4$, H_2O, Et_2O; (b) LAH, Et_2O, 88%; (vi) BCl_3, CH_2Cl_2, −78 °C, 95%. (vii) (a) triphenylchloromethane, py, DMAP, CH_2Cl_2; (b) PDC, 77%; (viii) (a) $NaBH_4$, MeOH; (b) BCl_3, CH_2Cl_2, −78 °C, 58%.

156, the required inversion of C_1 was performed by a three-step sequence, including protection of the primary hydroxy group, pyridinium dichromate (PDC) oxidation of the secondary alcohol, and stereoselective reduction with $NaBH_4$. Finally, deprotection with BCl_3 yielded the desired 4a-carba-α-D-ribofuranose (**39**).

As a continuation of this work, Griengl and co-workers[160] addressed the task of synthesizing all possible stereoisomeric carbapentofuranoses from **153**. Accordingly, they developed a general protocol which included Baeyer−Villiger oxidation of the latter followed by (i) stereodivergent hydroxylation of the $\Delta^{2,3}$ double bond to the desired pattern and (ii) degradation of the side chain by an oxidative protocol, which led to the lyxo-, arabino-, ribo-, and xylofuranose derivatives (Figure 44).

The synthesis of the α-D-lyxo isomer (**162**, Scheme 4) required the opposite facial selectivity in the *cis*-dihydroxylation of **158** than that observed previously in the preparation of the 4a-carba-D-ribofuranoses **39** and **157**. For this purpose, inversion of the configuration at C_1 in **158** was carried out by Mitsunobu reaction, leading to the corresponding benzoate. The latter, on treatment with OsO_4/NMO and protection, gave exclusively the desired stereoisomer **159**, which was reduced to give dioxolane **160**. The side-chain degradation to **161** and deprotection was achieved as described previously for the ribo series to finally yield 4a-carba-α-D-lyxofuranose (**162**). The β-anomer, 4a-carba-β-D-lyxofuranose (**163**), was also prepared from **161** using the same oxidation/reduction protocol described for **39** (see Scheme 3).

The synthesis of the DL-arabino carbasugar ((±)-**170**, Scheme 5) was carried out from (±)-**158** by conversion of the double bond into a *trans*-diol. Thus, reduction of (±)-**158** gave allylic alcohol (±)-**164**, which, after Sharpless epoxidation, gave epoxide (±)-**165** as a single diastereomer. Treatment of (±)-**165** with aqueous perchloric acid resulted

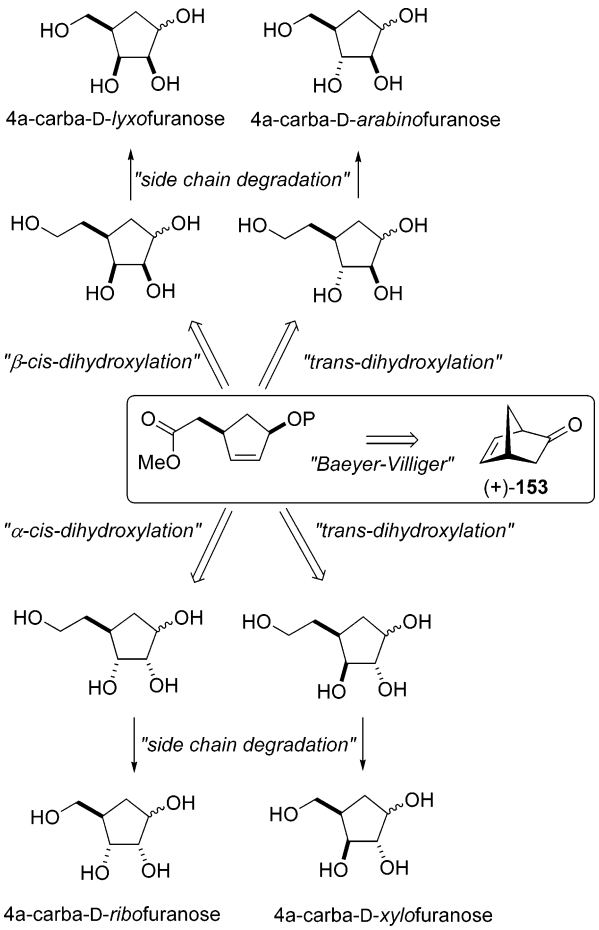
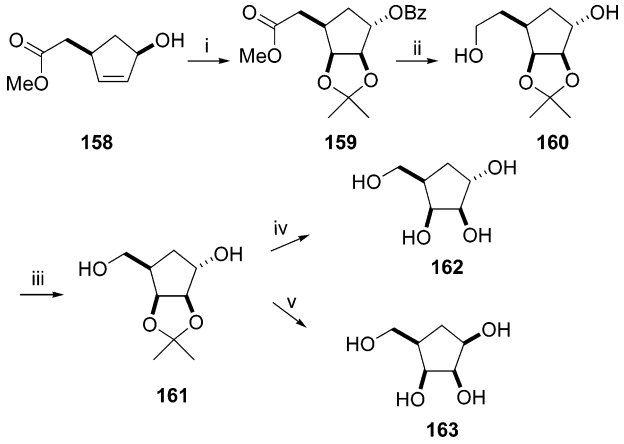


Figure 44. Synthesis of carbapentofuranoses by Griengl's group.

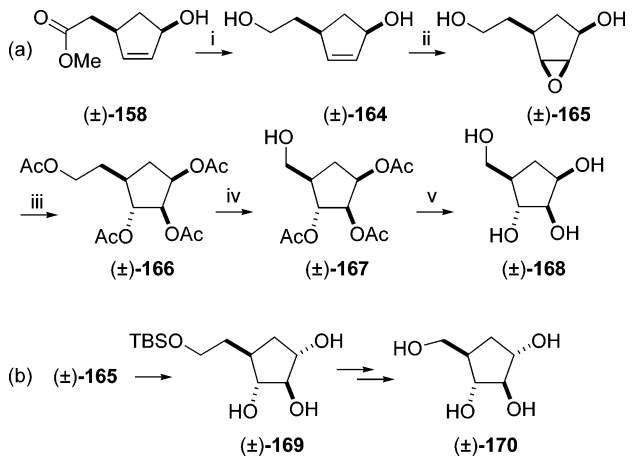
in a regioselective oxirane opening, leading, after acylation, to (±)-**166** with the desired β-arabino configuration. Conversion of (±)-**166** to 4a-carba-β-DL-arabinofuranose [(±)-**168**] proceeded as shown before, albeit, in this case, the cleavage of the terminal double bond was achieved via ozonolysis/reduction. The α-arabino configuration was obtained by inversion of configuration at C_1, after protection of the

Scheme 4. Synthesis of 4a-Carba-α- and -β-D-lyxofuranoses (162 and 163) by Griengl's Group[a]



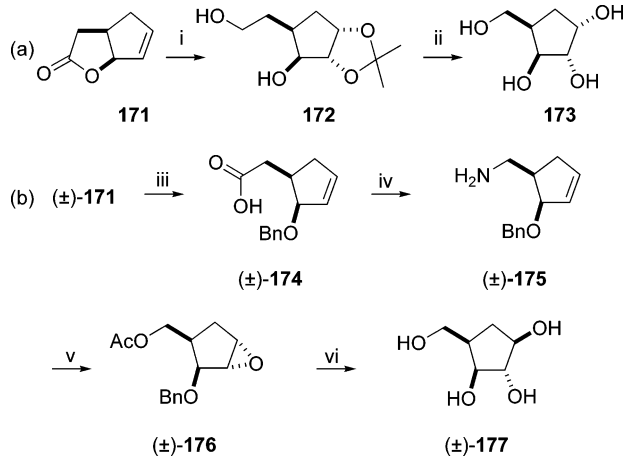
[a] Reagents: (i) (a) Ph_3P, DEAD, BzOH, THF; (b) OsO_4, NMMO, acetone; (c) 2,2-dimethoxypropane, TsOH, 40% from **158**; (ii) LAH, Et_2O, 86%; (iii) (a) Ph_3P, Br_2, Et_3N, CH_2Cl_2, 76%; (b) 2-nitrophenylselenocyanate, $NaBH_4$, EtOH; (c) H_2O_2, EtOH, 86% (two steps); (d) OsO_4, $NaIO_4$, Et_2O, H_2O; (e) $NaBH_4$, MeOH, 61% (two steps); (iv) HOAc, 80%, reflux; (v) (a) TrCl, py, CH_2Cl_2, 62%; (b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (Swern oxidation); (c) $NaBH_4$, MeOH, 0 °C, 93%; (d) HOAc, reflux, 80%.

Scheme 5. Synthesis of 4a-Carba-DL-arabinofuranoses 168 and 170 by Griengl and Co-workers (Only D-Enantiomers Are Shown)[a]



[a] Reagents: (i) LAH, Et_2O, 90%; (ii) $VO(acac)_2$, t-BuOOH, CH_2Cl_2, 70%; (iii) (a) $HClO_4$, H_2O; (b) Ac_2O, py, DMAP, CH_2Cl_2, 94%; (iv) (a) NaOMe, MeOH, 94%; (b) TrCl, py, CH_2Cl_2, 90%; (c) Ac_2O, py, DMAP, CH_2Cl_2, 86%; (d) H_2, 10% Pd−C, EtOH; (e) Ph_3P, Br_2, Et_3N, CH_2Cl_2; (f) 2-nitrophenylselenocyanate, $NaBH_4$, EtOH; (g) H_2O_2, EtOH; (h) O_3, MeOH, −80 to 0 °C; (i) $NaBH_4$, MeOH, 0 °C, 18% overall; (v) NaOMe, MeOH, 83%.

Scheme 6. Synthesis of 4a-Carbaxylofuranoses 173 and 177 by Griengl's Group (When Racemic, Only D-Enantiomers Are Shown)[a]

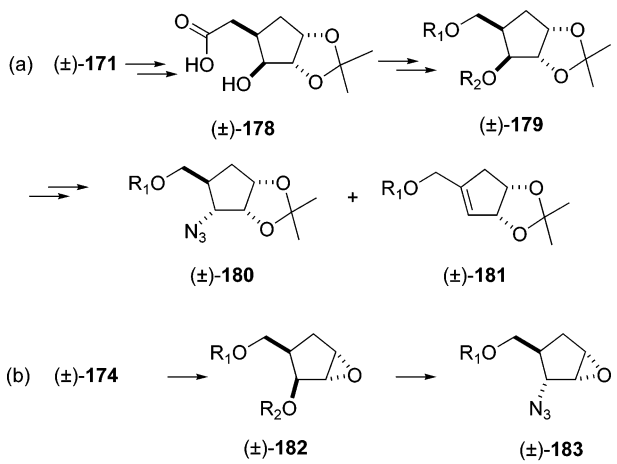


[a] Reagents: (i) (a) OsO_4, NMMO, acetone; (b) 2,2-dimethoxypropane, TsOH; (c) LAH, Et_2O, 69% (three steps); (ii) (a) Ph_3P, Br_2, Et_3N, CH_2Cl_2; (b) 2-nitrophenylselenocyanate, $NaBH_4$, EtOH; (c) H_2O_2, EtOH, $VO(acac)_2$, t-BuOOH, CH_2Cl_2; (d) OsO_4, $NaIO_4$, Et_2O, H_2O; (e) HOAc, reflux, 13% (five steps); (iii) KOH, BnBr, dioxane, reflux; (iv) (a) ethyl chloroformate, Et_3N, acetone, NaN_3; (b) $PhCH_3$, reflux, 97%, two steps; (v) (a) $NaNO_2$, HOAc, NaOAc; (b) MCPBA, CH_2Cl_2, 46% (two steps); (vi) (a) $HClO_4$, H_2O; (b) Ac_2O, py, DMAP, CH_2Cl_2; (c) H_2, 10% Pd−C, EtOH; (d) NaOMe, MeOH, 53% (four steps).

primary alcohol of (±)-**165** followed by addition of cesium acetate. The opening of the epoxide moiety required the presence of a free C_1−OH, because a C_1−OAc directs the attack of the oxygen nucleophile at C_2 rather than at C_3. Conversion of (±)-**169** into 4a-carba-α-DL-arabinofuranose [(±)-**170**] was carried out as mentioned before for the β isomer.

For the remaining carbasugars of xylo configuration, the authors used compound **171**, obtained by Baeyer−Villiger reaction of (+)-**153** under special conditions, as the starting material (Scheme 6). Thus, *cis*-hydroxylation of **171** yielded an α-xylo diol, which was protected as a dioxolane whereas

Scheme 7. Synthesis of 3-Azido-3-deoxy-4a-carba-α-DL-ribofuranose Derivatives by Griengl's Group (Only D-Enantiomers Are Shown)



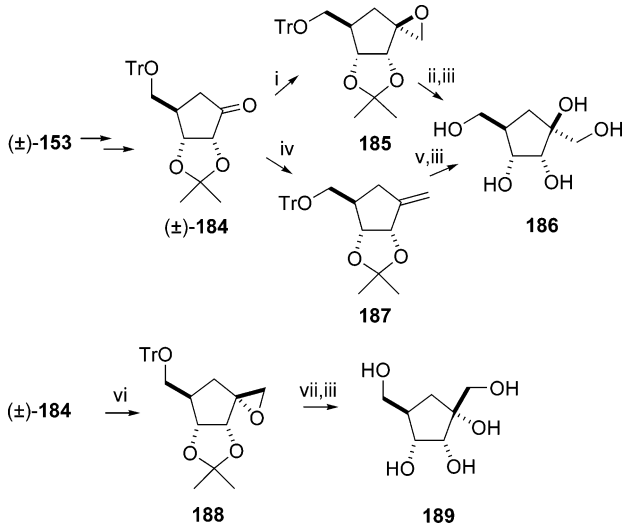
the lactone was reduced to diol **172**. 4a-Carba-α-D-xylofuranose (**173**) was obtained from compound **172**, as mentioned above (Scheme 6a). For the β-DL-xylo configuration, the authors, owing to problems in the regiochemistry of the *trans*-hydroxylation and side-chain degradation, used the procedure employed previously in the synthesis of carbocyclic nucleosides (Scheme 6b).[161] Compound (±)-**171** was converted into acid (±)-**174**. Curtius degradation gave amine (±)-**175**, which was stereoselectively transformed into the epoxide (±)-**176**. Regioselective ring opening of (±)-**176** with perchloric acid and deprotection gave 4a-carba-β-DL-xylofuranose (±)-**177**.

Following a similar approach, Griengl and co-workers[162] also described an entry to derivatives of 3-azido-3-deoxy-4a-carba-α-DL-ribofuranose (±)-**180** and (±)-**183** (Scheme 7) from (±)-**171** or (±)-**174**. Both intermediates were transformed by chain degradation and suitable functionalization of the double bond to compounds (±)-**178** or (±)-**182**. For (±)-**179**, the S_N2 reaction required to introduce the azide moiety was always accompanied by elimination yielding a mixture of the desired (±)-**180** and olefin (±)-**181**. In the case of epoxide (±)-**182**, the elimination was not the competing reaction but a slight extent of attack on the epoxide was observed.

The racemic ketone (±)-**184**, available from norbornen-2-one (±)-**153**, was also used as a convenient intermediate for preparing β- and α-DL-ribocarba-2-ulofuranoses **186** and **189** (Scheme 8).[163] In the first case, the required one-carbon side chain was introduced either via dimethylsulfoxonium methylide addition, which takes place from the more hindered α-side, and nucleophilic opening of the oxirane **185** or via methylenation with Tebbe's reagent and *cis*-hydroxylation. α-Epoxide **188** was prepared by stereoselective β-bromomethyllithium addition followed by nucleophilic bromine displacement. Opening of oxirane **188** followed by deprotection gave α-DL-ribocarba-2-ulofuranose (**189**).

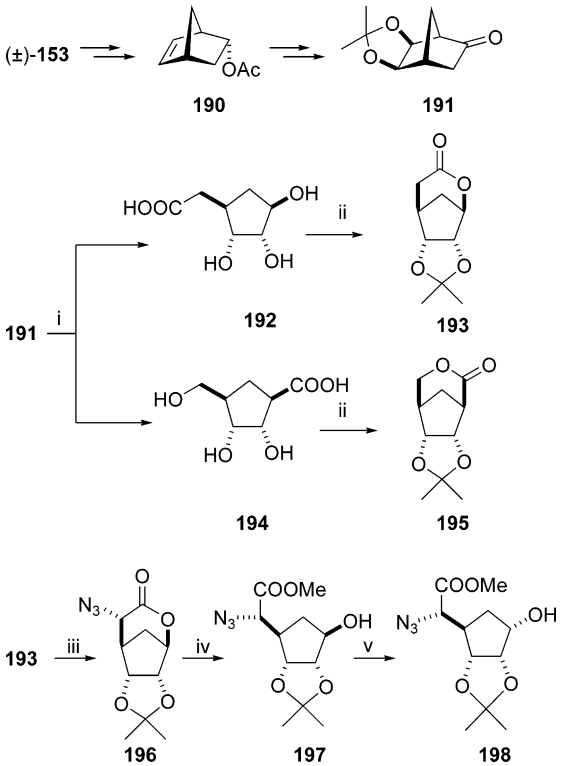
Griengl and co-workers also described the synthesis of the carbocyclic analogue of the sugar portion of the antibiotics nikkomycins and polyoxins.[164] The enantiomerically enriched starting material norborn-5-en-2-yl acetate (**190**) was easily obtained from racemic (±)-**153**, and the key step was the Baeyer−Villiger oxidation of **191** (Scheme 9). When the oxidation step was carried out in neutral or alkaline

Scheme 8. Synthesis of Carba-DL-ribo-2-ulofuranoses (186 and 189) by Griengl's Group (Only D-Enantiomers Are Shown)[a]



[a] Reagents: (i) NaH, $(CH_3)_3SOI$, DMSO, THF; (ii) NaOAc, DMF, 140 °C or CsOAc, DMF, 80 °C; (iii) (a) Amberlite IR-120, CH_3CN, H_2O, 50 °C; (b) Ac_2O, py, DMAP, CH_2Cl_2; (c) MeOH, NaOMe; (iv) $Cp_2Ti(CH_3)_2$, $PhCH_3$, 60−70 °C; (v) oxone, acetone, 18-crown-6, $NaHCO_3$, H_2O, CH_2Cl_2 or MCPBA, PhH, reflux; (vi) CH_2Br_2, n-BuLi, THF, −80 °C to rt; (vii) CsOAc, DMF, 90 °C.

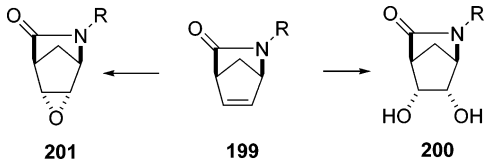
Scheme 9. Synthesis of a Carbocycle Analogue to the Sugar Portion of Polyoxins (Only D-Enantiomers Are Shown)[a]



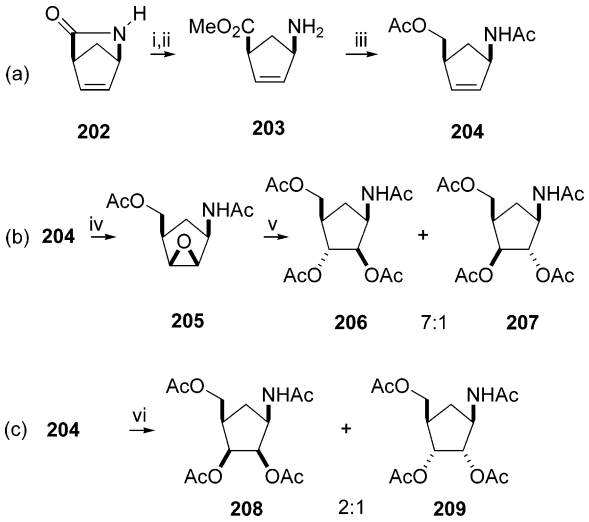
[a] Reagents: (i) MCPBA, H_2O, 80 °C; (ii) acetone, conc HCl, then Et_3N, ClC(O)OEt, 81% **193**, 19% **195**; (iii) KHMDS, 2,4,6-triisopropylbenzenesulphonyl azide, then HOAc, 79%; (iv) NaOMe, MeOH, 0 °C, 88%; (v) PCC, EtOAc, 80 °C, then $NaBH_4$, MeOH, 76%.

media, a mixture of lactones **193** and **195** was formed, but the undesired **195** was dominant. In acidic media, the percentage of **193** could be raised to 81% although the acetal moiety was cleaved and the products were a mixture of acids **192** and **194**. After acetalization and lactonization, the azido

Scheme 10. Compound 199, a Useful Starting Material for the Synthesis of Aminocarbafuranoses



Scheme 11. Synthesis of Protected 1-Amino-1-deoxy-4a-carba-β-D-furanoses by Vince's Group[a]



[a] Reagents: (i) 5% HCl, 3−5 days, then MeOH, reflux; (ii) Ac_2O, py, 89%, two steps; (iii) $CuBH_4$, THF, then Ac_2O, py, 89%; (iv) MCPBA, CCl_4, reflux, 2 h, 89%; (v) H_2SO_4, then Ac_2O, py, 68%; (vi) OsO_4, NMO, t-BuOH−H_2O, 85 °C, then Ac_2O, py, 89%.

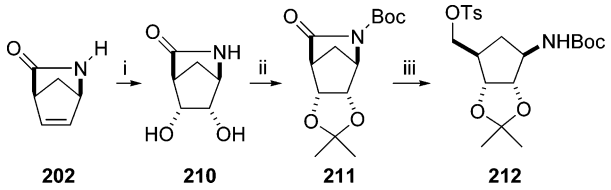
functionality was introduced in **193** and opened to hydroxy ester **197**, which through an oxidation−reduction sequence gave the desired carbasugar derivative **198**.

Several groups have reported the use of 2-azabicyclo[2.2.1]-hept-5-en-3-one (**199**) as a key starting material for the synthesis of carbasugars and nucleosides (Scheme 10). The commercial availability of this bicyclic lactam in both pure enantiomeric forms provides a direct entry into homochiral intermediates and products. All the reported procedures from **199** follow a general scheme involving (a) the stereocontrolled functionalization of the double bond, either by *cis*-hydroxylation (OsO_4, NMO) or epoxidation (MCPBA), leading to **200** or **201**, respectively, and (b) further transformations to the desired objective.

Daluge and Vince developed an early route to carbocyclic analogues of aminonucleosides based on compounds arising from the ring opening of lactam **202** followed by epoxidation or dihydroxylation (Scheme 11).[165] Accordingly, compound **204**, obtained from **202** (Scheme 11a) was converted to different carbafuranosylamines of known stereochemistry (Scheme 11b,c). Stereoselective epoxidation of **204**, with MCPBA, followed by hydrolysis with sulfuric acid[166] gave the carbocyclic furanosylamines **206** and **207** (Scheme 11b), whereas catalytic osmilation followed by mild acidic hydrolysis[167] gave the lyxo and ribo isomers **208** and **209** (Scheme 11c).

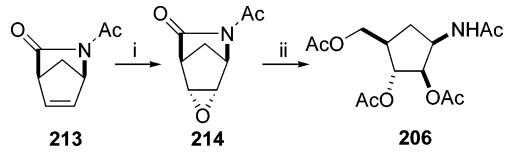
Blackburn and co-workers[168] utilized a related route for the preparation of protected 1-amino-1-deoxy-4a-carba-β-D-ribo-furanose (**212**), which was used as an intermediate in their stereospecific synthesis of a carbocyclic NAD^+ containing a methylenebisphosphonate linkage. The latter had been designed to act as an inhibitor of ADP-ribosyl cyclase

Scheme 12. Synthesis of Protected 1-Amino-1-deoxy-4a-carba-β-D-ribofuranose (212) by Blackburn's Group[a]



[a] Reagents: (i) OsO_4, NMMO, acetone, 91%; (ii) (a) 2,2-dimethoxypropane, TsOH, DMF; (b) Boc_2O, DMAP, CH_3CN, 85%; (iii) (a) $NaBH_4$, MeOH, 0 °C to rt, 85%; (b) TsCl, py, 88%.

Scheme 13. Synthesis of Cyclaradine by Katagiri's Group[a]



[a] Reagents: (i) MCPBA, $CHCl_3$, 68%; (ii) (a) $NaBH_4$, MeOH; (b) Ac_2O, py, 63%.

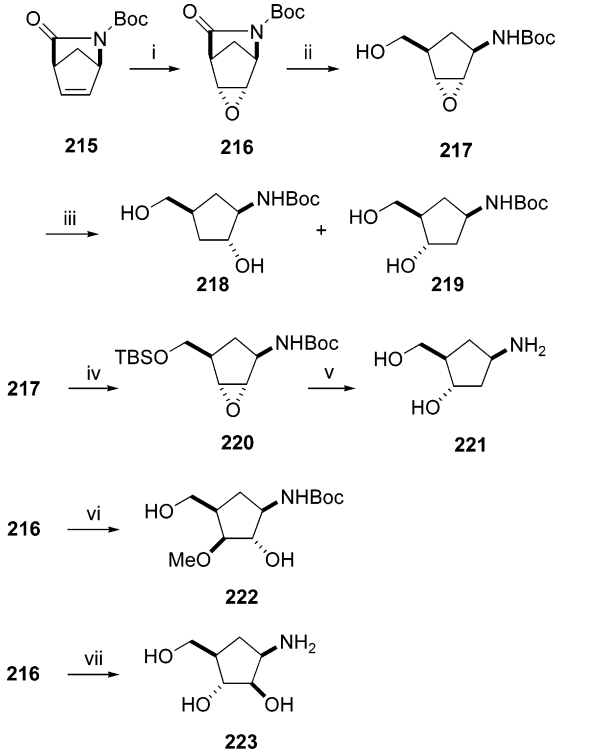
and to resist nonspecific phosphatases. Accordingly, unprotected lactam **202** was transformed into **212** through a sequence including *cis*-hydroxylation, double protection of the diol and lactam groups, and reductive cleavage of the lactam moiety (Scheme 12). The same approach has been recently used by Kuang, Saksena, and co-workers in their synthesis of carbocyclic ribavirin.[169]

The stereocontrolled epoxidation of the generic bicyclic system **199** was first described by Katagiri and co-workers[170] in their synthesis of the antiviral agent cyclaradine (Scheme 13). The essential features of their method involved stereocontrolled epoxidation with MCPBA over the enantiomerically pure *N*-acetyl derivative **213**, reductive amido-bond cleavage by reaction with $NaBH_4$, and selective ring opening of the epoxide ring by neighboring group participation of the acyl amine moiety to generate **206**.

The epoxide **216**, prepared from the chiral *N*-Boc derivative **215**, has also been used by Domínguez and Cullis[171] in the synthesis of carbocyclic analogues of deoxyribose nucleosides (Scheme 14). Reduction of the bicyclic lactam **216**, with $NaBH_4$ at 0 °C, gave cyclopentyl epoxide **217**, which was treated with DIBAL to give a 1:1 mixture of the two possible regioisomers **218** and **219**. Introduction of a bulky protecting group (TBS) at 5-OH resulted in an improved regioselectivity on the epoxide ring opening to give, after reduction and deprotection, carbocyclic 2-deoxyribose analogue **221**. On the other hand, when the reduction of the bicyclic system **216** was carried out with $NaBH_4$ in MeOH at 50 °C, not only the reductive cleavage of the lactam took place but also the regioselective methanolysis of the epoxide to **222**. A stereocomplementary ring opening of the epoxide **216** with aqueous sodium hydroxide afforded carbocyclic-arabino analogue **223**.

Mehta and co-workers[172] have described a new divergent access to trehazolamine analogues **231** and **232** and to the reported structure of salpantiol (**230**). As starting material they used racemic bicyclic alcohol **224** (Scheme 15), readily available from 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and vinyl acetate. Norbornyl derivative **224**, was transformed into 2,7-disubstituted keto-mesylate **225** through a multistep sequence including acetylation, dihydroxylation (OsO_4), Amberlyst-mediated one-pot diol protection, C_7-carbonyl deprotection, stereoselective carbonyl reduction,

Scheme 14. Synthesis of Carbasugar Analogues of 1-Deoxy-1-aminoribose by Dominguez and Cullis[a]



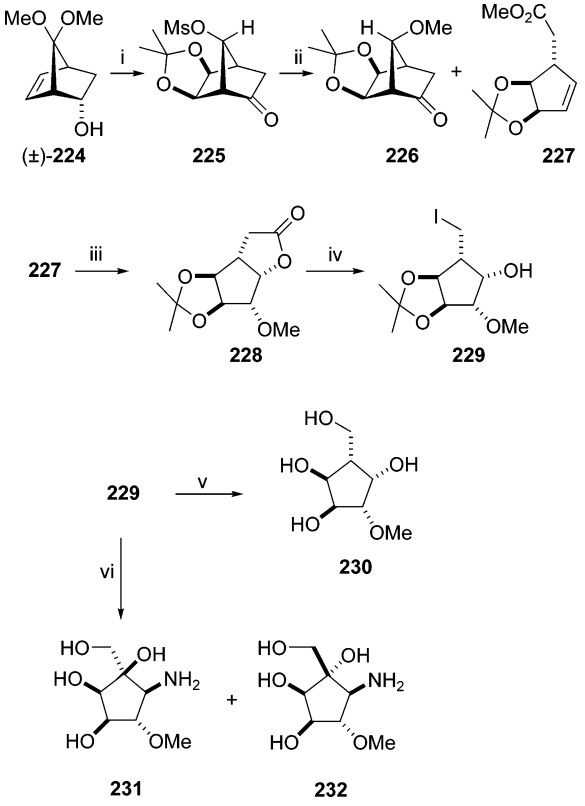
[a] Reagents: (i) MCPBA, CH_2Cl_2, 71%; (ii) (a) $NaBH_4$, MeOH; (b) Ac_2O, py 63%; (iii) DIBAL-H, THF, <25% or Red-Al, $PhCH_3$, 71%; (iv) TBSOTf, 2,6-lutidine, CH_2Cl_2, 97%; (v) (a) Red-Al, $PhCH_3$, 85%; (b) H_2O, reflux, quant; (vi) $NaBH_4$, MeOH, 50 °C, 85%; (vii) 1 M NaOH, then 1 M HCl, 62%.

mesylation, hydrolysis of the acetate, and oxidation. Exposure of **225** to NaOMe produced the fragmentation of the C_1-C_2 bond to generate the olefinic methyl ester **227** along with compound **226** (2:1 ratio), obtained by S_N2 substitution at the C_7 of the norbornyl system. Osmylation of **227** furnished lactone **228** as the major product (93:7) after methylation. The required one-carbon degradation of the lactone moiety was achieved by reduction to the hemiacetal followed by Suárez's hypervalent iodine-promoted alkoxy radical fragmentation[173] to give hydroxy-iodide **229**, which was used as the key intermediate in the syntheses of the alleged structure of salpantiol (**230**) (which turned out not to be identical to the reported salpantiol) and trehazolamine analogues **231** and **232**.

Another bicyclic starting material (bicyclo[2.2.1]hept-5-ene-2,3-dimethanol) has been used recently for the synthesis of higher homologues of carbocyclic aminocarbafuranoses.[174]

6.1.1.2. From Furan Derivatives. Casiraghi and coworkers have described a versatile procedure for the synthesis of enantiomerically pure carbafuranoses and derivatives based on the addition of furan-, pyrrole-, and thiophene-based 2-silyloxy dienes **E**, with a variety of chiral pool-derived aldehydes **F** (Figure 45).[175] Two sequential, highly diastereoselective carbon−carbon bond-forming maneuvers, i.e., a vinylogous crossed aldol addition between **E** and **F** to give **D** and an intramolecular aldolization of **C** to **B**, proved to be central for the construction of a varied repertoire of carbafuranoses and analogues. The synthetic options of this scheme are the nature of the atom X within the heterocycle **E**, the stereochemistry of aldol product **D** (1,2-*threo* or 1,2-*erythro*), and the stereochemistry of the cycloaldol construct **C** (2,3-*trans* or 2,3-*cis*).

Scheme 15. Synthesis of Trehazolamine Analogues 231 and 232 by Mehta's Group (Only One Enantiomer Is Shown)[a]



[a] Reagents: (i) (a) Ac_2O, py, DMAP, 80%; (b) OsO_4, NMMO, acetone, 89%; (c) Amberlyst-15, acetone, 70%; (d) $NaBH_4$, MeOH, 95%; 5 °C, MsCl, py, CH_2Cl_2, 91%; (ii) (a) KOH, MeOH, 88%; (b) PCC, CH_2Cl_2, 5 °C, 92%; (c) NaOMe, MeOH, 40% for **227**, 20% for **226**; (iii) (a) OsO_4, NMMO, acetone, 85%; (b) MeI, Ag_2O, molecular sieves, 93%; (iv) (a) DIBAL-H, CH_2Cl_2, −78 °C, 84%; (b) $PhI(OAc)_2$, I_2, cyclohexane, *hν*, 61%; (c) aq $NaHCO_3$, MeOH, 91%; (v) (a) Amberlyst-15, acetone, 90%; (b) NaOAc, DMF, 80 °C; (c) Ac_2O, py, 60% (two steps); (d) NH_3, MeOH, 100%; (vi) (a) MsCl, py, CH_2Cl_2, 93%; (b) DBU, CH_3CN, 90%; (c) OsO_4, NMMO, acetone, 65%; (d) NaN_3, DMF−HMPA (1:1), 110 °C, 89−96%; (e) H_2, Lindlar's catalyst, EtOH, HCl, Et_2O-H_2O, 90−95%.

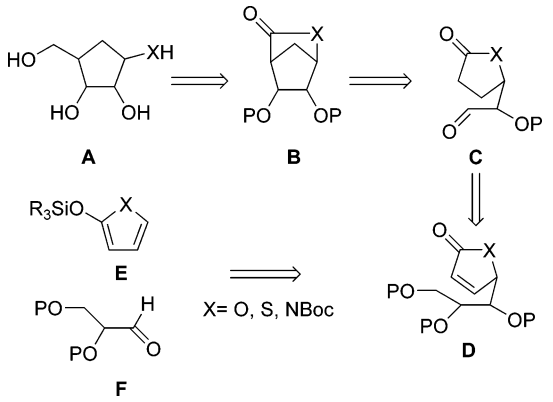
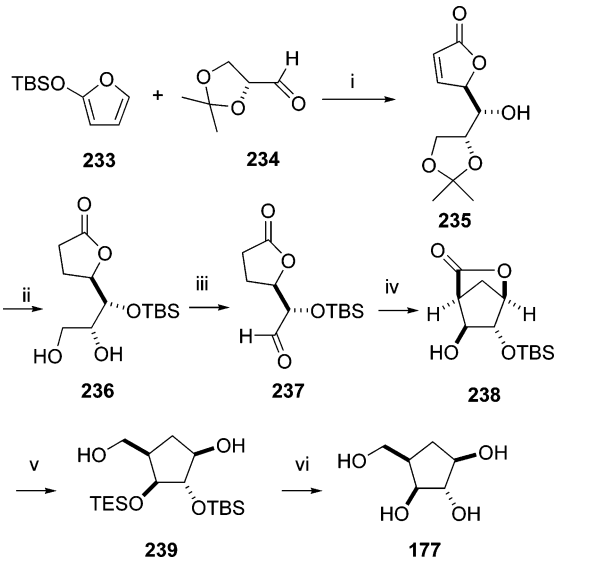


Figure 45. Casiraghi's approach to carbafuranoses.

Thus, the synthesis of 4a-carba-β-D-xylofuranose **177**[176] commenced with the boron trifluoride-assisted vinylogous aldolization between furan-based dienoxy silane **233** and 2,3-*O*-isopropylidene-D-glyceraldehyde (**234**), giving rise to a 94:6 mixture of two diastereoisomeric butenolides. The double bond of the major adduct, *syn-anti*-butenolide **235**, was hydrogenated, and the protecting groups were manipulated to give diol **236** (Scheme 16). The excision of the terminal carbon chain in **236** afforded aldehyde **237**, in which the key cycloaldolization was performed by briefly exposing

Scheme 16. Synthesis of 4a-Carba-β-D-xylofuranose (177) by Casiraghi's Group[a]



[a] Reagents: (i) BF_3Et_2O, −80 °C, 75%; (ii) (a) H_2, Pd−C, 91%; (b) aq AcOH, 50 °C, 96%; (c) TBSCl, py, imidazole, 45 °C, 70%; (iii) $NaIO_4$, 85%; (iv) LDA, THF, −80 °C, 50%; (v) (a) TESOTf, DMAP, py, 95%; (b) LAH, THF, 80−85%; (vi) aq HCl, THF, MeOH, 100%.

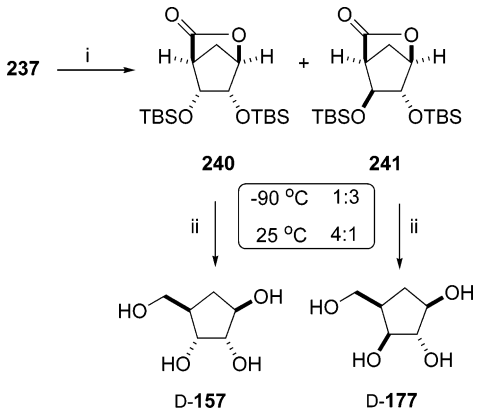
it to LDA to give diastereoselectively *cis*-bicyclic lactone **238** in 50% yield. Silylation of the free C_3-OH with TESOTf and treatment with $LiAlH_4$ gave carba-pentofuranose derivative **239**, which after silyl deprotection gave 4a-carba-β-D-xylofuranose (**177**). By adopting a nitrogen-containing dienoxy silane and following a reaction pathway which closely resembles the sequence used for **177**, the 4a-carba-β-D-xylofuranosyl amine was also synthesized.[176]

Subsequently, Casiraghi and co-workers improved the efficiency of their synthetic sequence by introducing a novel silylative cycloaldolization protocol and by adjusting a couple of minor transformations. They found that maximum efficiency in the ring-forming event was reached when an excess of the diisopropylethylamine/*tert*-butyldimethylsilyl triflate (DIPEA/TBSOTf) couple was used. Through a series of lactone/thiolactone aldehyde cyclization precursors, the authors managed to assemble four carbafuranoses and four (4a-carbafuranosyl)thiols with β-D-xylo-, β-D-ribo-, β-L-arabino, and β-L-lyxo configurations.[177]

Thus, after treatment of aldehyde **237** with an excess of the DIPEA/TBSOTf, either at −90 °C or at room temperature, the expected cycloadducts **240** and **241** were formed (Scheme 17). It is worthy of note that the temperature-dependent diastereocontrol switch allows the preparation of 2,3-*trans* adduct **241**, or its 2,3-*cis* counterpart **240**, in synthetically useful yields. In parallel, bicycloheptanoids **240** and **241** were subjected to reductive opening followed by acidic removal of the silyl protective groups to complete the synthesis of 4a-carba-β-D-xylo-furanose (D-**177**) and 4a-carba-β-D-ribofuranose (D-**157**).

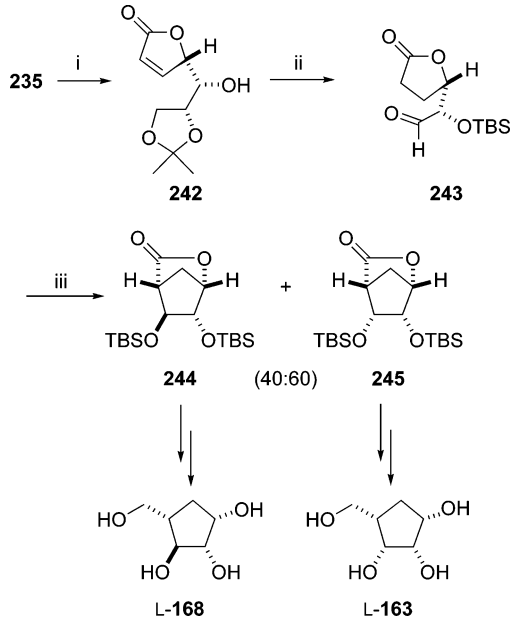
For the carbasugars of the L-series, L-**163** and L-**168**, the syntheses began with 4,5-*erythro*-configured butenolide **242**, prepared via Et_3N-promoted C_4 epimerization of *threo* derivative **235** (Scheme 18). By following their previously disclosed chemistry, reduction and silylation of the secondary hydroxyl, followed by acidic removal of the isopropylidene protection and sodium periodate oxidation, produced aldehyde **243**. Unlike the *threo*-aldehyde congener **237**, *erythro*-aldehyde **243** was reluctant to react at low temperatures, and

Scheme 17. Synthesis of 4a-Carba-β-D-xylofuranose (D-177) and 4a-Carba-β-D-ribofuranose (D-157) by Silylative Cycloaldolization[a]



[a] Reagents: (i) DIPEA, TBSOTf, CH_2Cl_2, 95−97%; (ii) (a) $LiBH_4$, THF, 80−85%; (b) aq HCl, THF, MeOH, 100%.

Scheme 18. Synthesis of 4a-Carba-β-L-arabinofuranose (L-168) and 4a-Carba-β-L-lyxofuranose (L-163) by Casiraghi's Group[a]

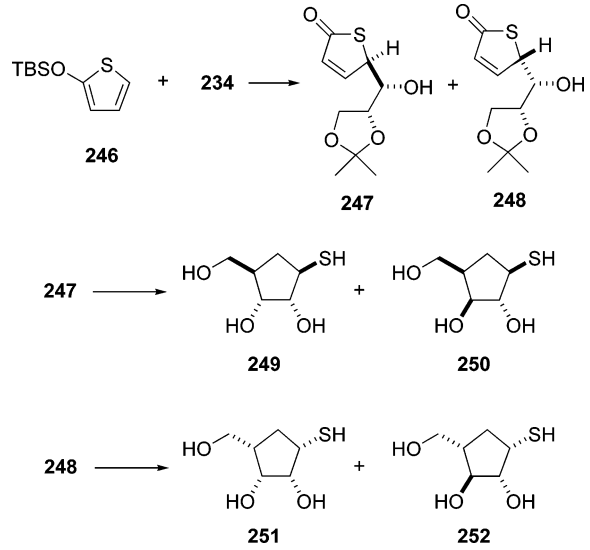


[a] Reagents: (i) Et_3N, 80%; (ii) (a) $NiCl_2$, $NaBH_4$, 83%; (b) TBSOTf; (c) aq AcOH; (d) $NaIO_4$, 72% overall; (iii) DIPEA, TBSOTf, 100%.

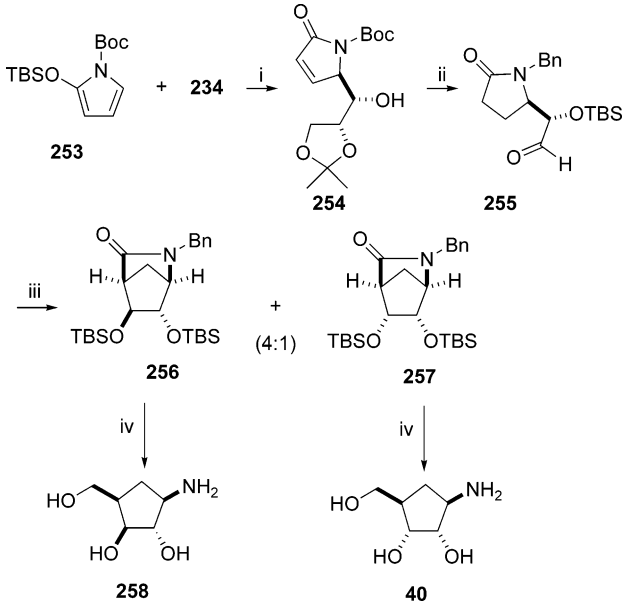
the DIPEA/TBSOTF-assisted cycloaldolization could only be performed at room temperature. In this case, a separable 40:60 mixture of **244** and **245** was obtained from which the desired 4a-carba-β-L-arabinofuranose (L-**168**) and 4a-carba-β-L-lyxofuranose (L-**163**) could be synthesized in 70% and 65% yield, respectively.

Having completed the synthesis of representatives of the 4a-carbafuranose family, Casiraghi and co-workers further illustrated the synthetic possibilities of this protocol with the preparation of structurally diverse carbafuranose entities. Following the same reaction sequence, but using 2-silyloxythiophene (**246**) (Scheme 18)[175] or 2-silyloxypyrrol (**253**)[178] (Scheme 19), they reported the synthesis of carbafuranosyl thiols (Scheme 20) [e.g., (4a-carba-β-D-ribofuranosyl)thiol (**249**), (4a-carba-β-D-xylofuranosyl)thiol (**250**), (4a-carba-β-L-lyxofuranosyl)thiol (**251**), and (4a-carba-β-L-arabinofuranosyl)thiol (**252**)] and carbafuranosyl amines [e.g., (4a-carba-β-D-xylofuranosyl)amine (**258**) and (4a-carba-β-D-ribofuranosyl)amine (**40**). They also reported the synthesis of C(2)-branched (methyl) 4a-carbafuranoses.[179]

Scheme 19. Synthesis of Carbafuranosyl Thiols by Casiraghi's Group



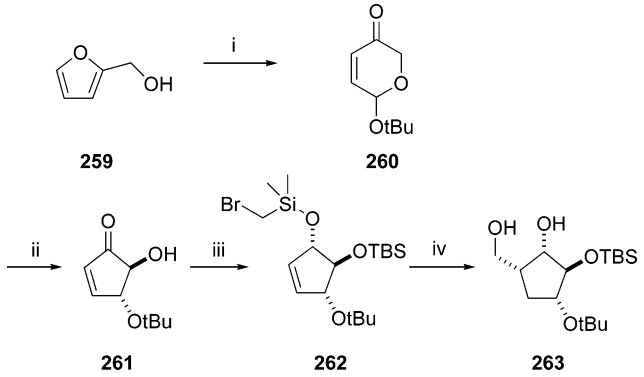
Scheme 20. Synthesis of Carbafuranosyl Amines by Casiraghi's Group[a]



[a] Reagents: (i) $SnCl_4$, −80 °C, 80%; (ii) (a) H_2, Pd−C, 92%; (b) TBSOTf, 92%; (c) aq AcOH, 90%; (d) $NaIO_4$, 95%; (iii) (a) LDA, THF, −80 °C, 52%; (b) TESOTf, 94%; (iv) (a) $NaBH_4$, 86%; (b) aq HCl, 94%.

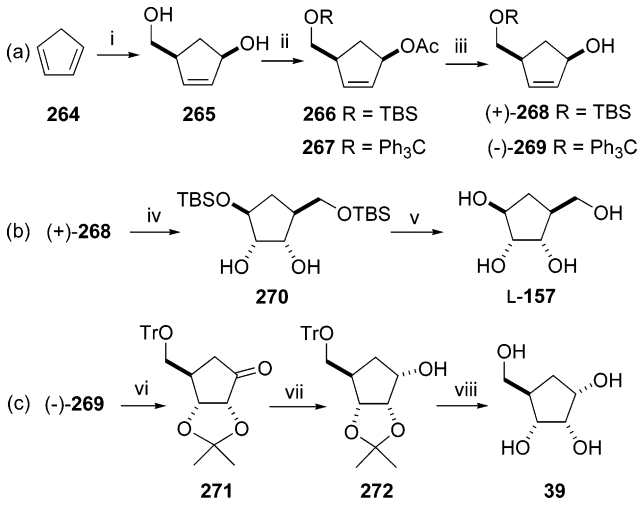
6.1.1.3. From Cyclopentadiene and Derivatives. Cyclopentadiene has also been a valuable starting material for the

Scheme 21. Synthesis of 4a-Carba-β-DL-xylofuranose Derivative 263, by Caddick's Group[a]



[a] Reagents: (i) (a) NBS or MCPBA; (b) Ac_2O, NaOAc, 57%; (c) $SnCl_4$, t-BuOH, 89%; (ii) Et_3N, MeOH, 76%; (iii) (a) TBSCl; (b) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 80%; (c) $BrCH_2SiMe_2Cl$, CH_2Cl_2, 0 °C, i-Pr_2NH, 64%; (iv) (a) n-Bu_3SnH, AIBN; (b) KF, K_2CO_3, MeOH, H_2O_2, 76%.

Scheme 22. Synthesis of 4a-Carba-β-L-ribofuranose (L-157) and 4a-Carba-α-D-ribofuranose (39) by Roberts's Group[a]

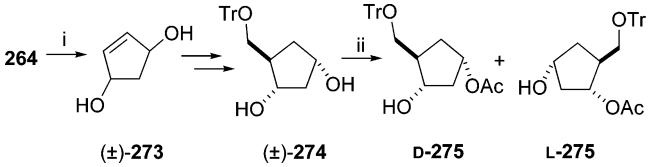


[a] Reagents: (i) HCHO, HCOOH; (ii) (a) TBSCl or TrCl; (b) Ac_2O; (iii) *Pseudomonas fluorescens* lipase, (+)-**268** (42%, >95% ee), (−)-**269** (46%, 95.5% ee); (iv) (a) TBSCl; (b) OsO_4, NMMO; (v) (a) TBAF; (b) Ac_2O, 99%; (c) NaOMe, 90%; (vi) (a) Ac_2O; (b) OsO_4, NMMO; (c) 2,2-dimethoxypropane; (d) NaOMe; (e) PCC; (vii) $NaBH_4$; (viii) (a) aq AcOH; (b) Amberlyst (H^+).

preparation of 4a-carbafuranoses and derivatives. It is a low-cost compound with the required carbocyclic structure. On the other hand, as a drawback, its transformation to optically pure compounds requires the use of classical resolution processes or asymmetric bond-forming reactions.

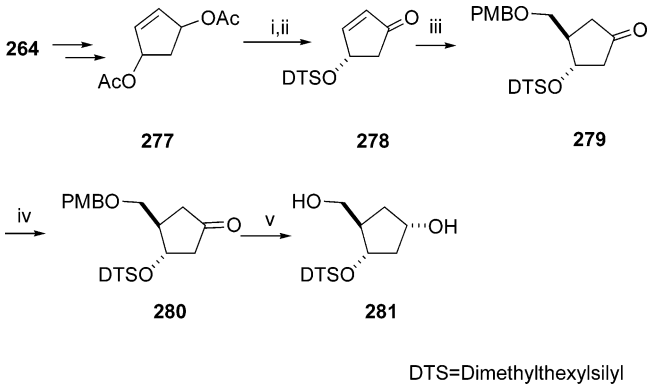
In 1992, Roberts and co-workers[182] reported a novel synthesis of 4a-carba-α-D-ribofuranose (**39**) in high optical purity (Scheme 22). They used an enzyme-catalyzed esterification reaction to obtain a suitable chiral synthon from cyclopentadiene **264**. Treatment of **264** with formaldehyde in formic acid (Prins reaction) furnished racemic diol (±)-**265**,[183] in which the primary hydroxyl group was later protected as a trityl or *tert*-butyldimethylsilyl (TBS) ether and the secondary hydroxyl group was protected as an acetate. From these compounds, cyclopentenols (+)-**266** and (−)-**267** were obtained using an enzyme-catalyzed reaction. Furthermore, the alcohol (+)-**268** was converted into a bis-*tert*-butyldimethylsilyl derivative and oxidized with osmium tetroxide to give diol **270**. Deprotection, acetylation, and saponification gave 4a-carba-β-L-ribofuranose (L-**157**). In an analogous way, tritylated alcohol (−)-**269** was acetylated, bis-hydroxylated, and converted into ketone **271**. Reduction of the keto group permitted the overall inversion at C_1 to **272**, which, after deprotection, led to the desired 4a-carba-α-D-ribofuranose (D-**39**).

Scheme 23. Synthesis of 2-Deoxy-4a-carba-α-D-ribofuranose Derivative 275 by Moser's Group[a]



[a] Reagents: (i) *hν*, rose bengal, thiourea, MeOH, 59%; (ii) CVL, 49% for D-**275**, 26% for L-**275**.

Scheme 24. Synthesis of 2-Deoxy-4a-carba-α-D-ribofuranose Derivative 281 by Borthwick's Group[a]



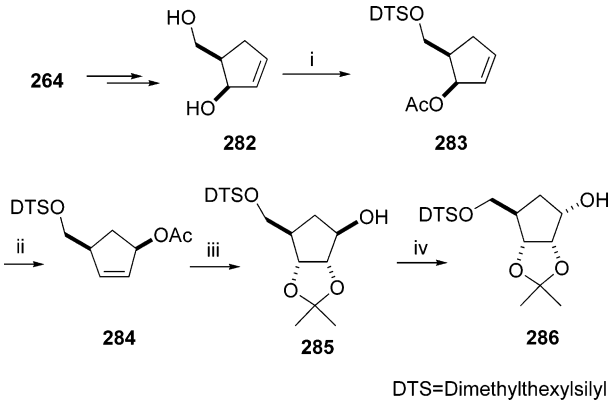
[a] Reagents: (i) (a) Baker's yeast; (b) MnO_2, petroleum ether−dioxane; (c) wheat germ lipase, 24%, three steps; (ii) DTSCl, Et_3N, DMAP; (iii) (2-Th)($PMBOCH_2$)$CuCNLi_2$, TMSCl, THF, −78 °C, 69%; (iv) DDQ, CH_2Cl_2, 86%; (v) $NaBH(OAc)_3$, EtOAc, reflux, 75%.

Moser and co-workers[184] developed a related enzyme-catalyzed acetylation for the synthesis of a carbocyclic 2-deoxyribose derivative (Scheme 23). The trityl-protected precursor (±)-**274**, readily available from cyclopentadiene via 1,4-addition of singlet oxygen,[185] hydroformylation, reduction, and tritylation, was subjected to enzymatic acyl transfer with *Chromobacterium viscosum* lipase, to give 2-deoxy-α-D-ribocarbafuranose derivative **275**, with high enantioselectivity.

In their route to chiral carbocyclic ribonucleosides, Borthwick and co-workers[186] used chiral cyclopentenone **278**, easily prepared[187] in enantiomerically pure form from cyclopentadiene **264**, as the starting material (Scheme 24). 1,4-Addition of a one-carbon fragment to **278**, followed by stereoselective reduction with triacetoxyborohydride paved the way to the 2-deoxyribocarbafuranose derivative **281**. The latter was also used in the preparation of two chiral antiviral agents.[186b]

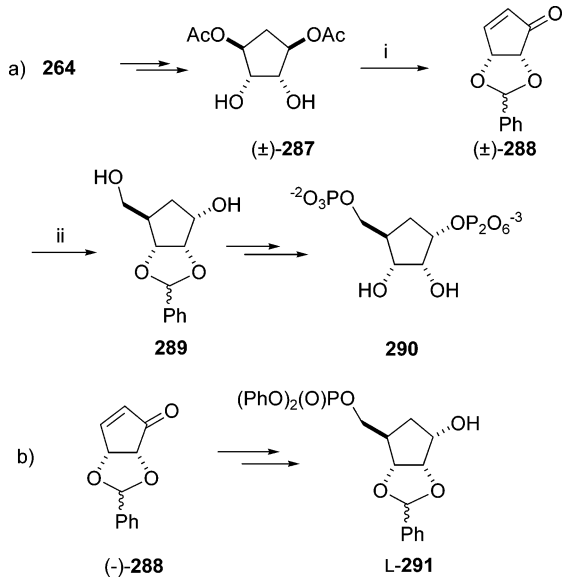
More recently, Shuto, Matsuda, and co-workers[188] have developed a related approach also starting from cyclopentadiene **264** (Scheme 25). They used an optically active diol, **282**, prepared by resolution with *Pseudomonas fluorescens* lipase, as starting material.[189] Protection of its hydroxyl groups led to **283**, which was submitted to an allylic rearrangement to generate compound **284**. Stereoselective *cis*-hydroxylation of the latter, followed by protection and deprotection steps, furnished alcohol **285**. Finally, an oxidation−reduction sequence at C_1−OH in **285** yielded the sought 4a-carba-α-D-ribofuranose derivative **286**. The latter was then used in the synthesis of a cyclic nucleotide.

Scheme 25. Synthesis of 4a-Carba-α-D-ribofuranose Derivative 286 by Shuto's Group[a]



[a] Reagents: (i) (a) DTSCl, Et_3N, DMAP; (b) Ac_2O, Et_3N, 69%; (ii) $PdCl_2(MeCN)_2$, *p*-benzoquinone, 60%; (iii) (a) OsO_4, NMMO, 55%; (b) 2,2-dimethoxypropane, TsOH; (c) K_2CO_3, MeOH; (iv) (a) PDC, 92%; (b) $NaBH_4$, 88%.

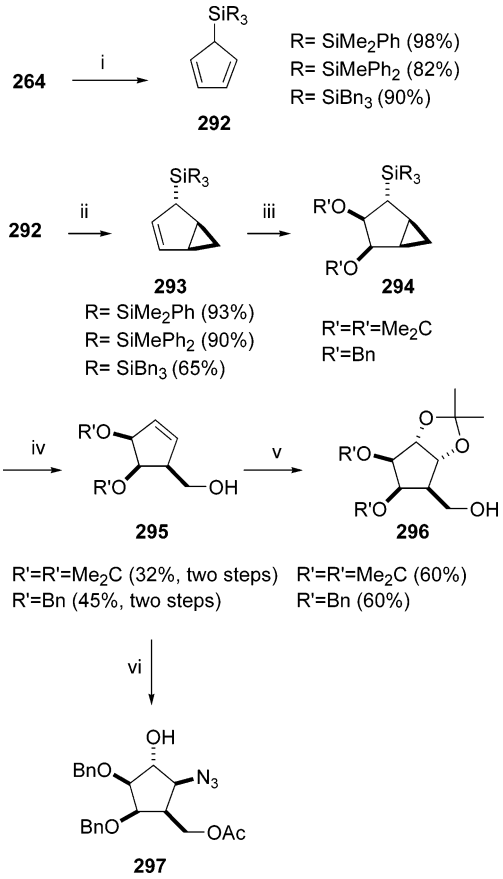
Scheme 26. Synthesis of 5-Phospho-1-pyrophosphate Derivatives by Parry's Group (When Racemic, Only the D-Enantiomer Is Shown)[a]



[a] Reagents: (i) (a) $PhCH(OMe)_2$, TsOH, CH_2Cl_2, −15 to 0 °C; (b) KOH, MeOH, DCC, DMSO, TFA, py; (ii) (a) Ph_2CO, MeOH, *hν*, 350 nm; (b) $NaBH(OAc)_3$, PhH.

In their earlier investigations on the biosynthesis of the carbocyclic nucleosides, Parry and co-workers[190] prepared 5-phospho-1-pyrophosphate derivatives of 4a-carba-α-ribofuranose (**290**) as interesting compounds for mechanistic and inhibitory studies (Scheme 25). The synthesis was initially carried out starting from racemic diacetoxydiol (±)-**287** (Scheme 26a), which in turn was prepared from cyclopentadiene (**264**) through a three-step sequence developed by Johnson and co-workers which included addition of singlet oxygen, *in situ* reduction of the adduct, acetylation, and *cis*-hydroxylation.[191] Diol (±)-**287** was then converted into *O*-benzylidene cyclopentenone (**288**). Photochemical addition of methanol to **288** and reduction, using sodium triacetoxyborohydride, gave the protected form of 4a-carba-α-DL-ribofuranose [(±)-**290**]. Use of (−)-**288** (Scheme 26b), obtained by optical resolution of the racemate,[192] allowed the preparation of enantiomerically pure 4a-carba-α-D-ribofuranose derivative **291**.

Scheme 27. Synthesis of Carbafuranoses by Landais and Parra-Rapado (Only D-Enantiomers Are Shown)[a]

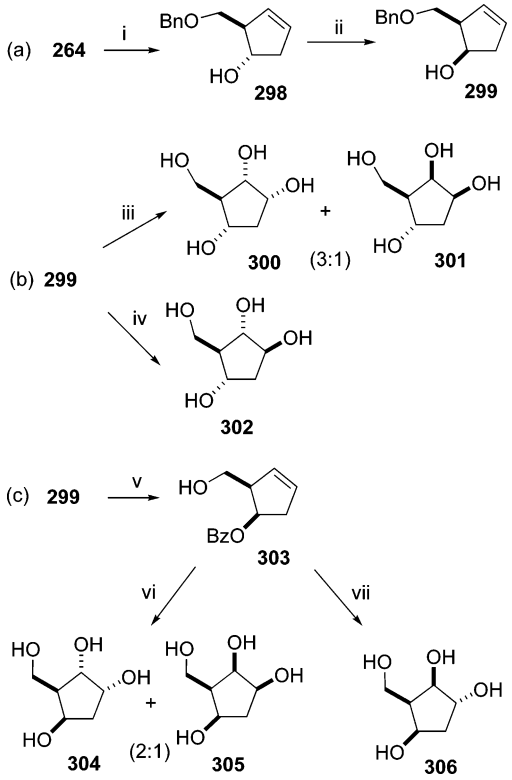


[a] Reagents: (i) (a) n-BuLi; (b) R_3SiCl; (ii) Et_2Zn, CH_2I_2, CH_2Cl_2, 65−93%; (iii) (a) OsO_4, NMMO; (b) 2,2-dimethoxypropane, TsOH or NaH, BnBr; (iv) (a) $Hg(NO_3)_2$, DME-CH_3CN; (b) aq KBr; (c) $NaBH_4$, DMF, O_2, 32−45%; (v) (a) OsO_4, NMMO; (b) 2,2-dimethoxypropane, TsOH, 60%; (vi) (a) MCPBA, 90%; (b) Ac_2O, py; (c) NaN_3, DMF, reflux, 40%.

Methodology based on cyclopentadienylsilane derivatives has been developed for the stereocontrolled synthesis of carbafuranoses by Landais and Parra-Rapado (Scheme 27).[193] Their route involves a mercury desilylation of cyclopropylmethylsilanes used as precursors of the carbasugar backbone. Cyclopentadienylsilanes **292**, prepared through lithiation and silylation of cyclopentadiene **264**, were subjected to the Furukawa conditions for cyclopropanation,[194] leading exclusively to the *anti* isomers **293**. The remaining double bond was dihydroxylated using either Sharpless conditions or the usual OsO_4−NMO protocol with variable levels of diastereoselection depending on the steric bulk at silicon. The mercury-induced desilylation of the cyclopropanes **294** using Collum's conditions[195] yielded the corresponding mercury intermediates, which were converted into the alcohols **295** using $NaBH_4$ under a saturated oxygen atmosphere. Finally, *cis*-dihydroxylation and protection gave the racemic carbafuranose analogue derivative **296** as a unique diastereomer. This approach also permits the introduction of heteroatoms in the ring, as is illustrated with the conversion of **291** into (±)-**297**.

Jorgensen and co-workers[196] have described the preparation of six optically active carbocyclic furanose derivatives from cyclopentadiene (**264**) and using an enantioselective hydroboration reaction as the key step, by which the first two stereogenic centers were introduced (Scheme 28a). The newly formed stereocenters are used to guide the formation of the remaining stereogenic centers in the carbocyclic

Scheme 28. Synthesis of Carbafuranose Derivatives by Jorgensen's Group[a]



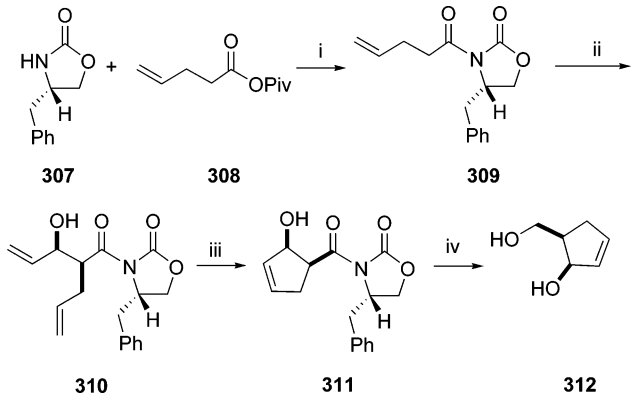
[a] Reagents: (i) (a) $BnOCH_2Cl$, NaH; (b) Ipc_2BH; (c) H_2O_2, 94% ee; (ii) (a) Ph_3P, BzOH, DEAD; (b) NaOH, MeOH; (iii) (a) NaH, BnBr, 95%; (b) OsO_4, NMMO, 70%; H_2, Pd−C, 59−62%; (iv) (a) t-BuOOH, $Mo(CO)_6$, 95%; (b) $HClO_4$, 95%; H_2, Pd/C, quant; (v) (a) PPh_3, BzOH, DEAD, 85%; (b) $FeCl_3$, 88%; (vi) (a) NaOH, 99%; (b) $Me_2C(OMe)_2$, 99%; (c) OsO_4, NMMO, 94%; (vii) (a) t-BuOOH, $Mo(CO)_6$, 96%; (b) $HClO_4$, 94%; H_2, Pd−C, quant.

skeleton. Cyclopentadiene (**264**) was deprotonated and treated with benzyl chloromethyl ether and then hydroborated with diisopinocamphenylborane.[197] Oxidative workup of the organoborane gave alcohol **298** (94% ee), which was then converted into alcohol **299** by inversion of the secondary hydroxyl by the Mitsunobu protocol. The six carbasugar analogues **300**−**302** (Scheme 28b) and **303**−**306** (Scheme 28c) were then prepared from these precursors by either osmylation or epoxidation/opening sequences.

6.1.1.4. Miscellaneous. A general and efficient synthesis of carbocyclic nucleosides has been developed by Crimmins and co-workers.[198] The strategy combines an asymmetric aldol addition, to establish the relative and absolute configuration of the pseudosugar, and a ring-closing metathesis, to construct the carbasugar ring. Thus, condensation of the lithiated (*S*)-4-benzyl-2-oxazolidinone (**307**) with the pentenoic pivalic mixed anhydride **308** provided the pentenoyloxazolidinone **309** in near-quantitative yield (Scheme 29). Use of the Evans' dialkylboron triflate protocol,[199] for diastereoselective *syn* aldol condensation, with acrolein produced the aldol product **310** in 82% yield (>99% de). The critical ring-closing metathesis was then accomplished in 97% yield by exposure of diene **310** to Grubbs' catalyst **523** to form the cyclopentenol **311**. The chiral auxiliary was reductively removed with lithium borohydride to provide the desired diol **312**.

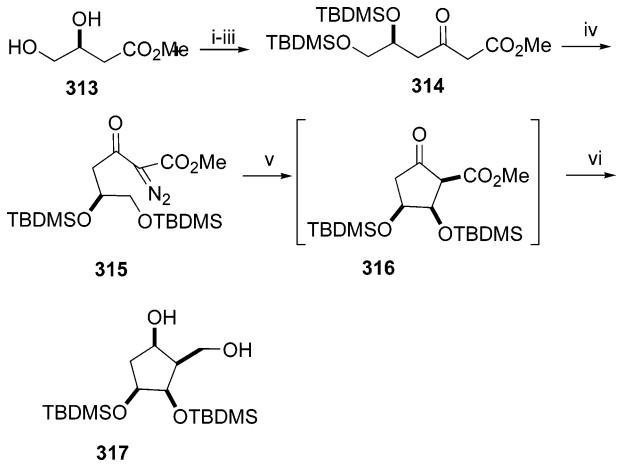
Studies involving CH-insertion processes have been carried out by Yakura, Ikeda, and co-workers in order to develop a new route to cyclopentitols (Scheme 30).[200] Treatment of

Scheme 29. Synthesis of 1,2-Dideoxycarbafuranose (312) by Crimmins' Group[a]



[a] Reagents: (i) n-BuLi, THF, −78 °C, 99%; (ii) Bu_2BOTf, Et_3N, CH_2Cl_2, acrolein, −78 °C, 82%; (iii) Grubbs' catalyst, CH_2Cl_2, 97%; (iv) $LiBH_4$, THF, MeOH, 78%.

Scheme 30. Synthesis of Cyclopentenemethanol (317) by a CH-Insertion Reaction[a]



[a] Reagents: (i) TBSCl, imidazole, DMF, 16 h (quant); (ii) DIBAL-H, CH_2Cl_2, −78 °C, 97%; (iii) N_2CHCO_2Me, $SnCl_2$, CH_2Cl_2, 0 °C, 97%; (iv) TsN_3, Et_3N, CH_3CN, 97%; (v) $Rh_2(OAc)_4$, CH_2Cl_2, reflux, LAH, Et_2O, 52% two steps.

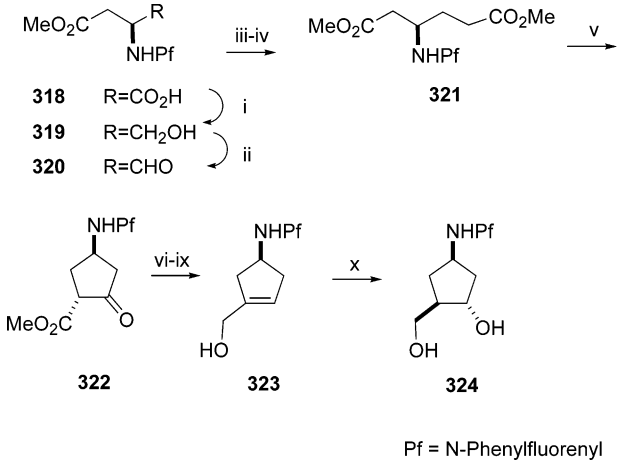
α-diazo-β-ketoester **315**, prepared from methyl (*S*)-3,4-dihydroxybutanoate (**313**), with dirhodium(II) tetraacetate gave the CH-insertion product **316**, which was stereoselectively reduced with lithium aluminum hydride to give cyclopentanemethanol **317**.

Rapoport and co-workers[201] developed a stereoselective synthesis of an aminocarbasugar using an L-aminoacid as the starting material (Scheme 31). Thus, the stereocenter in L-aspartic acid gives rise to the desired amine configuration in the sugar mimic and, in turn, controls the remaining stereocenters of the final target. Aldehyde **320** was prepared in a two-step sequence including borane reduction and Swern oxidation. Homologation to diester **321** and ring formation by regioselective Dieckman cyclization, followed by reduction and dehydration steps, afford the 4-amino-1-cyclopentenemethanol derivative **323**. Hydroboration and oxidation on the latter led stereospecifically to protected aminocyclopentanol **324**, the key aminocyclitol component of carbapentostatin.

6.1.2. Synthesis from Carbohydrate Precursors

It is clear that the use of carbohydrates provides important advantages for the preparation of their carbocyclic analogues.

Scheme 31. Synthesis of Aminocyclopentanol (324) by Rapoport and Co-workers[a]



[a] Reagents: (i) BH_3, THF, 0 °C; (ii) DMSO, $(COCl)_2$, 61% two steps; (iii) $Me_2O_3PCH_2CO_2Me$, NaH, THF, −40 °C, 92%; (iv) H_2, Pt/C, MeOH, EtOAc, 93%; (v) lithium 2,2,6,6-tetramethylpiperidine, −78 °C; (vi) $NaBH_4$, MeOH, THF, 88%; (vii) MsCl, py, THF, 0 °C; (viii) t-BuOK, THF, 0 °C, 69%; (ix) LAH, THF, 93%; (x) 9-BBN, THF, then 30% H_2O_2, 1 M NaOH, 90%.

On the one hand, the hydroxyl groups can be maintained throughout the synthetic sequence, with no need for "hydroxylation" reactions whereas the enantiomeric purity of the target carbasugars will be guaranteed. The challenge in these types of approaches rests on two main features: (a) an homologation step is required, because the carbasugar contains one more carbon atom than the parent carbohydrate, and (b) a cyclization reaction needs to be carried out at some point in the synthesis. The methods for the preparation of carbasugars from carbohydrates described in this section have been classified according to the type of ring-closing reaction.

6.1.2.1. Carbanion-Mediated Cyclizations. Most methods for the preparation of carbapentofuranoses from carbohydrate derivatives have involved intramolecular nucleophilic attack of simple carbanions to aldehyde or ketone groups as the key step. The carbanions can be adjacent either to phosporous atoms or to carbonyl or nitro groups.

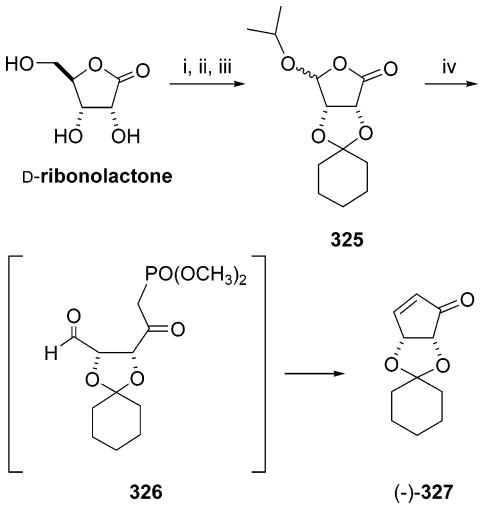
6.1.2.1.1. Cyclization of Phosphorus-Stabilized Carbanions. Aldol-like cyclization of carbanions, which are stabilized by both phosphonate and carbonyl neighboring groups, have been of particular value in the synthesis of carbapentofuranoses from carbohydrates. In this context, Borchardt et al. identified 2-cyclopentenones, e.g., **327**, as useful intermediates for the synthesis of carbasugars and carbocyclic nucleosides (Scheme 32).[202] In their initial work, they prepared chiral 2-cyclopentenone **327** from O2−O3-protected D-ribono-γ-lactone. The synthetic sequence involved (a) periodate oxidation of D-ribonolactone to yield acetal lactones **325** and (b) treatment of the latter with lithium dimethyl methylphosphonate to give an intermediate aldehydo ketophosphonate **326**, which underwent a base-promoted aldol cyclization leading to cyclopentenone **327**.

Alternatively, they prepared enantiomeric enone (+)-**327** from D-mannose via the optical antipode acetal lactones (+)-**325**, readily obtained from dicyclohexylidene mannonolactone **328** (Scheme 33).

More recently, the same group has reported the stereoselective syntheses of enone **330** and its enantiomer (−)-**330** from acetal lactones **329** and **331**, by improved three-step syntheses from D-lyxose and D-ribose, respectively (Scheme 34). The overall yields for the preparation of enones (+)-**330** and (−)-**330** are 41 and 42%, respectively.[203]

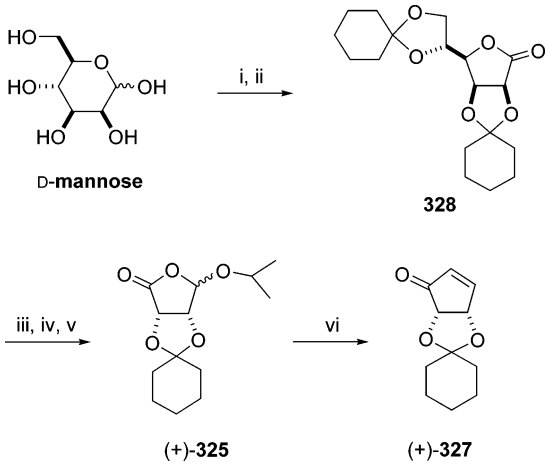
Enone **332** has been stereoselectively transformed into 4a-carba-α-D-ribofuranose derivative **334** (Scheme 35) by addition of lithium di(*tert*-butoxymethylene)cuprate followed by reduction with diisobutylaluminum hydride of the ketone **333**. The origin of the stereoselectivity in both steps is

Scheme 32. Synthesis of (−)-Dihydroxycyclopentenone (327)[a]



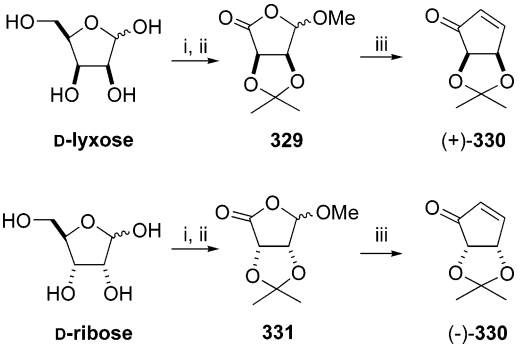
[a] Reagents: (i) cyclohexanone, $FeCl_3$; (ii) H_2O, NaOH, $NaIO_4$, 85% overall; (iii) 2-propanol, pyridinium *p*-toluenesulfonate (PPTS), 1.5 h, Δ, 95%; (iv) $CH_3PO(OCH_3)_2$, n-BuLi, −78 to 20 °C, 80%.

Scheme 33. Synthesis of (+)-Dihydroxycyclopentenone 327[a]



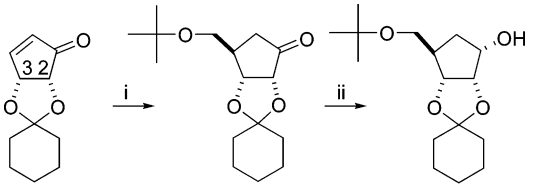
[a] Reagents: (i) cyclohexanone, H_2SO_4; (ii) Collins' reagent, 75% overall; (iii) Dowex 50W, H_2O; (iv) H_2O, NaOH, $NaIO_4$; (v) 2-propanol, PPTS, Δ; 78% from **328**; (vi) $CH_3PO(OCH_3)_2$, n-BuLi, −78 to 20 °C, 76%.

Scheme 34. Synthesis of Dihydroxycyclopentenone 330[a]



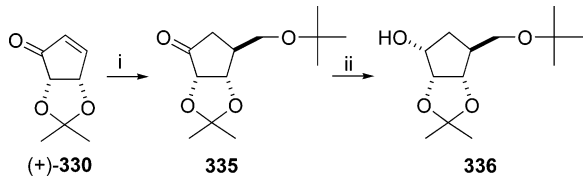
[a] Reagents: (i) dimethoxypropane, MeOH, $HClO_4$; (ii) PCC; (iii) $CH_3PO(OCH_3)_2$, n-BuLi.

Scheme 35. Synthesis of 4a-Carba-α-D-ribofuranose Derivative 334 from Enone 332[a]



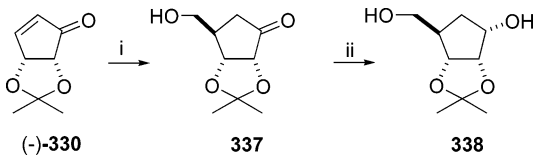
[a] Reagents: (i) $[(CH_3)_3COCH_2]_2CuLi$, −78 to −30 °C, 81%; (ii) DIBAL-H, 0 °C, 96%.

Scheme 36. Synthesis of 4a-Carba-α-L-ribofuranose (336) from Enone [(+)-330][a]



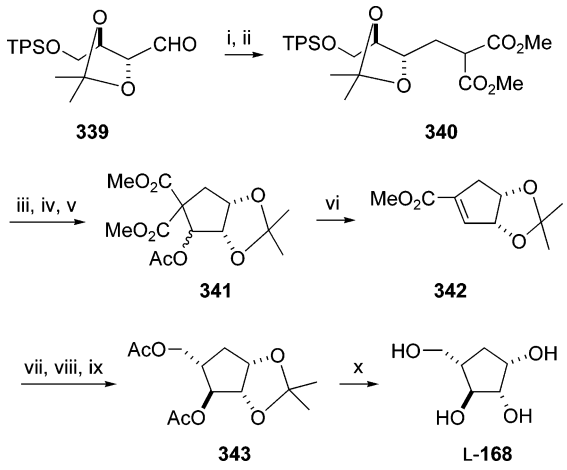
[a] Reagents: (i) $[(CH_3)_3COCH_2]_2CuLi$, t-BuOMe, −30 °C, 81%; (ii) DIBAL-H, −78 °C, 96%.

Scheme 37. Synthesis of 4a-Carba-α-D-ribofuranose (338) from Enone [(−)-330][a]



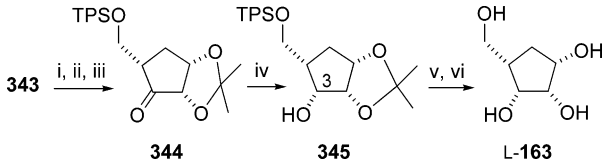
[a] Reagents: (i) *hν*, CH_3OH, benzophenone, 80%; (ii) $NaBH(OAc)_3$, 71%.

Scheme 38. Synthesis of 4a-Carba-β-L-arabinofuranose (L-168)[a]



[a] Reagents: (i) dimethyl malonate, py, Ac_2O, 85%; (ii) $NaBH_4$, 71%; (iii) TBAF, 51%; (iv) PCC; (v) Ac_2O, py, 71%; (vi) Me_2SO, H_2O, NaCl, 170 °C; (vii) DIBAL-H, −78 °C, 61%; (viii) BH_3, then H_2O_2, NaOH; (ix) Ac_2O, py; (x) AcOH, reflux.

Scheme 39. Synthesis of 4a-Carba-β-L-lyxofuranose (L-163)[a]



[a] Reagents: (i) NaOMe; (ii) imidazole, *tert*-butyldiphenylsilyl chloride (TPSCl), 91% from **343**; (iii) PCC; (iv) $NaBH_4$, 80% overall; (v) TBAF; (vi) AcOH, 95%.

associated with the presence of the 2,3-*O*-cyclohexylidene ring, which shields the α-face of the molecule.[204] Chu et al.[205] utilized a similar reaction sequence for the preparation of the carba α-L-ribofuranose derivative **336** starting from enone (+)-**320** (Scheme 36).

Finally, Parry et al. converted enone (−)-**330** to D-ribose-5-phosphate analogues (Scheme 37).[74a] The key step in their synthesis was the stereoselective photochemical 1,4-addition of methanol to the convex face of the enone to furnish hydroxyketone **337** (Scheme 37). The use of substrate-guided chelation-controlled hydride reduction of **337**, by reaction with triacetoxyborohydride, then produced the diol **338** with an α-configuration at C_1.[206]

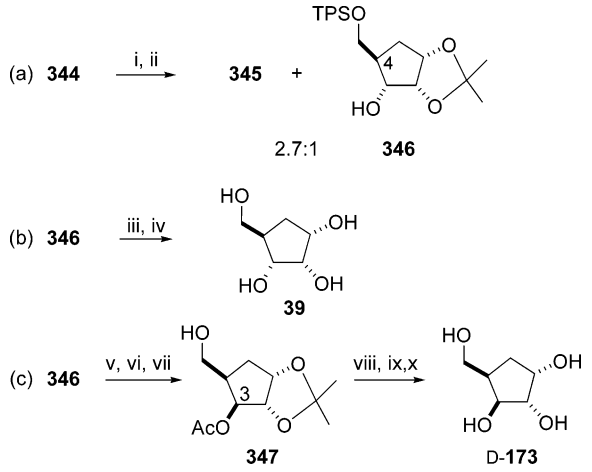
6.1.2.1.2. Cyclization of Carbonyl-Stabilized Carbanions. Studies involving intramolecular aldol condensation for the syntheses of carbapentofuranoses from sugars have been extensively considered. In this approach, the key ring-closing C−C bond formation takes place by addition of a carbanion into a suitably activated carbonyl group.

Tadano et al.[207] effected a chain elongation of the open-chain aldehydo-sugar **339** by Knoevenagel condensation with dimethyl malonate followed by reduction of the resulting unsaturated diesters (Scheme 38). Accordingly, D-erythrose derivative **339** was transformed into the saturated diester **340** by way of Knoevenagel condensation and $NaBH_4$ reduction. Deprotection of the primary alcohol in the latter followed by pyridinium chlorochromate (PCC) oxidation gave an intermediate aldehyde which cyclized spontaneously under the reaction conditions to yield, after acetylation, a 4:1 mixture of diastereomers **341**. Thermal demethoxycarbonylation of the mixture was accompanied by β-elimination and provided cyclopentene **342**. The latter was eventually transformed into a carbafuranose derivative **343**, by sequential reduction with diisobutylaluminum hydride and stereoselective hydroboration followed by oxidative workup. Final deprotection of **343** led to 4a-carba-β-L-arabinofuranose (L-**168**) (Scheme 38).

Alternatively, inversion of the configuration at the C_3−OH in compound **343**, by oxidation to ketone **344** and sodium borohydride reduction, provided alcohol **345**, which after deprotection led to 4a-carba-β-L-lyxofuranose (L-**163**) (Scheme 39). Silica gel treatment of ketone **344** promoted epimerization at C_4 and, upon sodium borohydride reduction of the ketone moiety, resulted in the formation of **345**[208] (Scheme 40a). Deprotection of compound **346** led to 4a-carba-α-D-ribofuranose (**39**) (Scheme 40b). Inversion of the configuration at the C_3−OH in compound **346**, via a S_N2 reaction of the corresponding 3-*O*-methanesulfonate followed by deprotection, paved the way to 4a-carba-α-D-xylofuranose (D-**173**) (Scheme 40c).

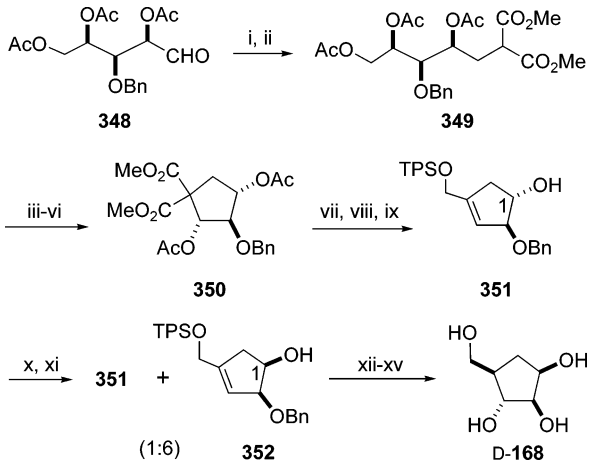
In a second set of experiments, 4a-carba-β-D-arabinofuranose (D-**168**) was synthesized from D-xylose[209] (Scheme 41). The chain-extended compound **349** was built by Knoevenagel condensation of 2,4,5-tri-*O*-acetyl-3-*O*-benzyl-D-xylose (**348**) with dimethyl malonate followed by borohydride reduction. *O*-Deacylation, glycol cleavage, and acetylation gave the highly oxygenated cyclopentane dicarboxylate **350** in 59% yield. The key intermediate **350** was subjected to thermal demethoxycarbonylation, which proceeded smoothly with β-elimination, and reduction of the remaining methoxy carbonyl group with diisobutylaluminum hydride followed by regioselective silylation of the primary hydroxyl group to give compound **351**. Inversion of the configuration at C_1−OH via the corresponding ketone led, mainly, to **352**.

Scheme 40. Synthesis of 4a-Carba-α-D-ribofuranose (39) and 4a-Carba-α-D-xylofuranose (D-173)[a]



[a] Reagents: (i) SiO_2, CH_2Cl_2; (ii) $NaBH_4$, 80%; (iii) TBAF; (iv) AcOH, 91% from **346**; (v) MsCl, py, 96%; (vi) TBAF, 97%; (vii) NaOAc, DMF, reflux; (viii) AcOH; (ix) Ac_2O, py, 50% overall; (x) NaOMe, 95%.

Scheme 41. Synthesis of 4a-Carba-β-D-arabinofuranose (D-168)[a]

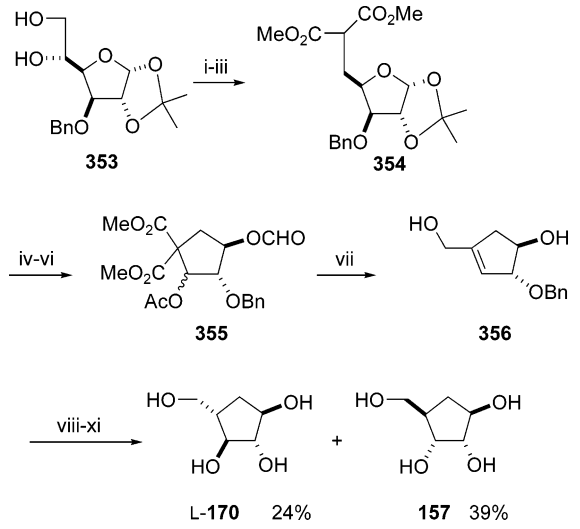


[a] Reagents: (i) dimethyl malonate, py, Ac_2O, 85%; (ii) $NaBH_4$, 62%; (iii) NaOMe; (iv) $NaIO_4$; (v) Amberlite IR-120, MeOH; (vi) Ac_2O, py, 59% from **349**; (vii) Me_2SO, H_2O, NaCl, 170 °C; (viii) DIBAL-H, −78 °C, 75% from **350**; (ix) TPSCl, imidazole, 73%; (x) PCC; (xi) $NaBH_4$, MeOH, 74%; (xii) TBAF, 90%; (xiii) BH_3, then H_2O_2, NaOH; (xiv) H_2, $Pd(OH)_2$, Ac_2O, py; (xv) AcOH, reflux, 64% from **352**.

Hydroboration of the latter, followed by oxidative workup and deprotection of the hydroxyl groups, gave the target 4a-carba-β-D-arabinofuranose (D-**168**).

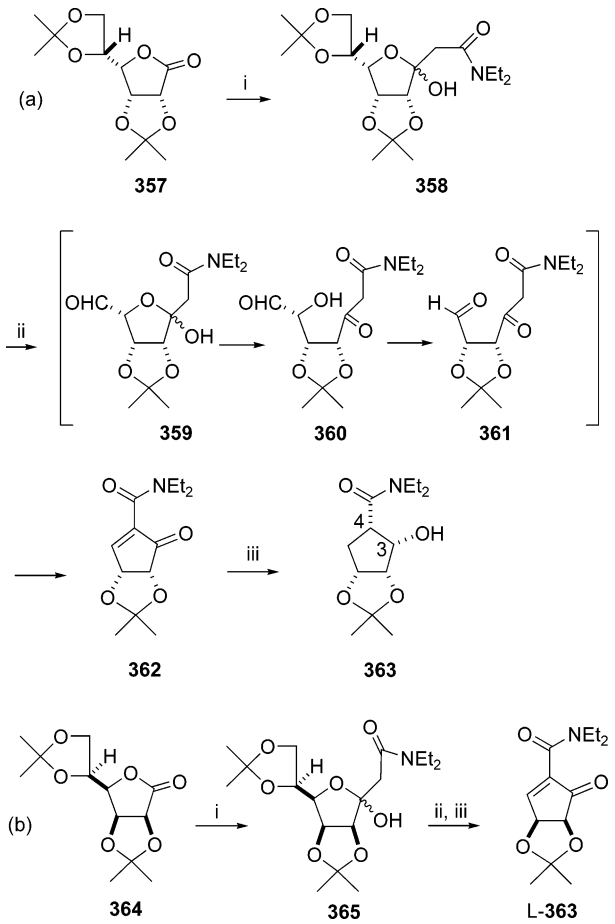
Tadano and co-workers[210] described an additional approach to carba-α-L-arabinofuranose (L-**170**) and carba-β-D-ribofuranose (D-**157**) from D-glucose derivative **353** (Scheme 42). Thus, glycol cleavage followed by successive Knoevenagel condensation and 1,4-conjugated reduction gave the chain-extended diester **354**. The isopropylidene group was then hydrolyzed, and the resulting glycol was cleaved with $NaIO_4$. Under the cleavage conditions, the intermediate cyclized spontaneously in an intramolecular aldol fashion to give, after acetylation, a mixture of acetates **355**. Thermal demethoxycarbonylation and treatment with diisobutylaluminum hydride provided intermediate **356**. Hydroboration of **356** followed by oxidative workup gave a mixture of alcohols (1.6:1 ratio) which were separated after *O*-deacylation. Hydrogenolytic debenzylation of the major isomer gave carba-α-L-arabinofuranose (L-**170**), while the minor diastereomer provided carba-β-D-ribofuranose (D-**157**).[210]

Scheme 42. Synthesis of 4a-Carba-α-L-arabinofuranose (L-170) and 4a-Carba-β-D-ribofuranose (157)[a]



[a] Reagents: (i) $NaIO_4$, MeOH; (ii) dimethyl malonate, py, Ac_2O; (iii) $NaBH_4$, 41%; (iv) 12 M HCl; (v) $NaIO_4$; (vi) Ac_2O, py, 30%; (vii) DMSO, NaCl, 65%; (viii) DIBAL-H, 93%; (ix) BH_3−THF, then H_2O_2, NaOH; (x) NaOMe; (xi) 10% Pd/C, H_2, 63%.

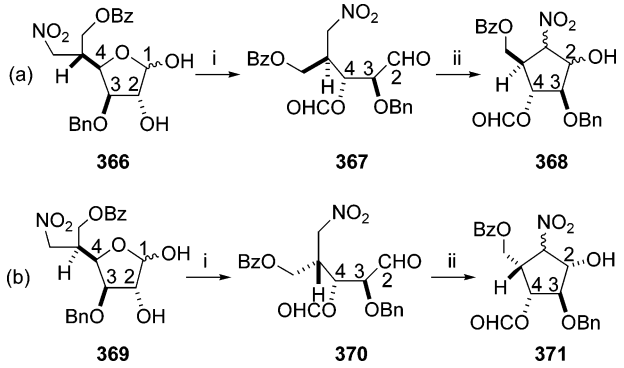
Scheme 43. Chapleur's Approach to Carbapentofuranoses[a]



[a] Reagents: (i) *N*,*N*-diethylacetamide, LDA; (a) 60%; (b) 90%; (ii) H_5IO_6; (a) 59%; (b) 50%; (iii) $NaBH_4$; (a) 21%; (b) not given.

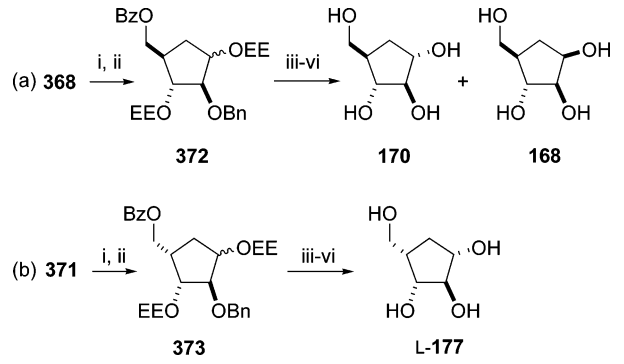
Chapleur and co-workers[211] studied an alternative route to carbapentofuranoses from sugar lactones using an intramolecular aldol reaction (Scheme 43). The known D-gulonolactone **357** (Scheme 43a) was transformed into amide **358** by addition of the lithiated anion derived from *N*,*N*-

Scheme 44. Cyclization of Nitro Sugars to Key Intermediates 368 and 371[a]



[a] Reagents: (i) $Pb(OAc)_4$; (ii) KF, 18-crown-6; (a) 52% from **366**; (b) 52% from **369**.

Scheme 45. Synthesis of 4a-Carba-α-D-arabinofuranose (170), 4a-Carba-β-D-arabinofuranose (168), and 4a-Carba-β-L-xylofuranose (L-177)[a]



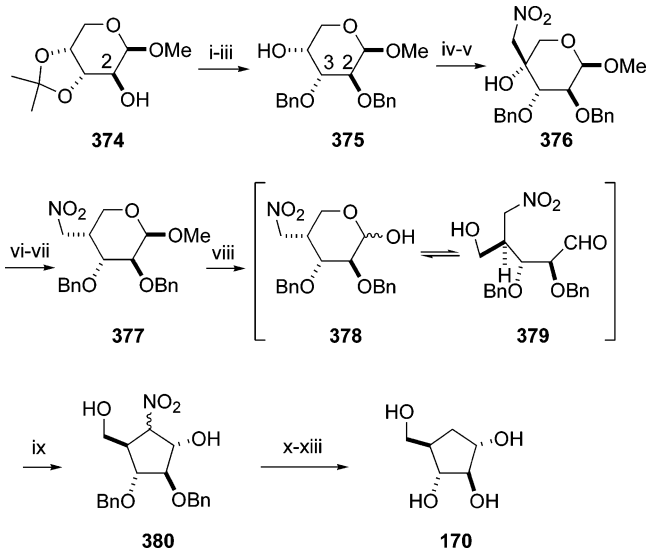
[a] Reagents: (i) NH_4OH, ethyl vinyl ether, CSA; (ii) n-Bu_3SnH, AlBN; (a) 48% from **368**; (b) 45% from **371**; (iii) AcOH, H_2O; (iv) Ac_2O, py; (v) NaOH−MeOH; (vi) Na, liq NH_3; (a) 60% from **372**; (b) 83% from **373**.

diethyl acetamide. Treatment of **358** with H_5IO_6 furnished cyclopentenone **362**. A key step in the overall transformation was the oxidative cleavage of the 5,6-*O*-isopropylidene acetal moiety, in **358**, to give aldehyde **359**. Further reaction of **359** was rationalized invoking its hemiketalic structure, which is in equilibrium with the open hydroxy-aldehyde form **360** and could be further oxidatively cleaved to **361**. Subsequent cyclization of **361** took place in the reaction media to give cyclopentenone **362** in 59% overall yield. This procedure worked equally well with L-gulonolactone derivative **364**, which gave L-**363** in 50% yield (Scheme 43b). Sodium borohydride reduction of enone **362** provided β-D-lyxocarbafuranose derivative **363**. The stereoselectivity at the two new stereocenters (C_3 and C_4, carbasugar numbering) in **363** was again rationalized by invoking a preferred approach of the hydride to the double bond *anti* to the dioxolane ring, with the subsequent protonation of the intermediate enolate also taking place from this face.[211]

6.1.2.1.3. Cyclization of Nitro-Stabilized Carbanions. Yoshikawa and co-workers have exploited the cyclization of nitro sugars to obtain carbapentofuranoses.[212] They initially converted D-glucose to nitrofuranoses **366** and **369** (Scheme 44), which had been previously used in carbahexopyranose syntheses. Reaction of **366** and **369** with lead tetraacetate led to open-chain aldehydes **367** and **370**, which upon treatment with potassium fluoride and 18-crown-6 in DMF gave nitrocyclopentanes **368** and **371**, respectively.

Denitrohydrogenation of **368** (Scheme 45) with tributyltin hydride furnished, after deprotection, 4a-carba-α- and 4a-carba-β-D-arabinofuranose (**170** and **168**), respectively, whereas similar treatment of cyclopentanol **371** afforded 4a-carba-β-L-xylofuranose (L-**177**). In this sequence, the overall yields were reduced because no stereoselectivity in the preparation of the nitrocyclitols could be achieved.

Scheme 46. Synthesis of 4a-Carba-α-D-arabinofuranose (170)[a]

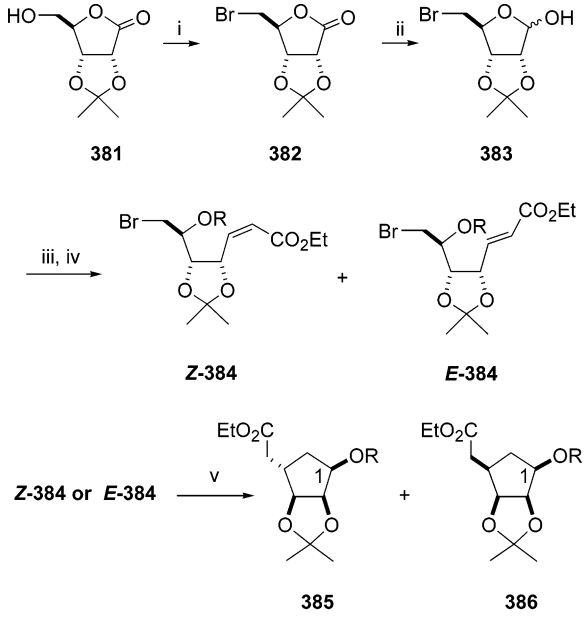


[a] Reagents: (i) BnCl, NaH, quant yield; (ii) 80% aq AcOH, quant yield; (iii) Bu_2SnO, then BnBr, CsF, 100% yield from **374**; (iv) DMSO, oxalyl chloride, Et_3N; (v) nitromethane, KF, 18-crown-6, 72% from **375**; (vi) Ac_2O, TsOH; (vii) $NaBH_4$, 85%; (viii) HCl, AcOH, 57%; (ix) CsF, 86%; (x) ethyl vinyl ether, PPTS; (xi) n-Bu_3SnH, AIBN, 110 °C; (xii) H_2, Pd−black; (xiii) PPTS, 80% aqueous acetone, 42% from **380**.

As an extension of this work, Yoshikawa et al. described a new synthesis of carba-α-D-arabinofuranose (**170**) from D-arabinose (Scheme 46).[213] 3,4-*O*-Isopropylidene-β-D-arabinopyranoside (**374**) was transformed into alcohol **375** by benzylation at O-2, removal of the isopropylidene group, and Bu_2SnO-mediated regioselective benzylation at O-3. The latter was then oxidized under Swern conditions to produce a ketone which upon treatment with nitromethane in the presence of KF and 18-crown-6 furnished stereoselectively nitromethane adduct **376**. The tertiary hydroxyl group was acetylated and subjected to deacetoxyhydrogenation with sodium borohydride to yield nitro derivative **377**. The stereochemical outcome of this reaction could be rationalized through nucleophilic attack of the hydride from the less hindered side of an intermediate nitroolefin. Acidic hydrolysis of **377** gave a branched nitropyranose **378**, which being at equilibrium with nitroaldehyde **379**, was subjected to an intramolecular condensation reaction with CsF to furnish carbocycle **380**, as a mixture of two isomers. Ethoxyethylation followed by denitrohydrogenation with tributyltin hydride and removal of the benzyl and ethoxyethyl protecting groups gave 4a-carba-α-D-arabinofuranose (**170**).

6.1.2.2. Free Radical Cyclizations. Radical cyclization of a suitable carbohydrate derivative possessing both a radical donor and a radical acceptor constitutes an attractive method for the preparation of carbapentoses. The process gives rise to cyclic products with preservation of all stereocenters, and in the best cases, stereocontrol is also observed at the new C−C bond formed in the ring-closing reaction. The intermediate radicals employed in the preparation of carbasugars from carbohydrate precursors have been generated using tributyltin hydride, samarium diodide, and cobalt and tellurium derivatives.

Scheme 47. Wilcox and Thomasco's Approach to Carbafuranoses, Based on 5-*exo-trig* Radical Cyclization[a]



Series: **a** R = H; **b** R = CH_3CO; **c** R = C_6H_5CO; **d** R = $(CH_3)_3CCO$

[a] Reagents: (i) Ph_3P, NBS; (ii) DIBAL-H, −78 °C, 82% overall; (iii) $Ph_3P{=}C(H)CO_2Et$ (***Z*** and ***E***, 67% and 13%); (iv) RCOCl, py; (v) n-Bu_3SnH, AIBN.

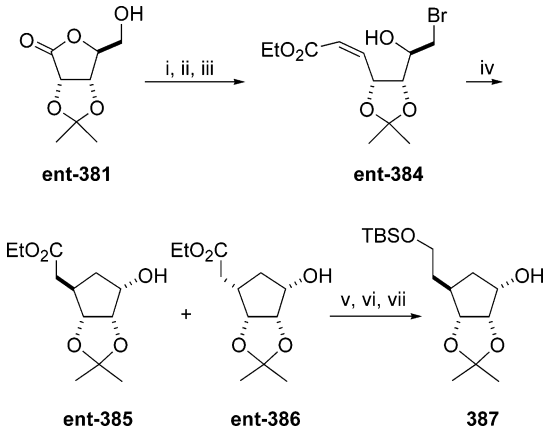
Table 1. Radical Cyclization of Unsaturated Aldose Derivatives

entry	substrate	R	ratio (**385**/**386**)	yield (%)
i	***Z*-384a**	H	6/1	80
ii	***E*-384a**	H	2/1	80
iii	***Z*-384b**	$COCH_3$	5/1	80
iv	***E*-384b**	$COCH_3$	1/1	82
v	***Z*-384c**	COC_6H_5	10/1	89
vi	***E*-384c**	COC_6H_5	1/1.2	87
vii	***Z*-384d**	COC_6H_5	11/1	87

6.1.2.2.1. Tin Method. Wilcox and Thomasco were the first to recognize the radical cyclization of unsaturated aldoses as an efficient, and general, method for the preparation of hydroxylated cyclopentane derivatives.[214] They reported the 5-*exo-trig* radical cyclization of unsaturated halo sugars leading to isomeric cyclopentanoid products (e.g., **385** and **386**, Scheme 47), which have since been used by several groups in the preparation of carbasugars and derivatives, *vide infra*. Their strategy, outlined in Scheme 47, involved the transformation of a D-ribonolactone derivative **381** into a bromo hemiacetal **383**. Treatment of this lactol with (carbethoxymethylidene)triphenylphosphorane afforded the olefinic halides ***Z*-384a** and ***E*-384a** in 67% and 13% yield, respectively. These isomers were separated by chromatography, and each was acylated to afford derivatives **385b**−**d**. Radical cyclization, in the presence of tributyltin hydride and a catalytic amount of AIBN, of each geometrical isomer of **384a** afforded the same two isomeric products **385a** and **386a**.

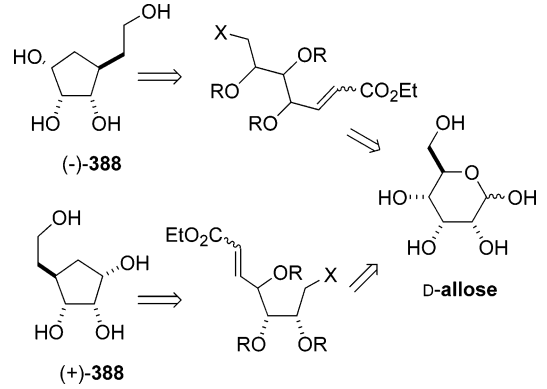
The authors found, however, that the ratio of **385** to **386** observed in the cyclization was influenced by the olefin stereochemistry and the nature of the protecting group at C_1−OH (carbasugar numbering). Their results, outlined in Table 1, showed that *Z* olefins afforded consistently greater stereocontrol when compared with the corresponding *E* isomers. The data in Table 1 also indicated that some degree of control was also exerted by the 1-OH substituents. More recently, the use of radical initiators others than AIBN, such as 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile) [V-70L] or Et_3B, has resulted in stereoselectivities of 98:2 and 99:1, respectively, for the cyclization depicted in Table 1, entry i.[215]

Scheme 48. Jones and Roberts' Synthesis of the Carbasugar Moiety in (−)-5′-Homoaristeromycin[a]



[a] Reagents: (i) Ph_3P, NBS; (ii) DIBAL-H, −78 °C; (iii) $Ph_3P{=}C(H)CO_2Et$; (iv) n-Bu_3SnH, AIBN; (v) DIBAL-H; (vi) TBSCl, NEt_3, DMAP; (vii) chromatography, 71% from the mixture **385** + **386**.

Scheme 49. Roberts and Shoberu's Enantiodivergent Route to (−)-388 and (+)-388 from D-Allose[a]

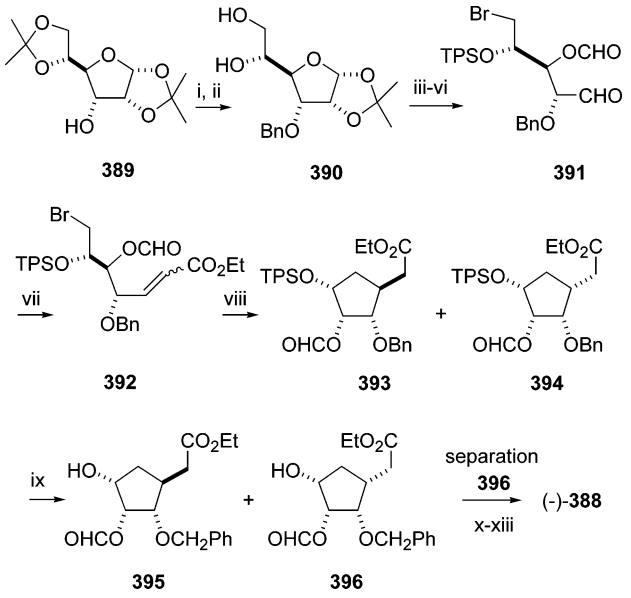


Jones and Roberts applied Wilcox's approach in their synthesis of the carbasugar moieties in (−)-5′-homoaristeromycin and analogues (Scheme 48).[216] Their synthetic route started from L-ribonolactone ***ent*-381**, which was processed according to Wilcox and Thomasco,[214] leading to bromide ***ent*-*Z*-384**. Radical cyclization of ***ent*-384** (*Z* isomer only) led to a mixture of cyclopentanoid esters **385a** and **386a**, which was reduced with diisobutylaluminium hydride, selectively protected at the primary alcohol function using *tert*-butyldimethylsilyl chloride, and purified chromatographically to give alcohol **387**. The latter was then processed to obtain homoaristeromycin analogues.

In an elegant approach, Roberts and Shoberu described an enantiodivergent route to both enantiomeric forms of homologated carbafuranoses (−)-**388** and (+)-**388** from D-allose (Scheme 49).[217] These tetraols had previously been shown by Roberts' group to be convenient precursors for the preparation of *Aristeromycin* analogues.

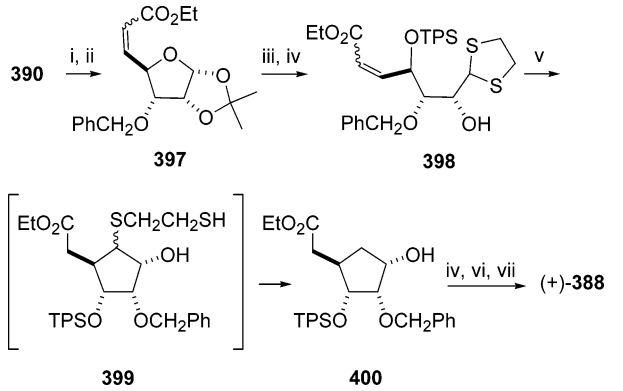
Both synthetic routes started from 1,2;5,6-di-*O*-isopropylidene-α-D-allose (**389**). Benzylation and acid hydrolysis of the latter gave diol **390** (Scheme 50). A sequence of reactions, which included chemoselective bromination, silylation of the remaining hydroxyl group, hydrolysis of the

Scheme 50. Synthesis of Carbafuranose (−)-388[a]



[a] Reagents: (i) $PhCH_2Br$, NaH, THF; (ii) HCl (conc) MeOH, 75%; (iii) CBr_4, Ph_3P, py, 71%; (iv) TPSCl, imidazole, DMAP; (v) 80% $MeCO_2H$, H_2O; (vi) $NaIO_4$, H_2O, MeOH (68%); (vii) $Ph_3P{=}C(H)CO_2Et$, $PhCO_2H$, PhH (1:9 *E*:*Z* ratio) 85%; (viii) n-Bu_3SnH, AIBN; (ix) TBAF, (82% **393**, 8% **394**); (x) $(MeO)_2CMe_2$, pTsOH; (xi) DIBAL-H, −78 °C; (xii) H_2, Pd−C; (xiii) Amberlyst 15 (H^+) resin, 64% (four steps).

Scheme 51. Synthesis of Carbafuranose (+)-388[a]

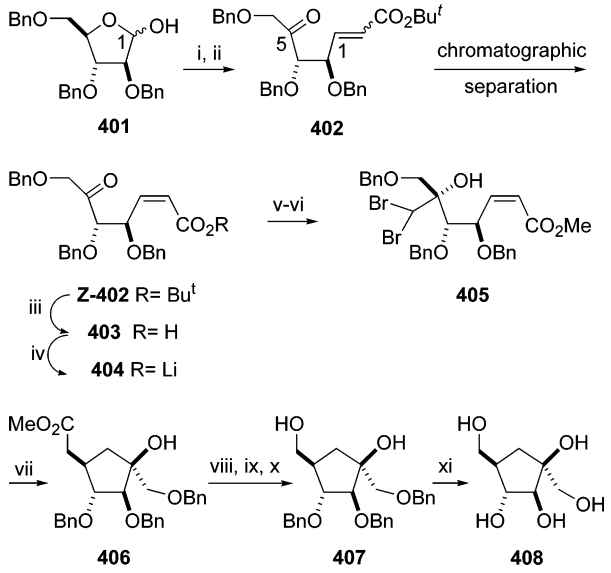


[a] Reagents: (i) $NaIO_4$, H_2O, MeOH; (ii) $Ph_3P{=}C(H)CO_2Et$, $PhCO_2H$, C_6H_6 (1:19 *E*:*Z* ratio), 80% from **390**; (iii) $ZnCl_2$, $HSCH_2CH_2SH$; (iv) TPSCl, imidazole, DMAP, 68% two steps; (v) n-Bu_3SnH, AIBN, 26%; (vi) DIBAL-H, 31%; (vii) H_2, Pd−C, 100%.

acetonide, and oxidative cleavage, furnished aldehyde **391**. This aldehyde was treated, without purification, with (ethoxycarbonylmethylene)triphenylphosphorane to give *Z*- and *E*-alkenes **392** (10:1 ratio). The stereochemical outcome of the radical cyclization of the mixture took place according to precedents[214] and furnished compound **393** and a small amount of isomeric **394**. The mixture of epimers was then treated with tetrabutylammonium fluoride to give the diols **395** and **396**, which were separated on silica. The major product **395** was converted into the target tetrol (−)-**388** in four steps.

The preparation of (+)-**388** was accomplished in seven steps and is outlined in Scheme 51. Thus, periodate cleavage of diol **390** followed by Wittig reaction of the ensuing aldehyde afforded ester **397** (*Z*/*E* ratio 1:19). A dithiolane moiety was next installed at the anomeric center, by reaction with ethane-1,2-thiol in the presence of anhydrous zinc(II) chloride, and the remaining hydroxyl group was then protected as a silyl ether, **398**. Carbocyclization of the

Scheme 52. Wilcox and Gaudino's Preparation of Carbafructofuranose (408)[a]



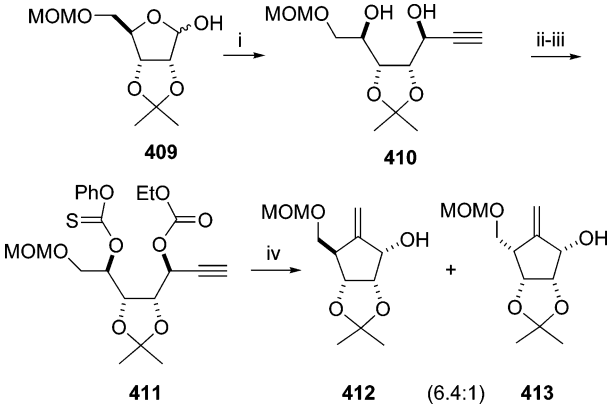
[a] Reagents: (i) t-$BuCO_2CH{=}PPh_3$; (ii) $Me_2SO/COCl_2$, Et_3N, 88% from **401**; *Z*/*E* 3:2; (iii) CF_3CO_2H; (iv) LDA; (v) CH_2Br_2, then LDA; (vi) AcOH, oxolane, then CH_2N_2, 78% from **Z-402**; (vii) n-Bu_3SnH, AIBN, 85%; (viii) PhMgBr; (ix) AcOH; (x) O_3, then $NaBH_4$, 50% from **405**; (xi) H_2, Pd-black, 98%.

heptenyl derivative **398**, using tributyltin hydride, gave the required cyclopentanol with complete stereocontrol, albeit in low yield (26%). The low yield was ascribed to the slow desulfurization of the intermediate **399** under the reaction conditions. Finally, reduction of the ester moiety in **399** and deprotection of the hydroxyl groups yielded (+)-**388**.

In 1986, Wilcox and Gaudino reported the preparation of carbafructofuranose **408** from an acyclic unsaturated carbohydrate derivative (Scheme 52).[218,219] Protected D-arabinofuranose derivative **401** was converted into the unsaturated ketoester **402** in two steps (3:2, *E*/*Z* mixture, 88% overall yield). These isomers were chromatographically separated, and the *Z* isomer was first treated with trifluoroacetic acid to liberate the acid function and then with lithium diisopropylamide to give the carboxylate anion of the acid **404**. Nucleophilic addition of (dibromomethyl)lithium to the keto group in **404** led to branched compound **405** as a single stereoisomer. The stereochemical outcome of the nucleophilic addition is in agreement with expectations based on stereoelectronic considerations. Subsequent 5-*exo*-*trig* radical cyclization of the unsaturated geminal dibromide **405** with tributyltin hydride and catalytic AIBN provided the desired carbocyclic compound **406** in high yield. The reaction seems to proceed through a cyclopentanoid bromohydrin intermediate, but the rate of formation and the rate of debromination of this intermediate must be closely competitive. The stereochemical preference in the formation of **406**, during this radical cyclization, was ascribed to differences in transition-states energies leading to the two possible diastereomers. Barbier−Wieland degradation of ester **406** afforded the key intermediate **407**, which was by hydrogenolysis deprotected to afford carba-D-fructofuranose (**408**) in excellent yield.

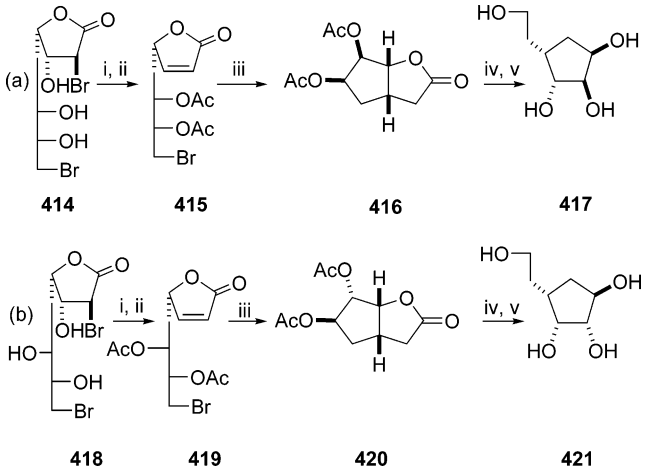
Wilcox and Gaudino also described a general strategy for the conversion of any given furanose into its corresponding carbocyclic analogue (Scheme 53).[220] The approach featured a 5-*exo*-*dig* radical cyclization as the key step. Accordingly, D-ribofuranose derivative **409** was treated with lithium

Scheme 53. Wilcox and Gaudino's Approach to Carbafuranoses Based on 6-*exo-dig* Radical Cyclization[a]



[a] Reagents: (i) lithium acetylide, 78%; (ii) ethyl chloroformate, py; (iii) phenyl chlorothionoformate, py, 80% from **409**; (iv) n-Bu_3SnH, AIBN, 85%.

Scheme 54. Synthesis of 4a-Carbahexofuranoses via Free Radical Cyclization of Bromodeoxyheptonolactones[a]

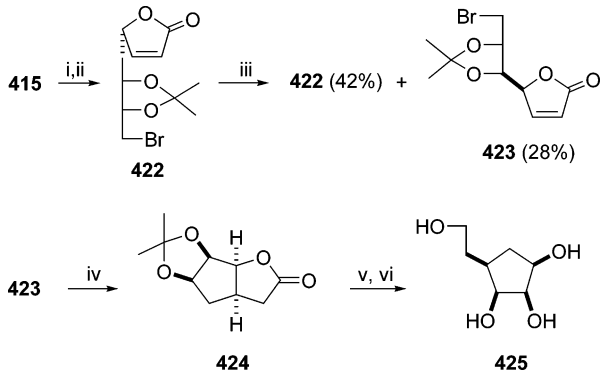


[a] Reagents: (i) Ac_2O, $HClO_4$; (ii) $Na_2S_2O_5$, Na_2SO_3, H_2O, MeOH; (a) 81% from **414**; (b) 75% from **418**; (iii) n-Bu_3SnH, AIBN; (a) 98%; (b) 91%; (iv) MeOH, HCl; (a) 94%; (b) 84%; (v) BH_3-SMe_2; (a) 85%; (b) 60%.

acetylide to furnish diol **410**, which was selectively protected at 1-OH and activated at 4-OH to afford the key intermediate **411**. This precursor, under treatment with tributyltin hydride and catalytic AIBN, provided a secondary radical which upon cyclization led to a 6.4:1 mixture of methylene cyclopentanoid products **412** and **413** in the remarkably good overall yield of 30% from D-ribose hemiacetal **409**. The exocyclic olefin was envisioned as a precursor for carba-α-D-ribofuranose analogues, e.g., spirocyclopropane derivatives.[219]

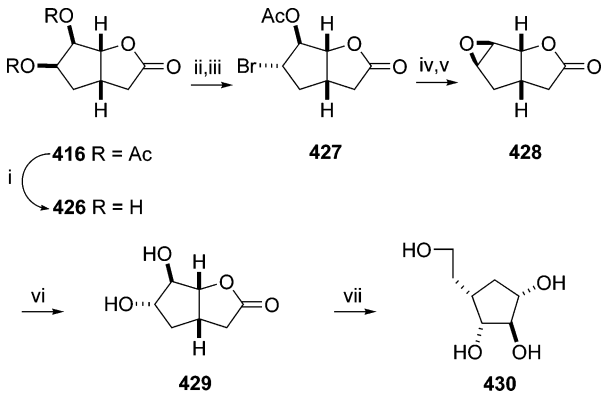
Lundt and co-workers disclosed a related strategy to carbahexo- and carbapentofuranoses via free radical cyclization of enantiomerically pure bromodeoxyheptonolactones (e.g., **414**, **418**; Scheme 54). In this case, the 5-*exo*-*trig* radical cyclization led to the formation of a cyclopentane fused to a five-membered lactone. In their initial report,[221] the readily available dibromoheptonolactone **414** was acetylated and subjected to a regioselective *trans*-β-bromo-acetoxy elimination to give unsaturated lactone **415**. Subsequent treatment with tributyltin hydride and AIBN led exclusively to the thermodynamically more stable, *cis*-fused cyclopentane derivative **416** in 98% yield (Scheme 54a). An analogous reaction sequence was carried out with the C_5 epimer **418** (Scheme 54b). Accordingly, 2,7-dibromo-2,7-dideoxy-D-glycero-L-gluco-heptono-1,4-lactone (**418**) was converted into

Scheme 55. Synthesis of 5-Deoxy-4a-carba-β-D-lyxohexofuranose (425)[a]



[a] Reagents: (i) MeOH, HCl, quant; (ii) acetone, camphorsulfonic acid, 71%; (iii) Et_3N, CH_2Cl_2, 28%; (iv) n-Bu_3SnH, AIBN, EtOAc, reflux, 90%; (v) 1 M HCl, 97%; (vi) BH_3-SMe_2, THF, reflux, 79%.

Scheme 56. Synthesis of 5-Deoxy-4a-carba-β-D-lyxohexofuranose (430)[a]



[a] Reagents: (i) MeOH, HCl, 94%; (ii) HBr, AcOH; (iii) Ac_2O, 85%; (iv) MeOH, HCl, quant; (v) K_2CO_3, acetone, 97%; (vi) $HClO_4$, H_2O, 95%; (vii) BH_3-SMe_2, dioxane, 62%.

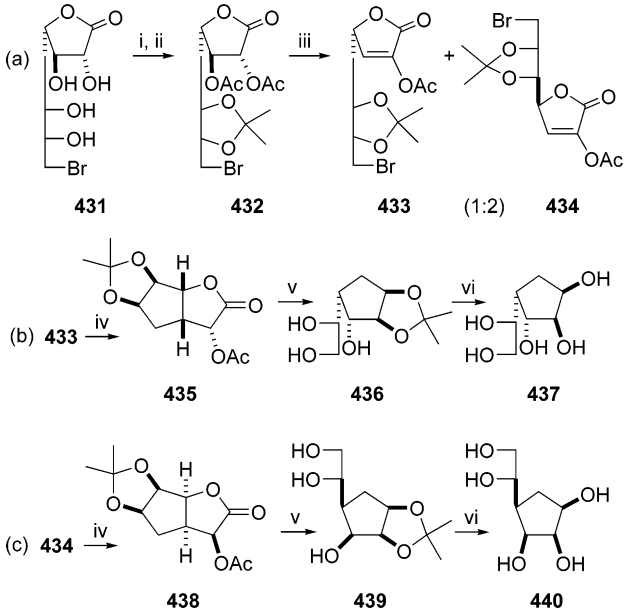
the cyclopentane derivative **420**. The bicyclic compounds **416** and **420** were readily converted into carbasugars by reduction of the lactone moiety to the corresponding alcohol using borane−dimethyl sulfide complex. Thus, **416** and **420** gave 5-deoxy-4a-carba-α-L-xylohexofuranose (**417**) and 5-deoxy-4a-carba-α-L-lyxohexofuranose (**421**), respectively.

Along this path, base treatment of unsaturated lactone **422**, readily obtained from **415** by treatment with CSA, promoted partial epimerization at C_4, leading to an equilibrium mixture consisting of 28% of 7-bromo-2,3,7-trideoxy-5,6-*O*-isopropylidene-D-ribo-hept-2-enono-1,4-lactone (**423**) and 42% of recovered starting material **422** (Scheme 55). The former was then cyclized with tributyltin hydride and catalytic AIBN to furnish bicycle **424** in 90% yield. Reduction of the lactone moiety then led to 5-deoxy-4a-carba-β-D-lyxohexofuranose (**425**).

On the other hand, when *cis*-diol **426**, readily obtained from **416**, was reacted with HBr/AcOH, the *trans*-bromoacetate **427** was obtained (Scheme 56).[222] Deacetylation and base treatment of **427** led to epoxide **428**. Ring opening of the oxirane moiety with H_2O in the presence of perchloric acid gave exclusively diol **429**. Reduction of the lactone with borane−dimethyl sulfide provided 5-deoxy-4a-carba-β-L-xylohexofuranose (**430**).

In a second set of experiments, 2-oxy-substituted 2,3-unsaturated heptono-1,4-lactones **433** and **434** (Scheme 57) were used in cyclization reactions to give carba-aldohexo-

Scheme 57. Synthesis of 4a-Carba-α-L-glucofuranose (437) and 4a-Carba-β-D-mannofuranose (440)[a]



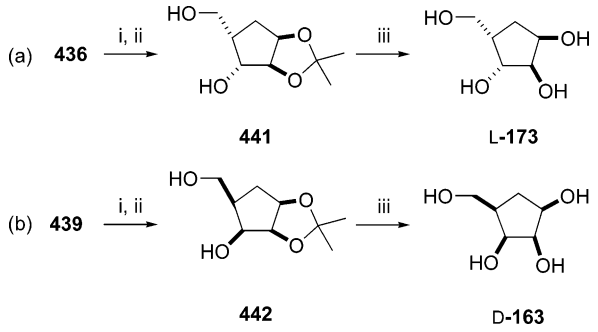
[a] Reagents: (i) acetone, camphorsulfonic acid, 86%; (ii) Ac_2O, py, 100%; (iii) Et_3N; (iv) n-Bu_3SnH, AIBN, 90%; (v) $NaBH_4$, NaOMe; (a) 88%; (b) 91%; (vi) aqueous HCl; (a) 94%; (b) 77%.

furanoses.[223] Lactone **431** was protected as a 5,6-di-*O*-isopropylidene derivative and then acetylated to give **432**. Treatment of the latter with triethylamine caused a β-elimination reaction accompanied by partial isomerization at C_4 to give two epimeric α,β-unsaturated lactones **433** and **434**, that were separated by crystallization followed by flash chromatography. Subsequent radical cyclization of lactones **433** and **434** with tributyltin hydride in the presence of AIBN led to single isomers **435** and **438**, respectively. These bicyclic lactones, **435** and **438**, were used in the preparation of carbahexofuranoses and carbapentofuranoses. Reduction of the lactone moiety in compounds **435** and **438**, using sodium borohydride, furnished carbahexose derivatives **436** and **439**, which, after deprotection, yielded the target 4a-carba-α-L-glucofuranose (**437**) and 4a-carba-β-D-mannofuranose (**440**), respectively.

Carbahexofuranoses **436** and **439** were oxidatively cleaved, at the exocyclic diol moiety, to furnish di-*O*-isopropylidene derivatives **441** and **442**, deprotection of which afforded 4a-carba-α-L-xylofuranose (L-**173**) and 4a-carba-β-D-lyxofuranose (D-**163**), respectively (Scheme 58).[223]

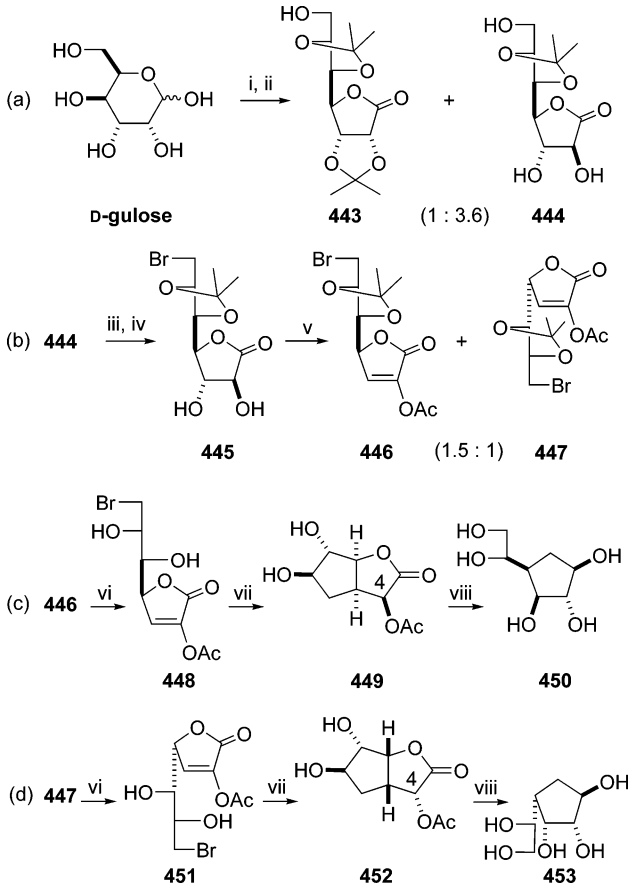
A similar sequence of reactions was applied to lactone **444**, prepared by cyanohydrin chain elongation of D-gulose (Scheme 59).[224] Accordingly, reaction of **444** with HBr in acetic acid provided bromolactone **445**, which was treated with triethylamine to cause a β-elimination of acetic acid and a partial isomerization at C_4 to give a mixture of the unsaturated lactones having D-xylo (**446**) and D-lyxo (**447**) configurations. Subsequent cleavage of the di-*O*-isopropylidene acetal in those lactones furnished bromo-diols **448** and **451**, respectively, which upon radical cyclization with tributyltin hydride in the presence of AIBN led to major isomers **449** and **452** (84 and 81% yield, respectively) accompanied with minor amounts of the corresponding C_4 epimers (4% and 10%, respectively). Reduction of the lactone and the acetoxy moieties in **449** and **452** yielded 4a-carba-β-D-glucofuranose (**450**) and 4a-carba-α-L-mannofuranose (**453**), respectively.

Scheme 58. Synthesis of 4a-Carba-α-L-xylofuranose (L-173) and 4a-Carba-β-D-lyxofuranose (D-163)[a]



[a] Reagents: (i) $NaIO_4$, H_2O; (ii) $NaBH_4$, H_2O; (a) 98%; (b) 91%; (iii) aqueous HCl, 96%.

Scheme 59. Synthesis of 4a-Carba-β-D-glucofuranose (450) and 4a-Carba-α-L-mannofuranose (453)[a]

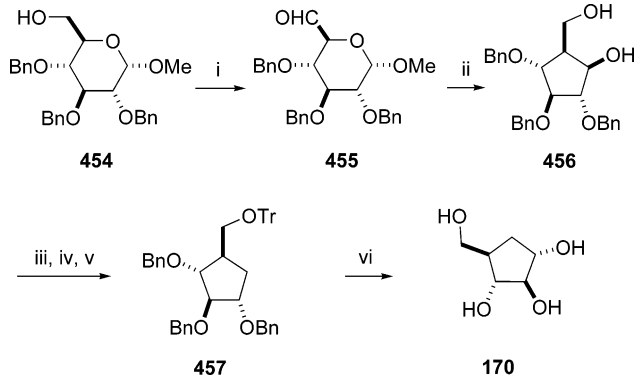


[a] Reagents: (i) NaCN; (ii) acetone, H^+, 46%; (iii) HBr, AcOH; (iv) acetone, H^+; (v) Ac_2O, Et_3N, 52%; (vi) TFA; (a) 63%; (b) 67%; (vii) n-Bu_3SnH, AIBN; (a) 89%; (b) 81%; (viii) BH_3-SMe_2; (a) 77%; (b) 68%.

6.1.2.2.2. Samarium(II) Iodide-Promoted Reactions. A recent alternative to tributyltin hydride-induced radical cyclizations is supplied by one-electron reducing agents such as samarium(II) iodide, which mediates in a variety of carbon−carbon bond-forming reactions by radical or carbanionic processes.

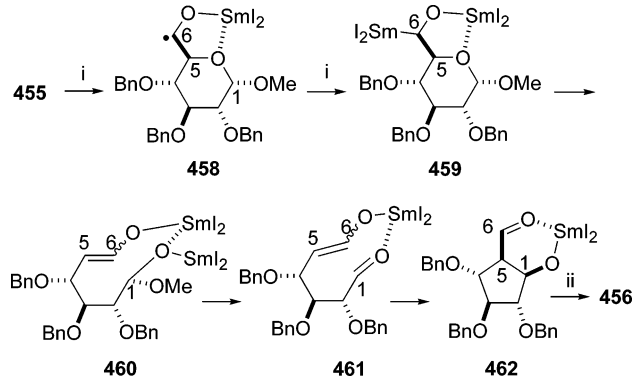
Sinaÿ and co-workers reported, in 1995, an efficient samarium(II) iodide-mediated stereoselective contraction of aldehydopyranose derivatives leading, in one single synthetic step, to highly functionalized cyclopentanes, which could be easily converted to carbapentofuranoses.[225] Aldehyde pyranoside **455** (Scheme 60), obtained by Swern oxidation of

Scheme 60. Synthesis of 4a-Carba-α-D-arabinofuranose (170)[a]



[a] Reagents: (i) DMSO, $(ClCO)_2$, Et_3N; (ii) SmI_2, THF, HMPA, t-BuOH, 46% from **454**; (iii) TrCl, py; (iv) NaH, CS_2, MeI; (v) n-Bu_3SnH, AIBN; (vi) AcOH, H_2O; (vii) H_2, Pd, 81% from **456**.

Scheme 61. Proposed Mechanism for the Transformation 455 to 456[a]



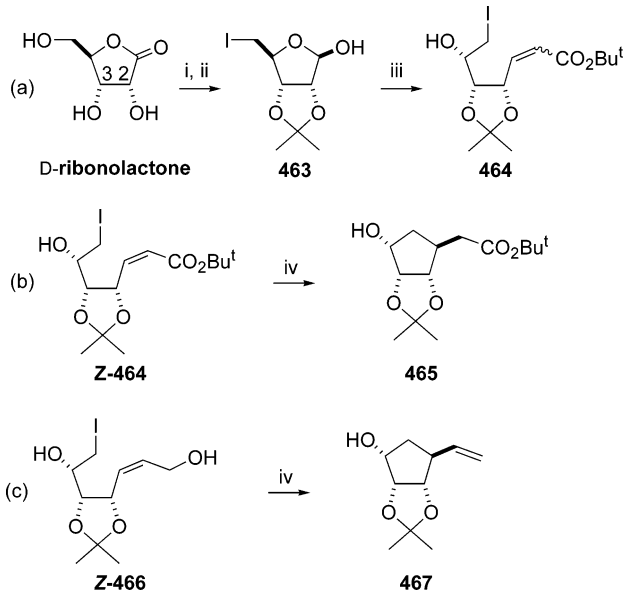
[a] Reagents: (i) SmI_2; (ii) $2SmI_2$, ROH.

alcohol **454**, was treated at room temperature with a solution of samarium(II) iodide, in the presence of HMPA and *tert*-butyl alcohol, to give cyclopentane **456** in 63% yield. Protection of the primary alcohol in **456** and deoxygenation of the secondary hydroxyl group by treatment of the corresponding xanthate with tributyltin hydride led to carbasugar precursor **457**, deprotection of which gave 4a-carba-α-D-arabinofuranose (**170**) in 81% overall yield.

A conceivable mechanistic rationale, which accounts for this transformation, is outlined in Scheme 61. A first equivalent of SmI_2 reduces the aldehyde **455** to the samarium ketyl **458**. A second equivalent of samarium reduces **458** to the disamarium species **459**, which then undergoes ring opening to **460** followed by methoxide elimination to give the key intermediate **461**. A subsequent aldol cyclization reaction involving intramolecular nucleophilic attack of the samarium enolate onto the aldehyde allows the formation of the cyclopentane **462**. This reaction takes place through a 5-enol *exo-exo-trig* process. The cyclization step is then formally an aldol reaction, although the anion had been initially generated by two single-electron-transfer steps; final reduction of **462** afforded the observed product **456**.[225]

In a different approach, Bennet et al. used a samarium iodide-mediated cyclization of some D-ribonolactone-derived alkenyl iodides to convert carbohydrates to carbasugar derivatives (Scheme 62).[226] D-Ribonolactone was converted in iodo-lactol **463** via a three-step sequence which involved protection of the 2-OH and 3-OH groups as a di-*O*-isopropylidene acetal, iodination of the remaining hydroxyl

Scheme 62. Synthesis of Carbasugar Analogue 467[a]



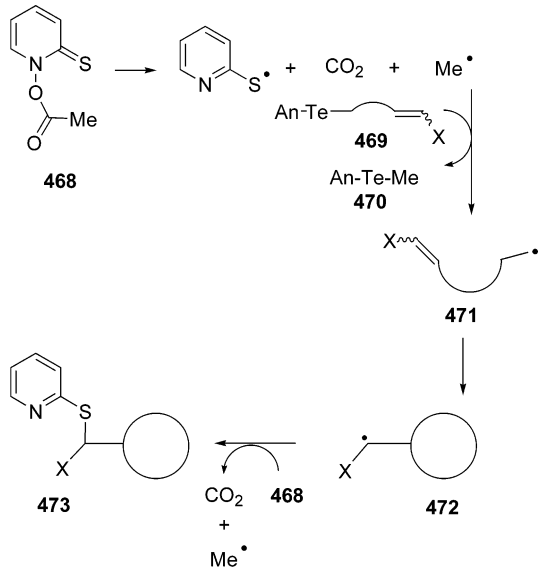
[a] Reagents: (i) Ph_3P, imidazole, I_2, 74%; (ii) DIBAL-H, −78 °C, 86%; (iii) $Bu^tCO_2CH{=}PPh_3$; (iv) SmI_2−THF, MeOH, HMPA; (b) 70%; (c) 51%.

group, and reduction of the lactone. Wittig reaction of hemiacetal **463**, with *tert*-butoxycarbonyl triphenylphosphorane, gave unsaturated ester **464** as an 8:1 mixture of *Z* and *E* isomers. Treatment of ***Z*-464** with 4 equiv of samarium iodide, in the presence of methanol and HMPA at low temperature, gave the carbasugar precursor **465** in 70% yield. When the same reaction conditions were applied to the unsaturated alcohol ***Z*-466**, vinylcyclopentane **467** was obtained as the only isomer. These reactions involved a 5-*exo-trig* radical cyclization of a primary radical onto an activated olefin to generate a secondary radical. This radical is then reduced by a second equivalent of samarium iodide to give an organosamarium intermediate, which could either be protonated (e.g., **464** → **465**) or undergo *β*-elimination (e.g., **466** → **467**).

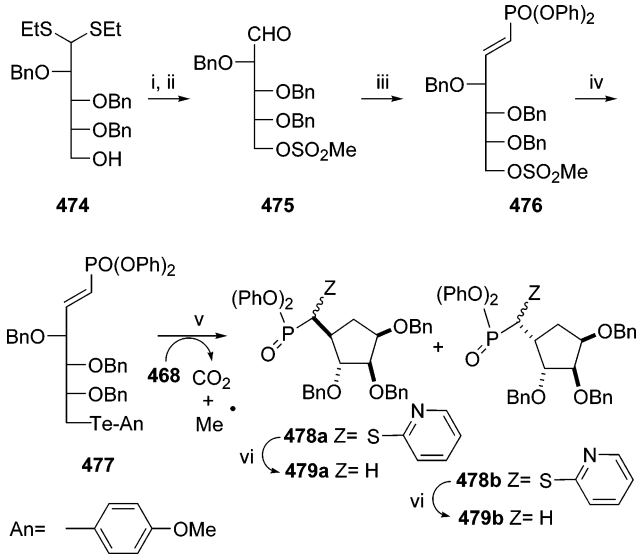
6.1.2.2.3. Others (Tellurium, Cobalt, and Mercury). Although the 5-hexenyl radical cyclization of carbohydrate halides in the presence of tributyltin hydride is an expeditious method for obtaining chiral carbasugars, tin residues are toxic and difficult to remove. These limitations led Barton and co-workers to "invent" a new source of alkyl radicals by radical exchange.[227] The idea, outlined in Scheme 63, involves the use of the acetyl derivative of *N*-hydroxy-2-thiopyridone (**468**), a convenient source of methyl radicals. The methyl radical so generated reacts with the anisyl telluride derivative **469** to afford anisylmethyl telluride **470** and the desired radical **471**, which can react (or cyclize as in Scheme 63) with a substituted olefin to generate a new radical **472**, which is "disciplined" by reaction with the thiocarbonyl group of **468** to give the cyclic compound **473**, with regeneration of the methyl radical.

2,3,4-Tri-*O*-benzyl-D-arabinose diethyl dithioacetal (**474**) (Scheme 64) was transformed into aldehydo-mesylate **475** by treatment with methanesulfonyl chloride and dethioacetalization in the presence of mercury(II) chloride. Wittig−Horner reaction of **475** with diphenyl[(triphenylphosphoranylidene)methyl]phosphonate gave ***E*-476** in 60% yield. Treatment of the latter with anisyl telluride anion afforded the crystalline telluride **477**. This compound, when treated with methyl radicals generated by photolysis of *N*-acetoxy-

Scheme 63. Radical Cyclization of Anisyl Telluride Derivatives of Carbohydrates 469 Leading to Carbocycles 473



Scheme 64. Synthesis of 4a-Carba-β-D-arabinofuranose Phosphonate Derivatives 479[a]

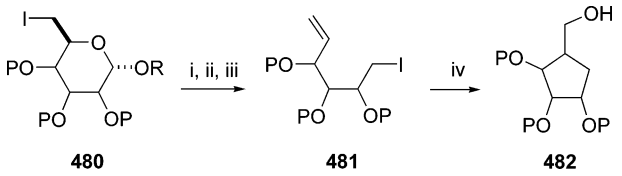


[a] Reagents: (i) $MeSO_2Cl$, DMAP, 91%; (ii) $Hg(OAc)_2$, $CaCO_3$, 90%; (iii) $(OPh)_2P(O)CH{=}PPh_3$, 60%; (iv) $(An\text{-}Te)_2$, $NaBH_4$, 84%; (v) **468**, *hν*, 92%; (vi) n-Bu_3SnH, AIBN, 60%.

2-thiopyridone, gave the expected carbocycles **478**, as a mixture of four isomers (92%). Reduction of the thiopyridyl derivatives, using tributyltin and catalytic AIBN, afforded 4a-carba-β-D-arabinofuranose phosphonate derivatives **479** as a (60:40) mixture of two isomers.

A different, radical-based, route to carbapentofuranoses which involves the use of cobalt has been recently developed by Prandi and co-workers.[228] Their approach to the synthesis of carbasugars relies on a cobalt-catalyzed radical cyclization with molecular oxygen of 6-deoxy-6-iodo-hex-1-enitols (**481** → **482**) (Scheme 65). The preparation of the starting hex-1-enitols, e.g., **481**, is conveniently carried out by reductive ring opening of *O*-protected 6-deoxy-6-iodohexopyranosides, e.g., **480**, with zinc and further elaboration of the aldehyde function to a primary hydroxyl group followed by iodination.

Scheme 65. Cobalt-Catalyzed Radical Cyclization of 6-Deoxy-6-iodo-hex-1-enitols Leading to Carbafuranoses[a]



[a] Reagents: (i) Zn, aqueous EtOH, reflux; (ii) $NaBH_4$, 38−70%; (iii) PPh_3, I_2, or TsCl, py, then NaI, HMPA, 40−98%; (iv) cobalt (salen) complex (3−5%), air, 25−74%.

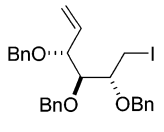
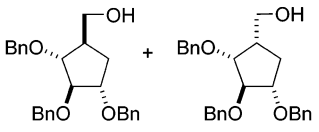
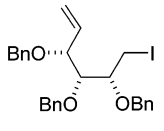
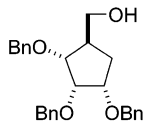
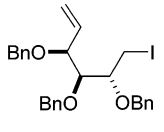
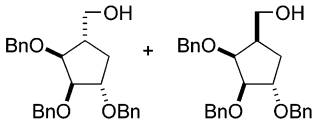
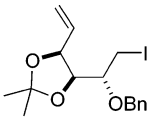
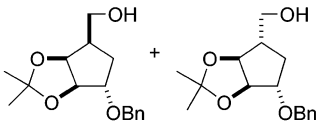
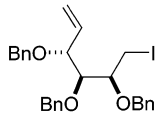
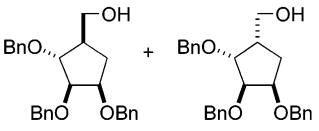
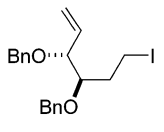
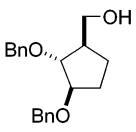
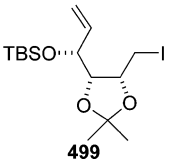
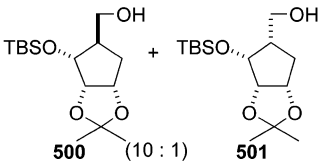
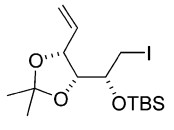
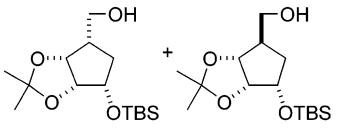
All the possible configurational isomers of 1,2-dideoxy-hex-1-enitols were prepared from available D-hexopyranosides as is shown in Table 2. Thus, for example, reductive opening of methyl 6-deoxy-6-iodo-α-D-glucohexopyranoside, using activated zinc in refluxing aqueous ethanol followed by reduction of the aldehyde group with sodium borohydride, and iodination gave 1,2-dideoxyhex-1-enitol (**483**) with the L-xylo configuration (Table 2, entry i). In an analogous manner, 1,2-dideoxyhex-1-enitols in the L-lyxo, D-arabino, and L-ribo series were available from the corresponding D-allo- (Table 2, entries ii, vii, viii), D-galacto- (Table 2, entries iii, iv), and D-manno- (Table 2, entry v) hexopyranosides. These compounds were treated at 40 °C in ethanol with a catalytic amount of cobalt(salen) complex under air. Radical cyclization was then followed by oxygenation of the cyclized radical to yield, normally, a mixture of carbafuranosides in moderate to good yields. Cyclization of the hexenitols **483** and **497**, in which all benzyloxy groups were able to occupy pseudoequatorial positions in the transition state, gave higher selectivities than that of hexenitols **488** and **494**, in which one benzyloxy group is forced into a pseudoaxial position. Benzyl groups were hydrogenolyzed while *tert*-butyldimethylsilyl and acetal groups were removed by acidic treatment in compounds **484**, **489**, **500**, and **495** to yield carbapentofuranoses of α-D-arabino (**170**), α-D-ribo (**39**), β-L-ribo (L-**157**), and β-D-arabino (**168**) configurations, respectively.

Finally, carbon-centered radicals generated from carbohydrate-derived organomercurials have been used in radical ring-closure reactions leading to carbasugars.[229] The method, developed by Gallos et al., involves (i) conversion of the sugar to a hepta-2,6-dienoate derivative, (ii) chemoselective mercuration of the terminal double bond, (iii) reductive radical cyclization, and (iv) standard reduction and deprotection manipulations. Since this work was carried out in the context of the preparation of (+)- and (−)-carbocyclic nucleosides, the authors carried out radical cyclization of enantiomeric substrates. Accordingly, their synthetic sequence started either from 5-deoxy-5-iodo-D-ribose derivative **505** or from alcohol **508** (prepared in two steps from D-arabinose) to obtain enantiomeric aldehydes (+)-**506** and/or (−)-**506** and thence dienoates (+)-**507** and/or (−)-**507** (Scheme 66).[230]

The mercuration of the terminal double bond was accomplished by treatment with $Hg(OAc)_2$, and the resulting mercurials were reacted without isolation with $NaHB(OMe)_3$ to afford good yields of the carbocyclic compounds (Scheme 67). The stereochemical outcome of the radical cyclization took place according to literature precedents, with the *Z* isomers displaying a higher diastereoselectivity. Finally, reduction of the esters (+)-**509** and (−)-**509** led to enantiomerically pure carbasugar derivatives (+)-**511** and (−)-**511**.

6.1.2.3. Cycloaddition Reactions. The intramolecular 1,3-dipolar cycloaddition of sugar derivatives is a flexible method

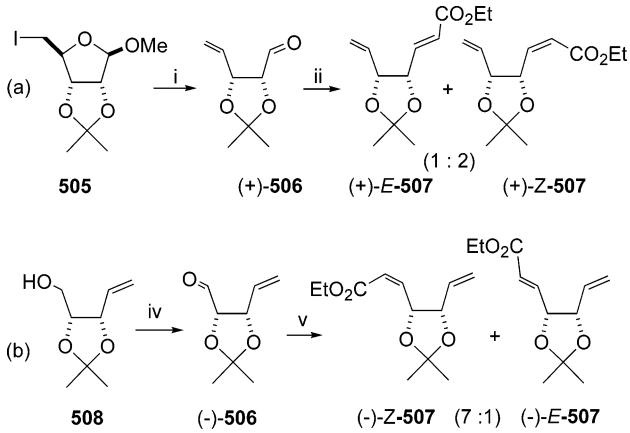
Table 2. Cobalt-Catalyzed Radical Cyclization of 6-Deoxy-6-iodo-hex-1-enitols

Entry	Substrate	Products (ratio)	Yield (%)
i	 **483**	 **484** (12 : 1) **485**	69
ii	 **486**	 **487**	25
iii	 **488**	 **489** (4 : 1) **490**	50
iv	 **491**	 **492** (1.2 : 1) **493**	80
v	 **494**	 **495** (4 : 1) **496**	30
vi	 **497**	 **498**	57
vii	 **499**	 **500** (10 : 1) **501**	50
viii	 **502**	 **503** (1 : 1) **504**	74

for preparing carbocyclic derivatives.[231] Shing and co-workers[232] described a short method for the synthesis of five- and six-membered oxygenated carbacycles involving a stereoselective intramolecular nitrone cycloaddition as the key step. In their synthesis, acetonide **512**, readily available from D-ribose, was converted into triol **513** (Scheme 68). Glycol cleavage of the vicinal diol moiety followed by immediate reaction with *N*-methylhydroxylamine and *in situ* cyclization gave isoxazolidine **515** as a single diastereomer. Acetylation of the latter followed by selective hydrogenolysis of the N−O bond then yielded the functionalized aminocarbasugar **516**.

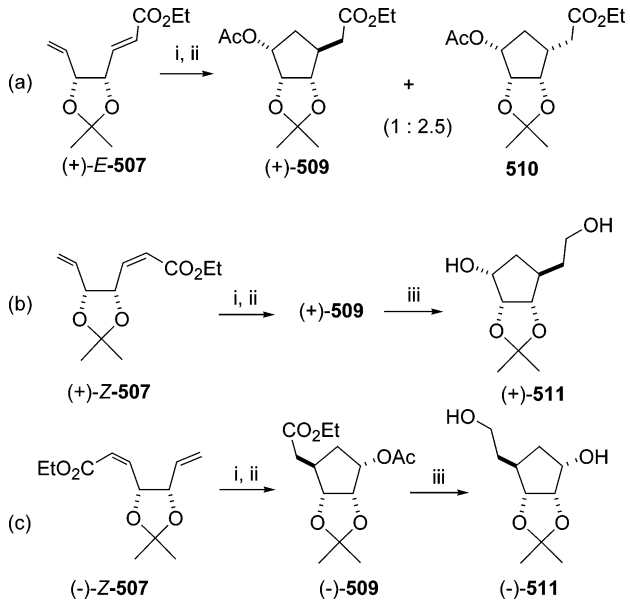
In a related report, Vandevalle and co-workers[233] described the synthesis of the cyclopentane nucleus of the carbocyclic nucleoside neplanocin A starting from L-ribulose and using

Scheme 66. Synthesis of Diene Intermediates 507[a]



[a] Reagents: (i) Zn, EtOH, reflux, 2 h; (ii) $EtCO_2CH{=}PPh_3$, EtOH, 24 h, 80% from **505**; (iii) $Me_2SO/(COCl)_2$, Et_3N; (iv) $EtCO_2CH{=}PPh_3$, EtOH, $PhCO_2H$ (1%), 24 h, 75% from **508**.

Scheme 67. Synthesis of Carbafuranoses by Radical Cyclization of Organomercurials[a]

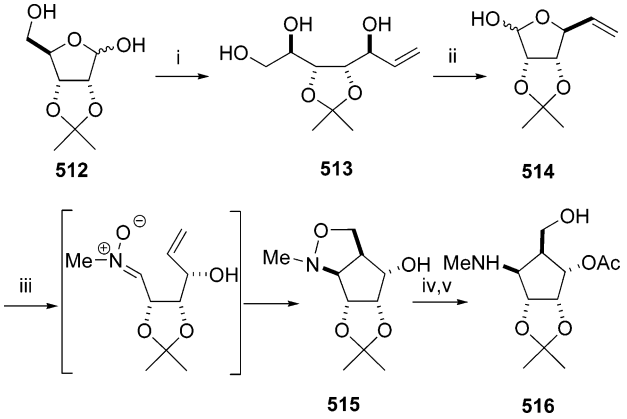


[a] Reagents: (i) $Hg(OAc)_2$, AcOH, 12 h; (ii) $NaBH(OMe)_3$, CH_2Cl_2, 24 h; (a) 52%; (b) 53%; (c) 53%; (iii) LAH, THF, reflux, 5 h; (a) 87%; (b) 87%.

as a key step an intramolecular [2 + 3] nitrone cycloaddition (Scheme 69). L-Ribulose was easily converted into ketal **517**, in which the carbonyl group was methylenated and the hydroxyl function oxidized to the corresponding aldehyde **518**. Treatment with benzyl hydroxylamine and cyclization gave isoxazolidine **519** as the sole product. Reductive cleavage of the N−O bond in **519** followed by selective hydrogenolysis of the benzylamine led to the adequately functionalized cyclopentylamine **520**, in which the neplanocin A stereochemistry was secured.

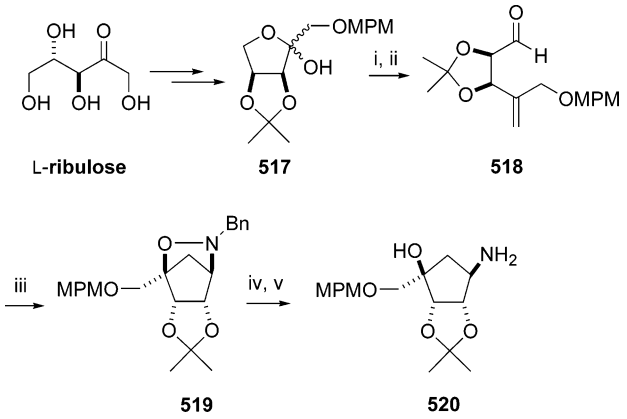
6.1.2.4. Ring-Closing Olefin Metathesis. Alkene metathesis, a reaction where the carbon−carbon double bond of an alkene is broken and reformed in the presence of an organometallic catalyst, is today firmly established as a valuable synthetic tool in organic chemistry.[234] A retrosynthetic analysis for carbafuranoses reveals that these compounds could be obtained from a ring-closing metathesis (RCM) reaction[235] of a diene[236] precursor **522** (generally assembled from carbohydrate sources) followed by appropri-

Scheme 68. Intramolecular 1,3-Dipolar Nitrone Cycloaddition[a]



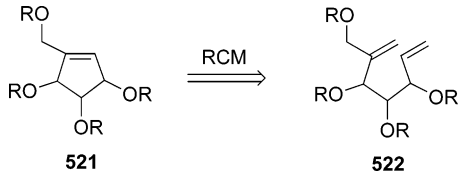
[a] Reagents: (i) $CH_2CHMgBr$, THF, 72%; (ii) $NaIO_4$, aq MeOH, 90%; (iii) MeHNOH·HCl, $NaHCO_3$, aq EtOH, reflux, 90%; (iv) Ac_2O, py, 85%; (v) $Pd(OH)_2$, H_2, EtOH/AcOH, 75%.

Scheme 69. Synthesis of the Cyclopentane Nucleus of Neplanocin A[a]



[a] Reagents: (i) Ph_3PCH_3Br, n-BuLi, 12-crown-4, THF, 95%; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, NEt_3, −60 °C; (iii) BnNHOH, $PhCH_3$, reflux, 85% from **518**; (iv) Zn, AcOH, Et_2O, 92%; (v) H_2, Pd/C, EtOAc, HOAc, 89%.

Scheme 70. Ring-Closing Metathesis (RCM) Approach to Carbafuranoses

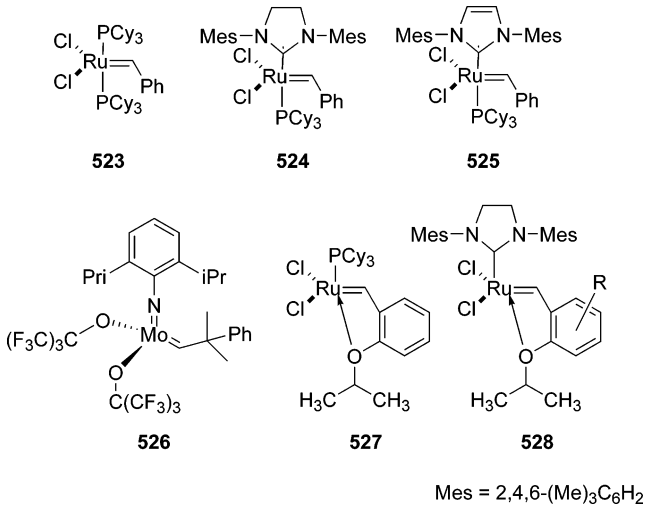


ate manipulation of the resulting cyclopentene derivative **521** (Scheme 70).

Many applications of the metathesis reaction have become possible thanks to the development of new, well-defined catalysts, that are easy to handle and tolerant with most functional groups.[237] Among others, first-generation Grubbs'[238] and Schrock's[239] carbene complexes **523** and **526**, respectively (Scheme 71), are the most popular, and both are commercially available. Other catalysts, such as imidazolinylidenes **524**[240] and **525**,[241] show higher reactivities. More recently, catalysts **527**[242] and **528**[243] (the Hoveyda−Grubbs' catalysts) have been successfully used. It was anticipated that the most common catalyst, **523**, would not be effective for producing trisubstituted double bonds,[244] and therefore, catalysts **524** and **525** were used in this synthetic approach.

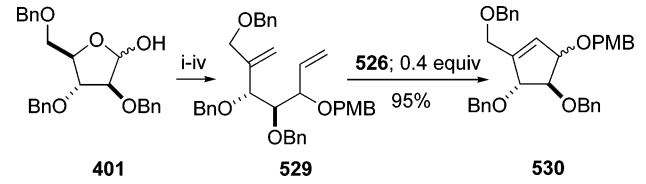
After the previous report[245] concerning the synthesis of highly functionalized cyclopentene derivatives via RCM, the

Scheme 71. Catalysts for the Ring-Closing Metathesis (RCM) Reaction



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

Scheme 72. Synthesis of Carbafuranose Derivative 530[a]



[a] Reagents: (i) vinylmagnesium bromide, THF, 87%; (ii) *p*-methoxybenzyl chloride, NaH, DMF, 0 °C, 83%; (iii) $(COCl)_2$, DMSO, Et_3N, 77%; (iv) methyltriphenylphosphonium bromide, n-BuLi, 89%.

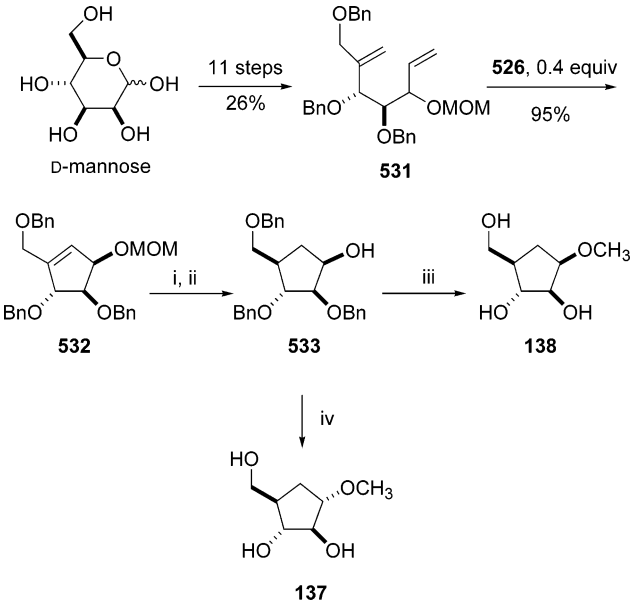
different syntheses of carbafuranoses using this reaction as a key step are summarized as follows.

α- and β- carba-D-arabinofuranoside derivatives have been synthesized independently by two research groups using RCM as the key step. However, both methods differ in the procedure for the synthesis of the diene precursor. In the report of Al-Abed and Seepersaud,[246] the diene **529** was obtained in four steps and 49% overall yield starting from the commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranoside (**401**) (Scheme 72). After refluxing of **529** with Schrock's catalyst (**526**) at 85 °C for 10 h, a mixture of cyclopentenes **530** (ratio $\alpha:\beta = 38:62$) was obtained. The β isomer can be converted into 4a-carba-β-D-arabinofuranose (**170**) via diastereoselective hydrogenation using the Willkinson's catalyst $(Ph_3P)_3RhCl$ under a hydrogen atmosphere.

In the synthesis of Lowary and Callam,[137,247] the diene **531** was prepared from D-mannose in 11 steps and 26% overall yield (Scheme 73). The transformation of diene **531** into the cyclopentane **532** was explored using the catalysts **523**−**526** (Table 3). Although catalyst **523** gave only poor yields of **532** under a range of conditions, the results obtained using **524**, **525**, and **526** were very similar. However, catalysts **524** and **525** are more convenient to use since they are substantially more stable to air, thus avoiding the need for a glove box. After manipulation of **532**, including hydrogenation using Wilkinson's catalyst, carbasugar derivative **533** was transformed into methyl 4a-carba-α- and β-D-arabinofuranosides (**137** and **138**), respectively.

Carba-L-furanose precursors of carbanucleosides have also been synthesized starting from tetra-*O*-benzyl-D-galactopyranoside (**534**) (Scheme 74).[248] In this way, diene **535** was obtained from **534** in three steps and 51% overall yield. Transformation of **535** into **536** was achieved using Schrock's

Scheme 73. Synthesis of Methyl 4a-Carba-α- and -β-D-arabinofuranosides by Lowary and Callam[a]

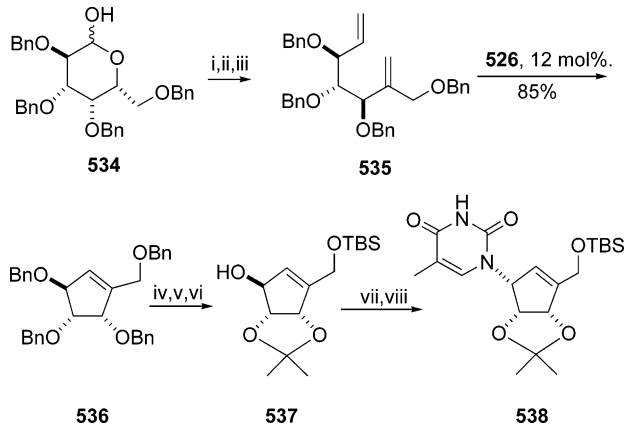


[a] Reagents: (i) $(Ph_3P_3)RhCl$ (30 mol %), H_2, $PhCH_3$, 83%; (ii) trace concentrated HCl, MeOH, 90%; (iii) CH_3I, NaH, THF, then Pd/C, H_2, MeOH, AcOH, 94%; (iv) DEAD, PPh_3, p-$O_2NC_6H_4COOH$, toluene, then NaOMe, MeOH, 83%; (v) CH_3I, NaH, THF, then Pd/C, H_2, CH_3OH, AcOH, 87%.

Table 3. Conversion of 531 to 532 by RCM

entry	catalyst/mol %	conditions	yield (%)
i	**523**/5%	CH_2Cl_2, rt, 24 h	12
ii	**523**/10%	toluene, 60 °C, 33 h	19
iii	**523**/10%	xylenes, reflux, 48 h	0
iv	**525**/20%	toluene, 60 °C, 2 h	74
v	**524**/10%	toluene, 60 °C, 2 h	78
vi	**525**/10%	toluene, 60 °C, 1.5 h	74

Scheme 74. Synthesis of Carbafuranoses by Agrofolio's Group[a]

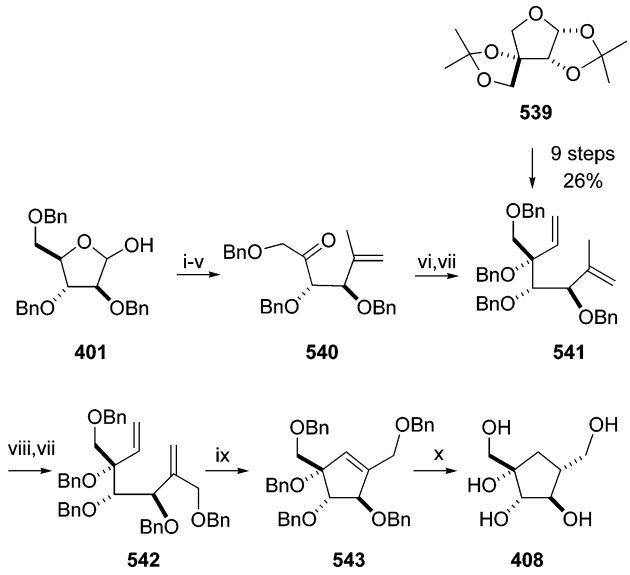


[a] Reagents: (i) Ph_3PCH_3Br, n-BuLi, THF, −78 °C to rt; (ii) PCC, NaOAc, molecular sieves 4 A, CH_2Cl_2, 67% (two steps); (iii) Ph_3PCH_3Br, n-BuLi, THF, −78 °C to rt, 77%; (iv) 1 M BCl_3 in CH_2Cl_2, −78 °C to rt; (v) acetone, cat TsOH, 56% (two steps); (vi) TBSCl, py, 0 °C, 61%; (vii) N^3-benzoylthymine, PPh_3, DEAD, THF; (viii) NaH, MeOH, 23% two steps.

catalyst, **526**. After several protection−deprotection steps, compound **538** (a thymidine nucleoside) was obtained (albeit in low yield) under Mitsunobu conditions by reaction of **537** with N^3-benzoylthymine and subsequent deprotection.

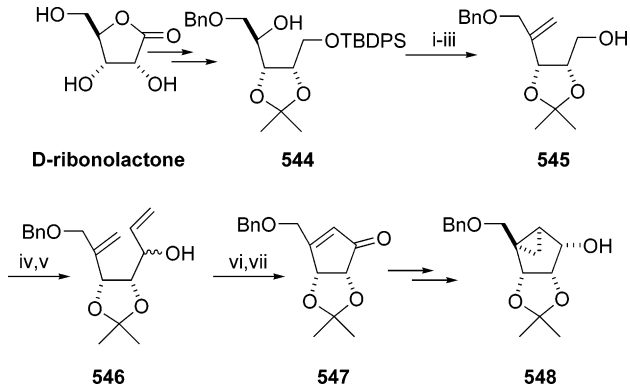
Carba-β-D-fructofuranose (**408**) was obtained using an analogous procedure.[249] Diene **541** (Scheme 75) was synthesized from 2,3,5-tri-*O*-benzoyl-D-arabinofuranoside (**401**)

Scheme 75. Synthesis of Carba-β-D-fructofuranose 408[a]



[a] Reagents: (i) TEMPO, NaOCl; (ii) MeMgBr, THF; (iii) Ac_2O, DMAP, EtOAc; (iv) $SOCl_2$, py, then NaOMe; (v) DMSO, $(COCl)_2$, Et_3N, 98% five steps; (vi) vinylmagnesium bromide, THF; (vii) BnBr, DMF, NaH, 95% for **541**, 53% for **542** (two steps); (viii) SeO_2, TBHP, CH_2Cl_2; (ix) **526**, hexane, reflux, 91%; Pd/H_2, EtOH, 99%.

Scheme 76. Synthesis of the Ring-Strained Derivative 548[a]



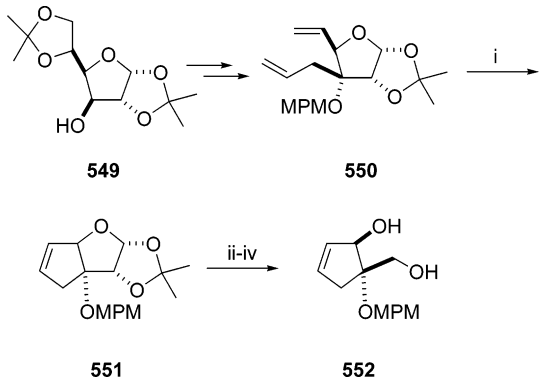
[a] Reagents: (i) $(COCl)_2$, DMSO, THF, −78 °C, then NEt_3, 72%; (ii) PPh_3CH_3Br, n-BuLi, THF, 93%; (iii) TBAF, CH_3CN, 85%; (iv) $(COCl)_2$, DMSO, THF, −78 °C, then NEt_3, 93%; (v) vinylmagnesium bromide, THF, −78 °C, 72%; (vi) **523**, CH_2Cl_2, 85%; (vii) MnO_2, $CHCl_3$, 80%.

in seven steps and 93% overall yield. Compound **541** could also be obtained from 1,2:3,5-di-*O*-isopropylidene-α-D-apiose (**539**), in nine steps and 26% overall yield.[250] Diene **541** was transformed into **542** in two steps and 53% overall yield. Addition of compound **542** to a solution of Schrock's catalyst (**526**) and refluxing the mixture for 18 h led to cyclopentene **543**, which, after hydrogenation with concomitant deprotection, afforded carba-β-D-fructofuranose (**408**).

In addition to these examples, RCM of carbohydrates has also been used in the preparation of cyclopentene precursors of carbocyclic nucleosides[251] and aminocarbafuranoses such as (+)-trehazolin.[252]

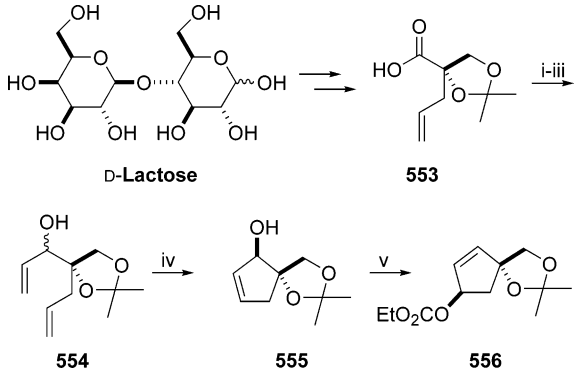
Along these lines, Jacobson and co-workers used the RCM reaction for the preparation of ring-constrained carbanucleosides.[253] Starting from the protected alcohol **544**, readily accessible from D-(+)-ribono-γ-lactone in four steps, the required diene **546** was easily constructed in good yield (Scheme 76). The critical olefin metathesis reaction was then accomplished using Grubbs' catalyst **523**, to give a diastereomeric mixture of cyclopentenols. Allylic oxidation of the

Scheme 77. Synthesis of the Carbocyclic Derivative 552[a]



[a] Reagents: (i) **523**, CH_2Cl_2, 80%; (ii) 0.4% H_2SO_4, dioxane, reflux; (iii) $NaIO_4$, CH_2Cl_2, SiO_2; (iv) $NaBH_4$, MeOH, 70% three steps.

Scheme 78. Synthesis of Carbafuranose Intermediate 556[a]



[a] Reagents: (i) *N*,*O*-dihydroxymethylamine hydrochloride, DCC, DMAP, CH_2Cl_2, 88%; (ii) 1.0 M LAH in THF, THF, −78 °C, 82%; (iii) CH_2═CHMgBr, THF, −78 °C, 96%; (iv) **523**, PhH, reflux, 97%; (v) $ClCO_2Et$, py, DMAP, 80%.

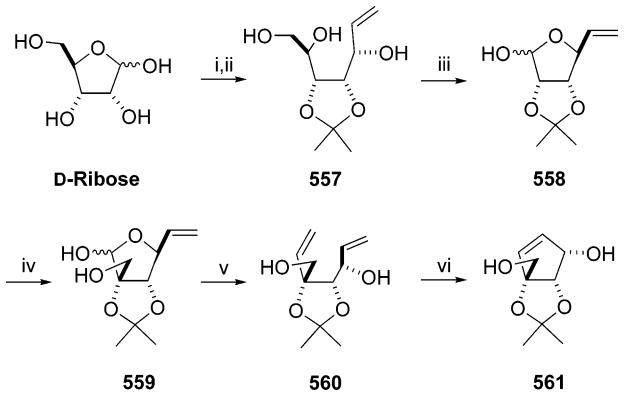
alcohol moiety furnished the intermediate key enone **547**, which was finally reduced ($NaBH_4$ and $CeCl_3$) and cyclopropanated, according to the reported procedure,[254] to provide the ring-strained bicyclic compound **548**.

In related work, Gurjar and Maheshwar[255] prepared a structurally modified carbocyclic nucleoside having a tertiary hydroxyl group and an unsaturation in its framework (Scheme 77). Starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**549**), the requisite diene **550** was uneventfully prepared. Ring-closing metathesis of **550** using Grubbs' catalyst gave the bicyclic derivative **551**. Transformation of the latter into diol **552** was accomplished by a sequence that included hydrolysis of the isopropylidene group, $NaIO_4$-promoted oxidative cleavage, and $NaBH_4$ reduction.

A similar route to several types of 4′-hydroxycarbocyclic nucleosides has been developed by Hong and co-workers.[256] Using a known procedure,[257] lactose was converted into the acid derivative **553**, which was transformed into the diene **554**. Direct cyclization with Grubbs' catalyst afforded cyclopentene derivative **555**, which, by reaction with $ClCO_2$-Et, yielded the key intermediate **556** (Scheme 78).

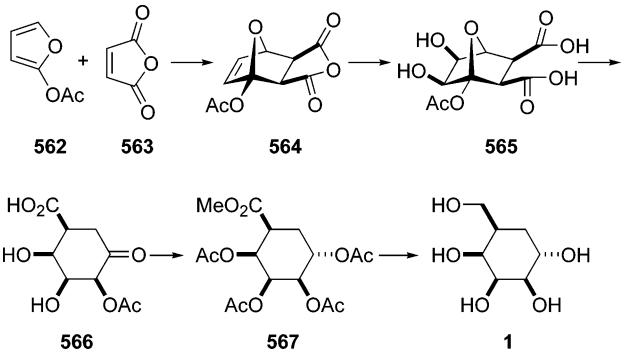
In addition to these examples, Jeong and co-workers used the RCM reaction for the preparation of apio carbocyclic nucleosides, in which the 4′-hydroxymethyl group of the carbasugar moiety has been moved to the $C_{3'}$ position.[258] The synthetic procedure, highlighted in Scheme 79, made use of a stereoselective hydoxymethylation of **558**, easily prepared from D-ribose, and a ring-closing methathesis of the ensuing diene, **560**, to pave the way to **561**.

Scheme 79. Synthesis of the Apio Analogue 561[a]



[a] Reagents: (i) acetone, H_2SO_4, 93%; (ii) CH_2═CHMgBr, THF, from −78 to 0 °C, 81%; (iii) $NaIO_4$, CH_2Cl_2, H_2O, from 0 °C to rt; (iv) K_2CO_3, 37% CH_2O, MeOH, 80 °C, 95%; (v) Ph_3P, CH_3Br, t-BuOK, THF, 81%; (vi) Grubbs' catalyst **524**, CH_2Cl_2, 99%.

Scheme 80. McCasland's Synthesis of 5a-Carba-α-DL-talopyranose (1) (Only D-Enantiomers Are Shown)



6.2. Synthesis of Carbapyranoses

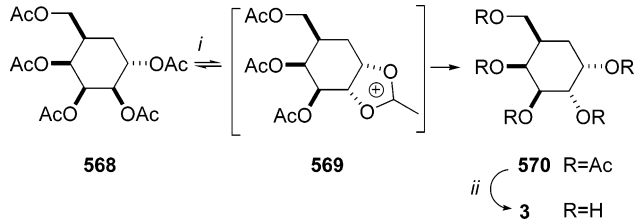
6.2.1. Synthesis from Non-carbohydrate Precursors

Different approaches to carbapyranoses from non-carbohydrate precursors, in either racemic or enantiomerically pure form, have been devised and will be classified according to the type of compounds employed as starting materials: (1) from 7-oxanorbornene derivatives; (2) from other bicyclic compounds; (3) from aromatic derivatives; (4) miscellaneous.

6.2.1.1. From 7-Oxanorbornene Derivatives. 5a-Carba-α-DL-talopyranose (**1**) was first synthesized in 1966 by McCasland using ketoacid **566** as the key intermediate (Scheme 80).[10] The synthesis of **566** was carried out using a route previously used by Daniels and co-workers[259] in their synthesis of shikimic acid and based on a Diels−Alder reaction of 2-acetoxyfuran (**562**) and maleic anhydride (**563**). Hydroxylation and hydrolysis of the ensuing Diels−Alder adduct, **564**, gave diol diacid **565**, which, on prolonged reaction with water, undergoes a series of transformations (acetyl migration, opening of the 1,4-oxacyclic ring, carbonyl liberation, and decarboxylation) leading to **566** (Scheme 80). Sodium borohydride reduction of **566**, and subsequent esterification with methanol and trifluoracetic acid, followed by acetylation gave the tetraacetate **567**, which was converted into the target carbasugar **1**, by reduction with lithium aluminum hydride followed by hydrolysis.

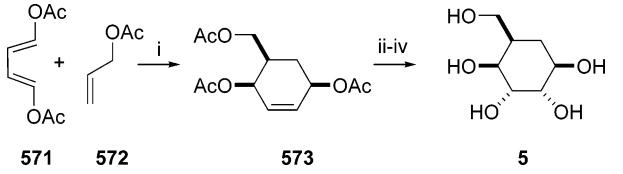
5a-Carba-α-DL-galactopyranose [(±)-**3**] (Scheme 81) was prepared by deacetylation of pentaacetate **570**, which in its turn was readily obtained from 5a-carba-α-DL-talopyranose pentaacetate **568** by acid-induced epimerization at C_2 through

Scheme 81. McCasland's Synthesis of 5a-carba-α-DL-galactopyranose, (3) (Only D-Enantiomers Are Shown)[a]



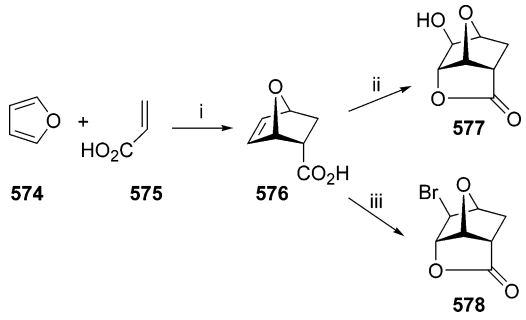
[a] Reagents: (i) AcOH, H_2SO_4, reflux, 14%; (ii) HCl, EtOH, H_2O, reflux, 71%.

Scheme 82. McCasland's Synthesis of 5a-Carba-β-DL-guloyranose (5)[a]



[a] Reagents: (i) 210 °C, 48 h, 70%; (ii) OsO_4, H_2O_2, t-BuOH; (iii) Ac_2O, py, 38% from **573**; (iv) HCl, EtOH, H_2O, reflux, 88%.

Scheme 83. Suami and Ogawa's Precursors for Carbahexopyranoses (Only D-Enantiomers Are Shown)[a]



[a] Reagents: (i) hydroquinone, Δ, sealed tube, 45%; (ii) HCO_2H, H_2O_2; (iii) HOBr, 91%.

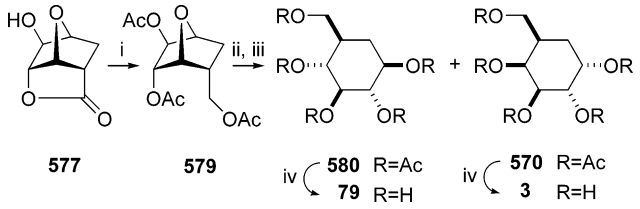
an intermediary cyclic acetoxonium ion (**569**) which was formed by anchimeric assistance of the neighboring acetoxyl group.[11]

5a-Carba-β-DL-gulopyranose (**5**) (Scheme 82) was synthesized by hydroxylation of the adduct **573**, obtained by Diels−Alder cycloaddition of 1,4-diacetoxy-1,3-butadiene (**571**) and allyl acetate (**572**). Successive acetylation and hydrolysis afforded the free carbasugar in 33% overall yield.[12]

After the pioneering work of McCasland and co-workers, 7-oxanorbornene derivatives have been extensively used as starting materials for the synthesis of carbapyranoses and derivatives.[260] Since then, much credit for the development of this field must go to Profs. Seiichiro Ogawa and Tetsuo Suami, who have made an impressive contribution to the study of these compounds. They have reviewed most of their work prior to 1990, and readers are referred to these articles for thorough coverage.[16] In spite of that, a brief survey of the carbapyranoses and related compounds prepared by Ogawa and co-workers is displayed in Table 4, and only selected examples will be presented in this review in order to illustrate their methodologies (Schemes 83−94).

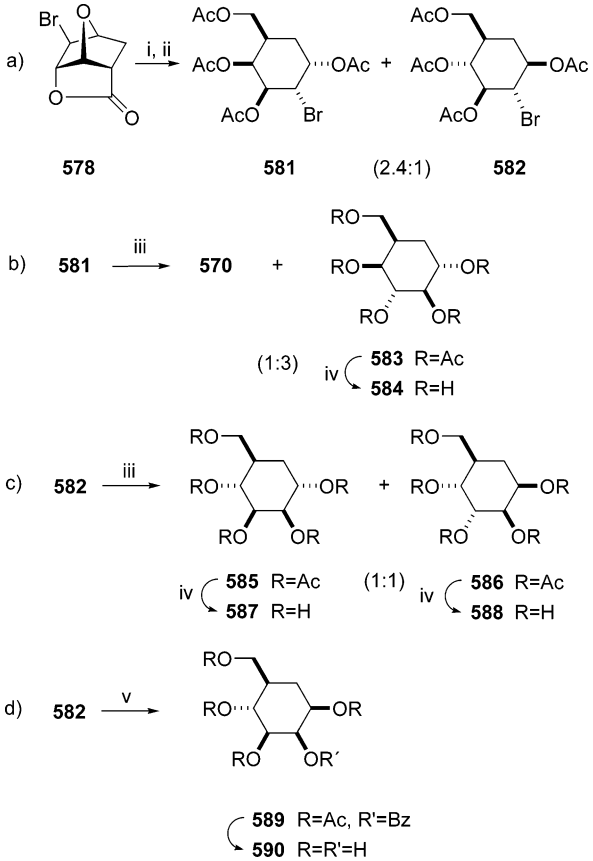
The key intermediate in their approach, 7-oxabicyclo-[2.2.1]hepten-5-ene-2-carboxylic acid (**576**) is readily prepared by Diels−Alder cycloaddition of furan (**574**) and acrylic acid (**575**) (Scheme 83). Adduct **576** was shown to

Scheme 84. Synthesis of 5a-Carba-β-DL-glucopyranose (79) and 5a-Carba-α-DL-galactopyranose (3) (Only One Enantiomer Is Shown)[a]



[a] Reagents: (i) LAH; (ii) Ac_2O, py, DMAP; (iii) AcOH, Ac_2O, H_2SO_4, 18% **580** overall, 19% **570** overall; (iv) NaOMe, MeOH, quant.

Scheme 85. Synthesis of Carba-DL-hexopyranoses from Bromo Derivatives 581 and 582 (Only One Enantiomer Is Shown)[a]



[a] Reagents: (i) LAH; (ii) AcOH, Ac_2O, H_2SO_4, 46%; (iii) NaOAc, 41% for **581**; 56% for **582**; (iv) NaOMe, MeOH, quant; (v) NaOBz.

be an ideal starting material in the forthcoming synthesis of carbasugars, and 11 of the original 16 racemic syntheses have made use of it. When acid **576** was treated with hydrogen peroxide and formic acid, the hydroxylactone **577** was formed. This compound has been the key intermediate in the syntheses of β-DL-gluco-,[261] α-DL-galacto-,[261] β-DL-allo-,[262] and α-DL-gulocarbapyranoses[263] and the carbasugar analogues of KDO[264] and NANA.[264] The majority of the remaining carbapyranoses, α-DL-manno-[261], β-DL-manno-[261], β-DL-altro-[261], α-DL-ido-[261] α-DL-gluco-[262], and α-DL-allopyranose,[262] were derived from lactone **578**, also prepared from **576** by the action of hydrobromous acid (Scheme 83).

In the synthetic protocols originating from norbornane lactones **577** and **578**, the cyclohexane ring of the carbasugar is unveiled by ring opening of the 1,4-cyclic ether moiety, and the use of these derivatives in the preparation of carbasugars and derivatives is illustrated in Schemes 84 and 85.

Table 4. Carba Analogues of Aldohexo- and Ketohexopyranoses, Glycosylamines, Carba-disaccharides, Carba-oligosaccharides, and Other Carba Derivatives Prepared by Suami and Ogawa from 7-Oxanorbornene Derivatives

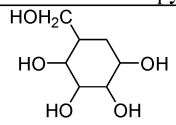
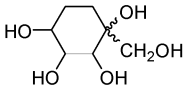
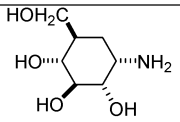
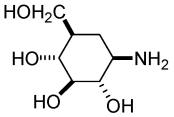
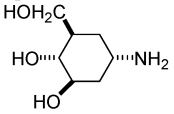
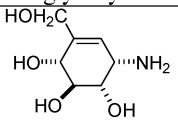
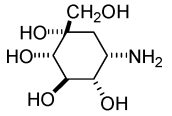
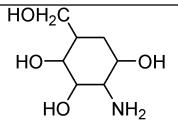
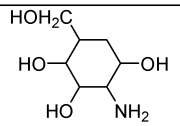
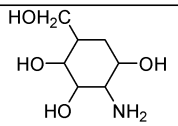
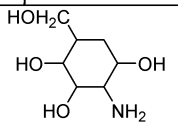
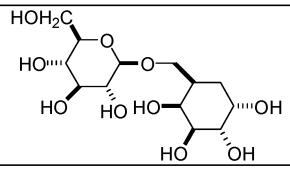
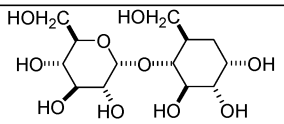
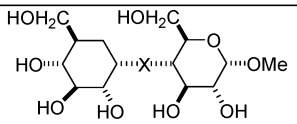
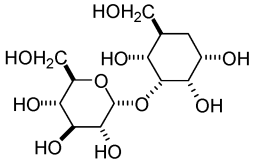
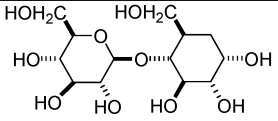
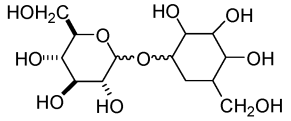
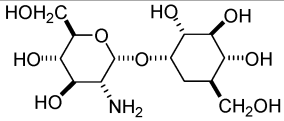
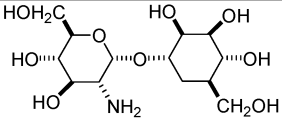
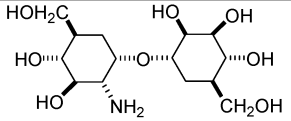
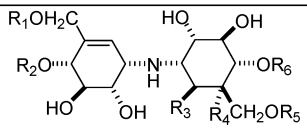
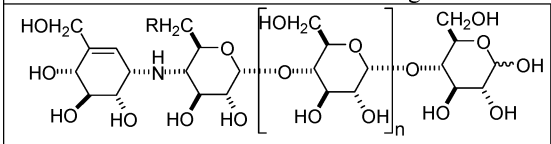
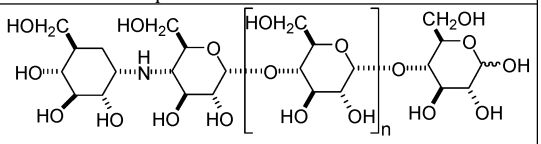
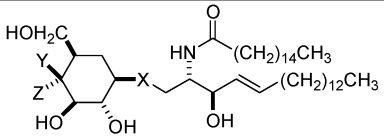
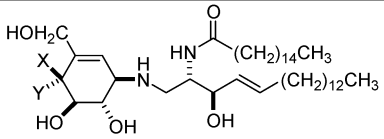
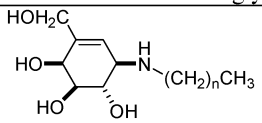
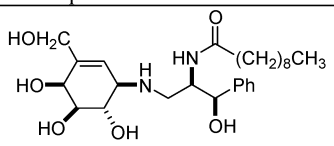
<table>
<tr><td colspan="4">Carba-aldohexopyranoses and carba-ketohexopyranoses</td></tr>
<tr><td colspan="3"> 
5a-carba-hexopyranoses</td><td> 
6a-carba-fructopyranoses</td></tr>
<tr><td>α-DL-allo
β-DL-allo
β-DL-altro
α-DL-galacto
α-DL-gluco
β-DL-gluco</td><td>α-DL-gulo
α-DL-ido
β-DL-ido
α-DL-manno
β-DL-manno
β-DL-talo</td><td>α-D-galacto
α-D-gluco
β-D-gluco
α-L-gluco</td><td>β-DL
β-D
β-L</td></tr>
<tr><td colspan="4">Carba-glycosylamines</td></tr>
<tr><td> 
Validamine DL and (+)- D
 
1-epi-validamine DL
 
2-deoxy-validamine DL</td><td> 
Valienamine DL and (+)-D
 
Valiolamine DL</td><td> 
2-amino-2-deoxy-5a-carba-hexopyranoses
α-DL-allo
β-DL-allo
α-DL-galacto
β-DL-galacto
β-DL-gluco
α-DL-gulo
β-DL-gulo
α-DL-manno
β-DL-manno</td></tr>
<tr><td> 
3-amino-3-deoxy-5a-carba-hexopyranoses</td><td> 
4-amino-4-deoxy-5a-carba-hexopyranoses</td><td> 
7-amino-7-deoxy-5a-carba-hexopyranoses</td></tr>
<tr><td>β-DL-altro
α-DL-gluco
β-DL-gluco</td><td>α-DL-ido
β-DL-manno</td><td>α-DL-gluco</td><td>α-DL-gluco
β-DL-gluco</td></tr>
<tr><td colspan="4">Mono carba-disaccharides and related compounds</td></tr>
<tr><td>  </td><td>  </td><td> 
X=NH, O, S</td></tr>
<tr><td>  </td><td>  </td><td> 
α,α/ α,β/ β,α/ β,β
(D-glucopyranose and D- or L-carba-glucopyranose</td></tr>
<tr><td>  </td><td>  </td><td>  </td></tr>
</table>

Table 4. Continued

Validamycin and related compounds	
	Validamycin A, R_1,R_2,R_3,R_4,R_5=H; R_6=β-Glcp Validamycin B, R_1,R_2,R_4,R_5=H; R_3=OH; R_6=β-Glcp Validamycin D, R_1,R_2,R_3,R_4,R_6=H; R_5=α-Glcp Validoxylamine A, R_1,R_2,R_3,R_4,R_5, R_6=H Validoxylamine B, R_1,R_2, ,R_4,R_5,R_6=H; R_3=OH

Carba-oligosaccharides and related compounds	
	
Acarbose, R=H; n=1 Amylostatin G, R=H; n=0 Adiposin 2, R=OH; n=1 Adiposin 1, R=OH; n=0	Oligostatin

Carba-glycosylceramides and related compounds	
	
X=NH; Y=H; Z=OH X=NH; Y=H; Z=H X=O; Y=H; Z=OH X=S; Y=H; Z=OH	X=H; Y=OH X=OH; Y=H

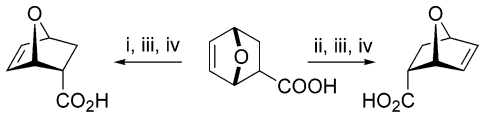
Carba-glycocerebrosides and related compounds	
	
n=3, 5, 7, 9, 13, 17	

For instance, reduction and peracetylation of hydroxylactone **577** furnished triacetate **579**, which under acidic conditions underwent a non-regioselective cleavage of the 1,4-oxa-bridge to yield 5a-carba-β-DL-glucopyranose pentaacetate (**580**) and 5a-carba-α-DL-galactopyranose pentaacetate (**570**) (Scheme 84).[261]

Alternatively, reduction, acetylation, and acetolysis of **578** gave a mixture of bromo derivatives **581** and **582** (Scheme 85a), which were independently subjected to substitution reactions with acetate ion to furnish 5a-carba-α-DL-galactopyranose pentaacetate (**570**), 5a-carba-α-DL-idopyranose (**584**) (Scheme 85b), 5a-carba-α-DL-mannopyranose (**587**), and 5a-carba-β-DL-altropyranose (**588**) (Scheme 85c). The substitution reactions appear to involve acetoxonium cations as intermediates. However, if sodium benzoate was used instead of sodium acetate (Scheme 85d), direct S_N2 reaction occurred and 5a-carba-β-DL-mannopyranose (**590**) was obtained, via intermediate **589**.[261]

These protocols have also been tailored for enantiopure carbasugar synthesis. Accordingly, optically pure (+)- and (−)-**576** were obtained by fractional crystallization of the

Scheme 86. Enantiomeric Resolution of (±)-576 by Fractional Crystallization of Its Diastereomeric Salts[a]



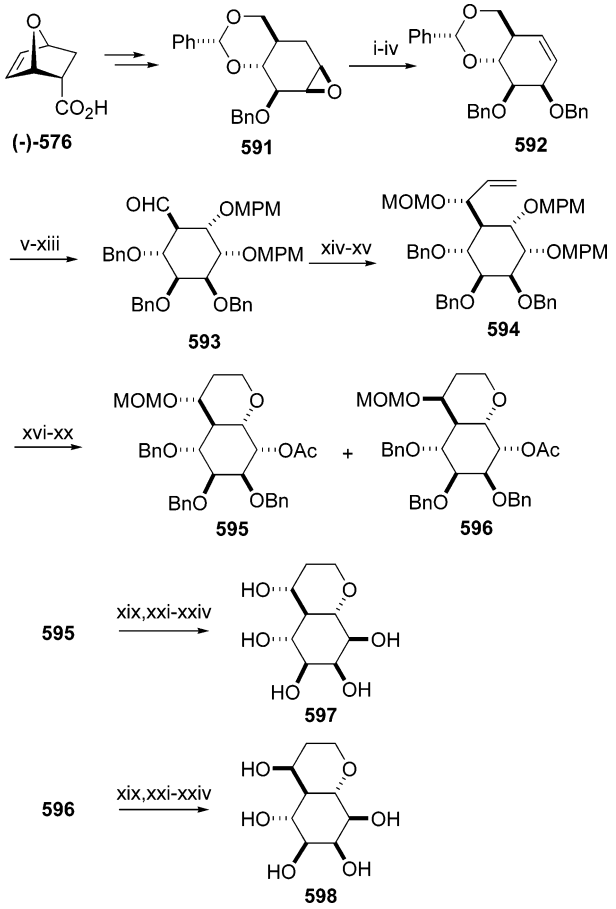
(-)-**576** (±)-**576** (+)-**576**

[a] Reagents: (i) (*R*)-phenylethylamine, EtOH; (ii) (*S*)-phenylethylamine, EtOH; (iii) fractional crystallization; (iv) Dowex 50W X2.

diastereoisomeric salts arising from the treatment of (±)-**576** with optically active 1-phenylethylamine (Scheme 86),[265] and both enantiomers have been used for the synthesis of the optically active carbasugar series. The acid (−)-**576** gave 5a-carba-β-D-glucopyranose (**79**),[266] 5a-carba-α-D-galactopyranose (**3**),[266] and 5a-carba-α-D-glucopyranose (**81**).[267] On the other hand, (+)-**576** gave the corresponding carbapyranoses of the L-series (Scheme 86).[265,266]

More recent contributions from Ogawa's group include the preparation of bicyclic derivatives of 5a-carba-α- and -β-D-mannopyranoses[268] (**597** and **598**) from (−)-**576** (Scheme

Scheme 87. Synthesis of Bicyclic Derivatives of Carbasugars[a]



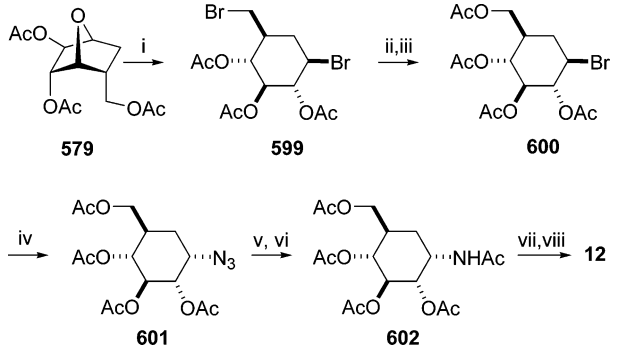
[a] Reagents: (i) LiBr, NaBr, THF; (ii) Ac_2O, py; (iii) DBU, 88%, three steps; (iv) NaOMe, MeOH; (v) OsO_4; (vi) Ac_2O, 100%, two steps; (vii) NaOMe, MeOH; (viii) NaH, PMBCl, DMF, 90%; (ix) AcOH−H_2O; (x) BzCl, py, 87%, two steps; (xi) NaH, BnCl, 58%; (xii) DIBAL-H, 97%; (xiii) DMSO, oxalylchloride; (xiv) EtMgBr, THF, 80%, two steps; (xv) methoxymethylation, 92%; (xvi) hydroboration, 86%; (xvii) tosylation, 85%; (xviii) CAN, CH_3CN; (xix) NaOMe, MeOH; (xx) Ac_2O, py, 30% **595**, 25% **596**, (xxi) Ac_2O, DMSO, 100%; (xxii) L-Selectride, THF, 74%; (xxiii) HCl, H_2O−THF; (xxiv) H_2, Pd−C, 95% **597**, 40% **598**.

87). These conformationally restricted compounds have been synthesized to provide key components for elucidation of the mechanism and action of *N*-acetylglucosaminyltransferase (GlcNAcT-V). The synthetic scheme implies transformations of the epoxide **591** readily available from (−)-**576**.[121]

These strategies have also been applied to the preparation of aminocarbasugars in both racemic and enantiomerically pure forms. The synthesis of DL-validamine (**12**) (Scheme 88) was reported[261a] in the mid-1970s from hydroxylactone **577**.[269] When triacetate **579** was treated with 20% hydrogen bromide at 85 °C, it gave dibromide **599**, in which the primary bromide was selectively replaced with an acetoxy group and the secondary bromo function was displaced with azide ion to give **601**, which was hydrogenated and acetylated to give, after deprotection, racemic validamine (**12**).

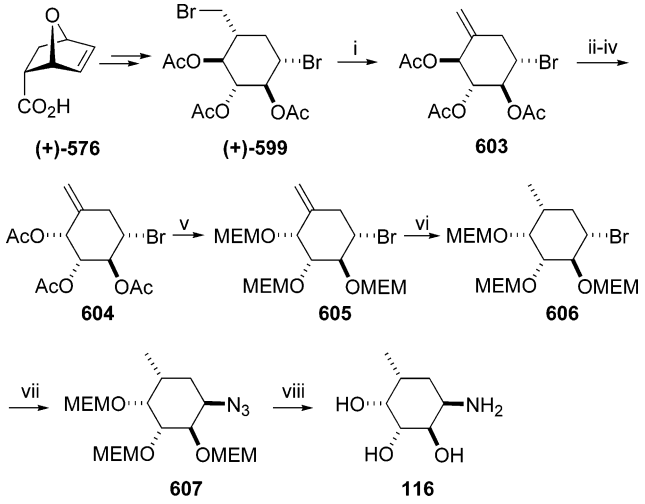
Since then, DL-valienamine,[102b,270−272] DL-hydroxyvalidamine,[273] DL-valiolamine,[274] 2-amino-5a-carbadeoxy-DL-pyranoses,[275,276] 3-amino-5a-deoxy-DL-pyranoses,[277] DL-hydroxyvalidamine,[278] DL-1-epi-validamine,[102a] DL-2-epi-validamine,[261b] DL-2-amino-2-deoxyvalidamine having α- and β-gluco and α- and β-manno configurations,[279] 5a-carba-α-DL-fucopyranosylamine,[114a] 5a-carba-α-DL-galactopyranosylamine,[114a] and fucose-type α- and β-valienamine derivatives,[115] all in racemic form, have also been synthesized using Diels−Alder adduct **576** as starting material.

Scheme 88. Synthesis of (±)-Validamine (12) by Ogawa et al. (Only D-Enantiomers Are Shown)[a]



[a] Reagents: (i) 30% HBr−AcOH, AcOH, 80 °C, 24 h, 53%; (ii) NaOAc, $MeOCH_2CH_2OH$, 90%; (iii) Ac_2O, py; (iv) NaN_3; (v) H_2, Ra−Ni; (vi) Ac_2O, py, 50%; (vii) NaOMe, MeOH, 3 h; (viii) NH_2NH_2, sealed tube, 100 °C.

Scheme 89. Synthesis of 5a-Carba-α-L-fucopyranosylamine (116)[a]

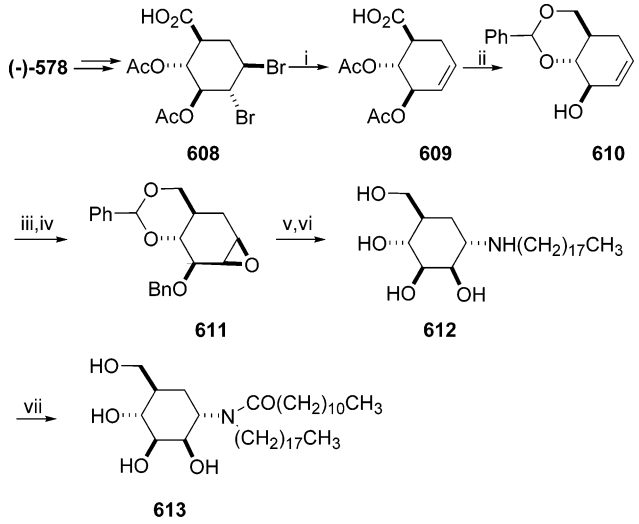


[a] Reagents: (i) AgF, py, 5 h, 77%; (ii) 4 M HCl, THF, 72 h, 60 °C, then 2,2-dimethoxypropane, TsOH, DMF, 60 °C, 72%; (iii) MsCl, py, 0 °C; (iv) AcOH, 4 h, then Ac_2O, py, 73% (two steps); (v) 4 M HCl, THF, chloromethoxymethane, $(i\text{-}Pr)_2NH$, 14 h, 40 °C, 84%; (vi) H_2, Wilkinson catalyst, PhH, 16 h, 80%; (vii) NaN_3, DMF, 9 h, 90 °C, 86%; (viii) 4 M HCl, THF, then Ph_3P, THF, 72 h, 60 °C, 66%.

Enantiopure (+)-validamine (**12**)[266] and (+)-valienamine (**11**)[280] were later prepared from chiral (−)-**576** following the same procedure previously employed for the synthesis of their racemates. Alternatively, to obtain pure L-antipodes, Ogawa and co-workers used the optically resolved (+)-**576**[265] as the starting material. For instance, selective dehydrobromination of 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-5a-carba-β-L-glucopyranosyl bromide [(+)-**599**], obtained from (+)-**576**, followed by inversion of the configuration at C_4 and exchange of protecting groups, afforded the *exo*-methylene derivative **605**. Selective hydrogenation, azidolysis, deprotection, and subsequent reduction of the azido group allowed the synthesis of 5a-carba-α-L-fucopyranosylamine (L-**116**)[114b] (Scheme 89).

Ogawa and co-workers have also contributed to the development of methods for the preparation of 5a-carbaglycosylamide and 5a-carbaglycosylceramide analogues, structurally related to glycosphingolipids and glycoglycerolipids. The strategy for the synthesis of carbaglycosylamides is based on the coupling of 1,2-epoxides of 5a-carbapyranoses

Scheme 90. Synthesis of Carbapyranosylamides[a]



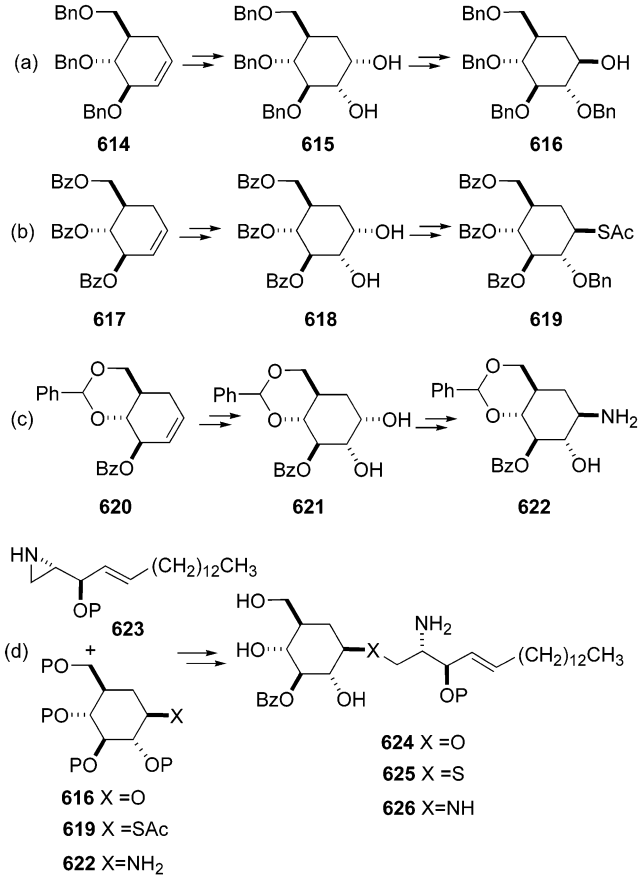
[a] Reagents: (i) HBr, AcOH; (ii) Zn, AcOH; (iii) LAH, THF, 2 h; (iv) DMF, α,α-dimethoxytoluene, TsOH, 60 °C, 2 h, 60% (two steps); (v) MCPBA, phosphate buffer, CH_2Cl_2, 2 h; (vi) NaH, DMF, BnCl, 2 h, 88%; (vii) octadecylamine, 2-propanol, sealed tube, 120 °C, 20 h, 87%; (viii) dodecanolyl chloride, DMAP, CH_2Cl_2, 0 °C, 1 h, 61%; (ix) AcOH, THF, H_2O, 5 h, 80 °C; (x) H_2, EtOH, Pd−C, 2 h; (xi) 0.1 M NaOMe, MeOH, 1 h, 0 °C, 69% (three steps).

with aliphatic amines and successive *N*-acylation with acyl chlorides.[107a] An example is shown in Scheme 90. Treatment of bromolactone (−)-**578** with hydrogen bromide in acetic acid resulted in the cleavage of the 1,4-cyclic ether to give carboxylic acid **608**. Debromination with zinc dust in acetic acid afforded the cyclohexene derivative **609**, which was converted into the 5a-carba-glucal derivative **610**.[261] Epoxidation of **610** with *m*-chloroperbenzoic acid followed by conventional *O*-benzylation produced the *β*-epoxide **611**[281] together with a minor amount of the α isomer. Coupling of the *β*-epoxide with octadecylamine gave diaxially opened product **612**, which was *N*,*O*-acetylated with dodecanoyl chloride to give, after deprotection, 5a-carba-α-D-mannosylamide (**613**).[107a]

For the preparation of carbocyclic analogues of glycoceramides, Ogawa's group has elaborated a general method based on the opening of aziridines of sphingosine derivatives with the appropriate derivatives of 5a-carbapyranoses, which, in turn, were prepared using 5a-carba-D-glycals[282] (Scheme 91).[107a] For instance, 5a-carba-D-glucal derivatives **614**, **617**, and **620** were oxidized with OsO_4 and NMO to give respectively **615**, **618**, and **621**. In these derivatives the equatorial 2-OH group was protected and the axial 1-OH function was inverted or exchanged by an amine or thiol moiety according to established procedures to afford 1-hydroxy, 1-mercapto, or 1-amino derivatives **616**, **619**, or **622**, respectively. Coupling of these compounds with aziridine **623** as the sphingosine precursor and subsequent deprotection and *N*-acylation gave 5a-carba-*β*-D-glucosylceramide analogues linked by ether, sulfide, and imino linkages (**624**, **625**, and **626**).

The contribution from Ogawa's laboratory in the area of carbadisaccharides is also impressive, and their general strategies are outlined in Figure 46. Initially, they described a strategy based on the glycosyl coupling of monosaccharide donors with suitably protected carbasugar acceptors leading to carbasaccharides with the carbasugar located at the reducing end (Figure 46a). For the synthesis of carbasaccharides with carbasugars at the nonreducing end, Ogawa

Scheme 91. Synthesis of Carbapyranosylceramides



et al. developed the use of 1,2-epoxides of 5a-carbapyranoses as versatile 5a-carbahexopyranosyl donors (Figure 46b). Carbasugar oxiranes were also used in the preparation of "bis" carbadisaccharides (Figure 46c).

Examples of the first approach include the synthesis of 5a-carbatrehaloses,[283] 5a-carbamaltoses,[284] 5a-carbacellobioses,[284] 5a-carbalaminarabioses,[284] and 5a-carbatrisaccharides.[121] For instance, condensation of equimolecular amounts of 5a-carba-1,2:4,6-di-*O*-isopropylidene-α-DL-glucopyranose (**627**) with D-glucosyl bromide (**628**) in the presence of Hg(II) cyanide afforded a diastereomeric mixture of protected laminarabioses **629** and **630** (Scheme 92). In an analogous

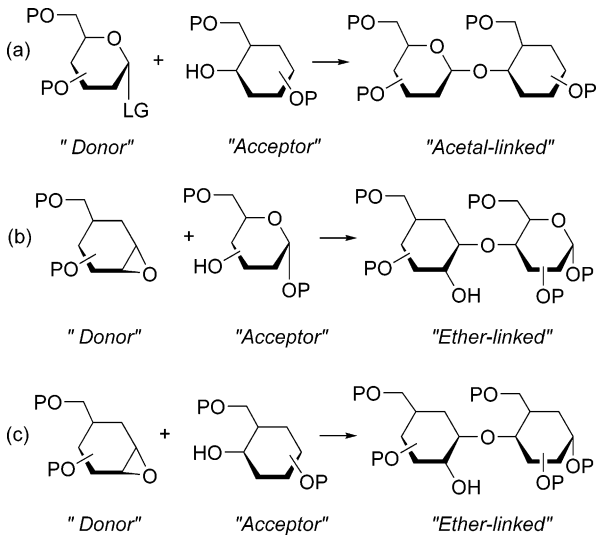
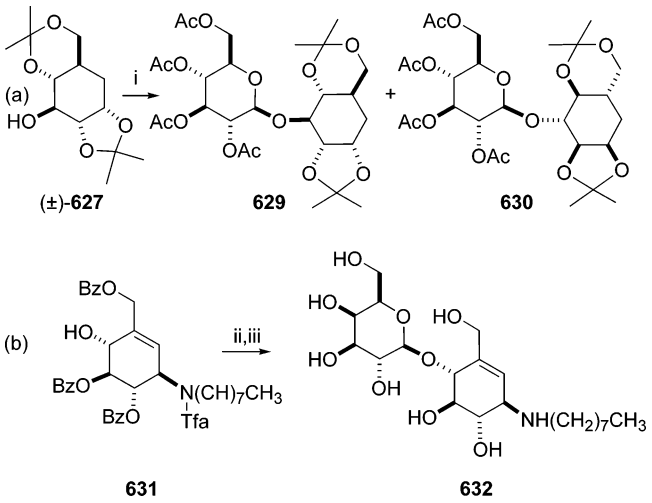


Figure 46. Ogawa's approaches to carbaoligosaccharide synthesis.

Scheme 92. Synthesis of Carbadisaccharides[a]



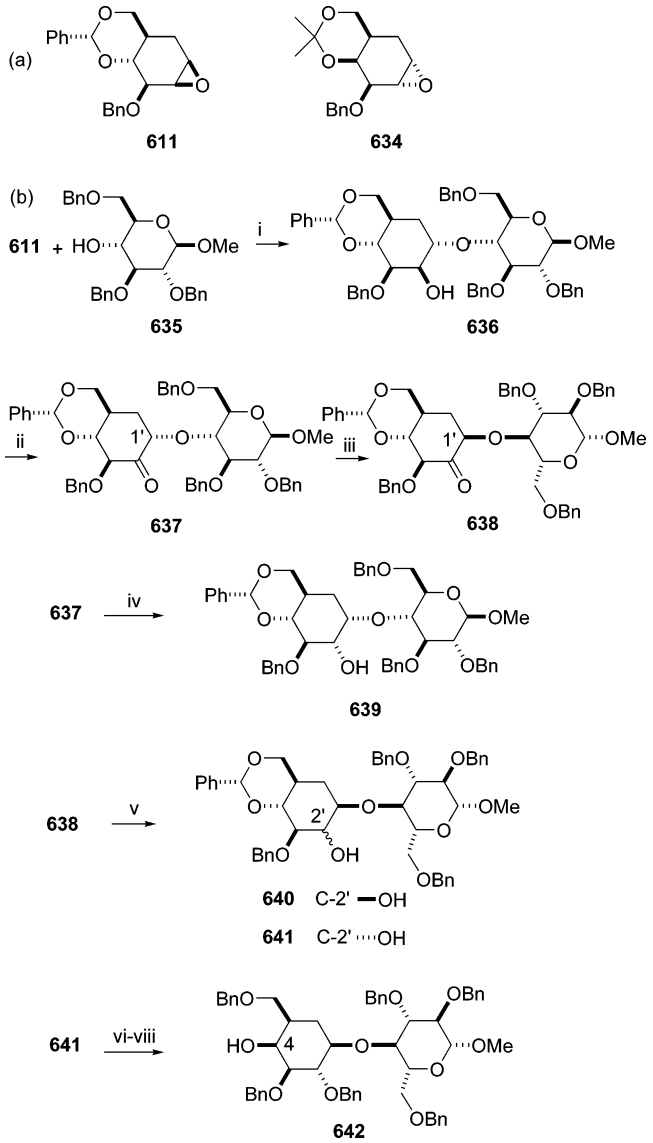
[a] Reagents: (i) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**628**), $Hg(CN)_2$, Drierite, benzene, reflux, 72%; (ii) 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (**632**), $BF_3{\cdot}Et_2O$, molecular sieves 4A, CH_2Cl_2, 0 °C, 19%; (iii) K_2CO_3, MeOH, 1 h, 73%.

manner, when protected *N*-octyl-β-valienamine (**631**)[109,111] was reacted with the D-galactosyl trichloroacetimidate **632**, the *N*-octyl-5a′-carba-β-lactosylamine **633** was obtained.[285]

In the second route, 1,2-epoxides of 5a-carbapyranoses[279,281] were developed as "5a-carbahexopyranosyl donors" (Scheme 93).[286] 1,2-Anhydro-3-*O*-benzyl-4,6-*O*-benzylidene-5a-carba-β-D-mannopyranose (**611**)[106] was initially used, and it was shown to be a very versatile donor for introduction of 5a-carba-α-D-mannopyranose residues into an oligosaccharide chain.[125,287,288] For example, condensation of **611** with the oxide anion derived by treatment of the 4-hydroxy unprotected acceptor **635** with NaH in DMF in the presence of 15-crown-5-ether at 70 °C gave the 5a′-carbadisaccharide derivative **636** in high yield. However, 5a-carbagalactopyranosyl donors, for example **634**, were shown to be poor substrates for nucleophilic attack of bulky oxide anions, giving a complex mixture of products. Because of this situation and oriented to the synthesis of biologically interesting lactosaminides, Ogawa and co-workers followed a strategy based on the transformation of the 5a-carbamannopyranose moiety into those of 5a-carba-D-galactopyranose by a sequence of consecutive epimerizations. Initially, the 2′-OH group in **636** was oxidized and subsequently reduced to the epimeric 5a′-carba-α-glucose-containing disaccharide **639**. Under the influence of a base, the α-ketone **637** was epimerized to afford the β-ketone **638** in good yield, which was reduced to give carbapyranose residues with β-gluco- and β-manno configurations (**640** and **641**, respectively). Incorporation of a 5a′-carba-β-galactopyranose residue in **642** was carried out through epimerization at $C_{4'}$ of the carba-β-glucopyranose structure **641**.[289]

Likewise, the preparation of carbaoligosaccharides comprising such linkages as *N*-glycosidic or imino, *S*-glycosidic or thio ether, and *C*-glycosidic or methylene is also possible with the routes developed by Ogawa.[106] The consideration of the synthetic approaches for these compounds lies beyond the scope of this review, and only one representative example will be presented. Thus, for instance, the 5a-carbagalactopyranose donor **643**[107a] was able to couple successfully with amines[107a] to provide directly imino-linked carbalactosaminides and -isolactosaminides. Therefore, condensation of **643** with aminodeoxy derivative **644** gave selectively the diequatorially

Scheme 93. Synthesis of 5a′-Carbadisacccharides[a]



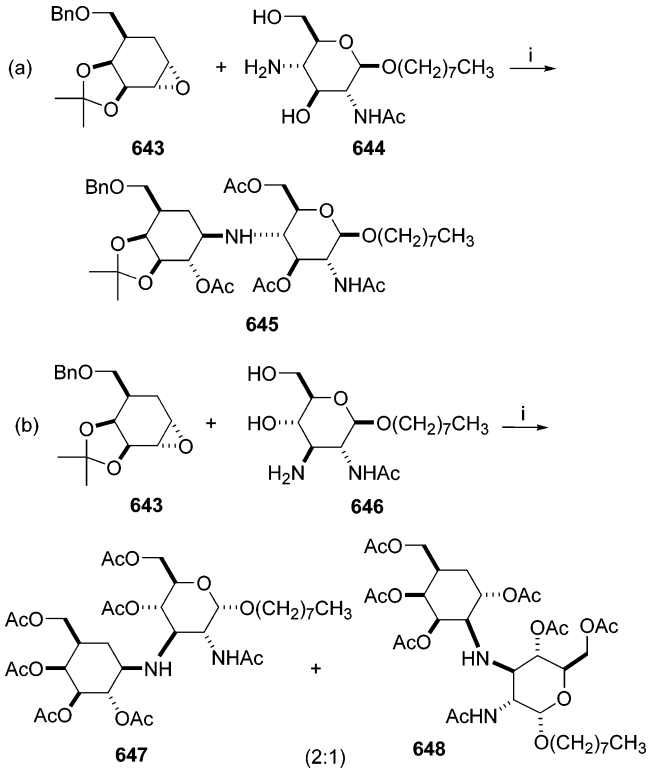
[a] Reagents: (i) NaH, DMF, 15-crown-5 ether, 70 °C, 70%; (ii) DMSO, Ac_2O, 95%; (iii) DBU, $PhCH_3$, 60 °C, 58%; (iv) L-Selectride, THF, −15 °C, 78%; (v) $NaBH_4$, CH_2Cl_2−MeOH; $CeCl_3$, 47% **640**, 50% **641**; (vi) NaH, DMF, benzyl bromide, 24 h, 92%; (vii) BH_3NMe_3, $AlCl_3$, 92%; (viii) PCC, CH_2Cl_2, then L-Selectride, THF, 0 °C, 54%.

opened product **645** whereas the coupling with the *N*-acetylglucosamine derivative **646** gave the two positional isomers **647** and **648** (Scheme 94).[126]

Tatibonët, Rollin, and co-workers[84] have synthesized the 5a-carba analogue of glucotropaeolin (**85**), a compound which was shown to display a good inhibition power against myrosinase, the only enzyme able to hydrolyze glucosinolates. The authors followed Ogawa's approach for the preparation of the required 5a-carba-α-DL-glucopyranose tetrabenzoate **649**, which after introduction of the thiol group at C_1 provided the analogue of the naturally occurring thiosugars found in the botanical order *Brassicales* (Scheme 95).

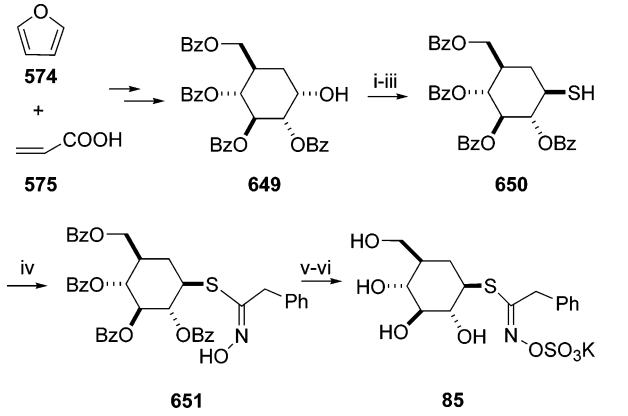
Koizumi and co-workers also exploited 7-oxanorbornene derivatives in their synthesis of optically pure carbapyranoses[290] and related compounds such as (−)-gabosine C and (−)-COTC (2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-trihydroxycyclohex-2-enone).[291] The key feature in their approach involved an asymmetric Diels−Alder reaction of menthyl

Scheme 94. Synthesis of Imino-Linked 5a′-Carbalactosaminide (645) and -isolactosaminide (648)[a]



[a] Reagents: (i) 2-propanol, sealed tube, 3 weeks, then Ac_2O, py; 37% for **645** and 62% for **647** + **648**.

Scheme 95. Synthesis of the 5a-Carba Analogue of Glucotropaeolin, 85[a]

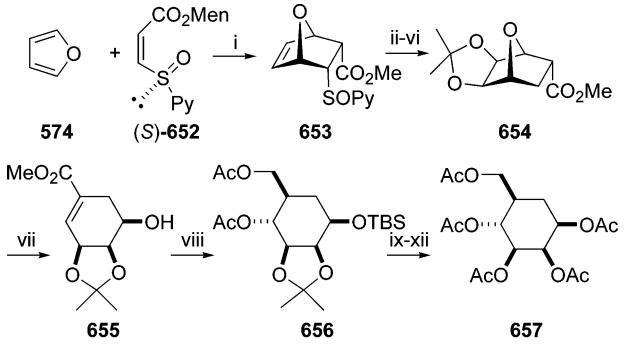


[a] Reagents: (i) Tf_2O, py, DMAP; (ii) thiourea, butanone, two steps, 60%; (iii) $Na_2S_2O_5$, H_2O, $CHCl_3$, 80%; (iv) benzhydroxymoyl chloride, Et_3N, CH_2Cl_2, 70%; (v) SO_3py, DMF, 77%; (vi) KOMe, MeOH, 52%.

(*S*)-(2*E*)-3-(2-pyridylsulfinyl)propenoate (**652**) with furan derivatives.[292,293] For instance, combination of (−)-menthyl-(*S*)-(2*E*)-3-(2-pyridylsulfinyl)propenoate (**652**) with furan **574** gave, with high diastereoselectivity, adduct **653**, which was converted by the usual transformations into (−)-epi-shikimate (**655**). Protection of the free alcohol as its TBS ether and reduction of the ester was followed by stereoselective hydroboration of the alkene to provide, after deprotection and peracetylation, 5a-carba-β-D-mannopyranose pentaacetate (**657**) (Scheme 96).[290]

Alternatively, the cycloaddition reaction of **652** with 3,4-dibenzyloxyfuran (**658**) gave the *endo* and *exo* cycloadducts **659** and **660**. The major *endo* adduct **659** was reduced, desulphenylated, and hydrogenated to furnish methyl ester

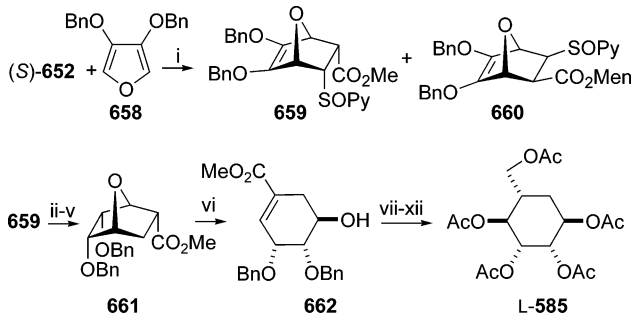
Scheme 96. Synthesis of 5a-Carba-β-D-mannopyranose Pentaacetate (657)[a]



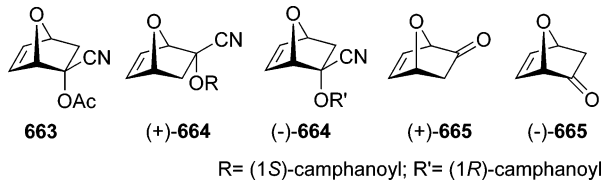
Men= (-)-menthyl

[a] Reagents: (i) Et_2ClAl, CH_2Cl_2; (ii) $TiCl_3$, EtOH; (iii) OsO_4, Me_3NO, acetone, $Me_2C(OMe)_2$, TsOH, 65 °C; (iv) LAH, Et_2O; (v) Raney-Ni (W-4), EtOH; (vi) Jones reagent, acetone, CH_2N_2, MeOH−EtO_2; (vii) LiN(TMS)$_2$, THF, −78 °C; (viii) TBSOTf, Et_3N; (ix) LAH, THF; (x) borane·THF, H_2O_2, NaOH, Ac_2O, py; (xi) TBAF, THF; (xii) aq AcOH, 55 °C, Ac_2O, py, overall yield 11%; (xiii) MsCl, Et_3N, CH_2Cl_2, 0 °C; (xiv) Bu_4NN_3, PhH; (xv) H_2, Raney-Ni (T-4), Ac_2O, EtOH; (xvi) aq AcOH, 60 °C, Ac_2O, py, overall yield 8%.

Scheme 97. Synthesis of 5a-Carba-α-L-mannopyranose Pentaacetatate (L-585) by Koizumi et al.[a]



[a] Reagents: (i) Et_2AlCl, CH_2Cl_2, −20 °C; 50% **659**, 29% **660**; (ii) PBr_3, DMF, 0 °C; (iii) LAH, Et_2O; (iv) Raney-Ni, EtOH; (v) Jones reagent, CH_2N_2, MeOH−Et_2O; (vi) LiN(TMS)$_2$, THF, −78 °C; (vii) TBDPSCl, imidazole, DMF; (viii) DIBAL-H, Et_2O; (ix) BH_3 THF, H_2O_2, NaOH; (x) Ac_2O, py; (xi) TBAF, THF; (xii) H_2, Pd−C, EtOH, Ac_2O, py, overall yield, 2%.



R= (1*S*)-camphanoyl; R'= (1*R*)-camphanoyl

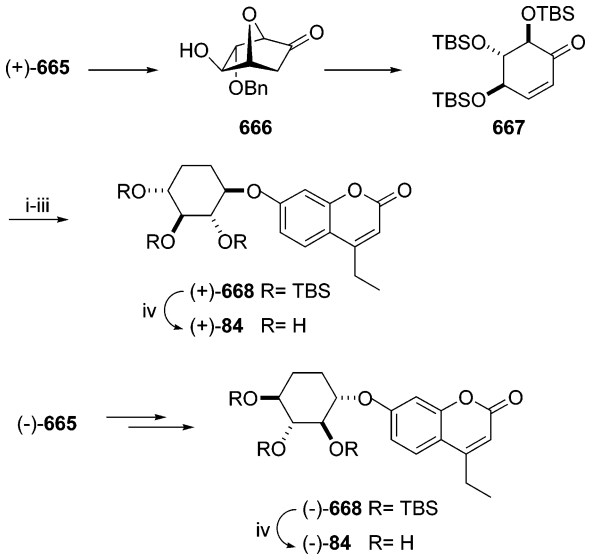
Figure 47. Vogel's 7-oxanorbornene derivatives.

661. Ring opening gave (−)-shikimate (**662**), which was converted to 5a-carba-α-L-mannopyranose pentaacetate (L-**585**) using the reaction sequence shown in Scheme 97.[290]

Different types of 7-oxa-norbornene derivatives, including racemic and optically pure 7-oxabicyclyo[2.2.1]hept-5-en-2-yl derivatives **663**, **664**, and **665** (Figure 47), whose chemistry[294] and previous applications in the preparation of natural products and analogues[295] had been developed by Vogel and co-workers, have also become useful precursors for the synthesis of carbasugars and derivatives.

Derivative **663** was obtained via Diels−Alder addition of furan to 1-cyanovinyl acetate catalyzed by copper or zinc salts. Compound **663** was transformed, after saponification and treatment with formaline, into (±)-**665**. Enantiomerically

Scheme 98. Synthesis of 5a-Carba-β-xylopyranosides[a]



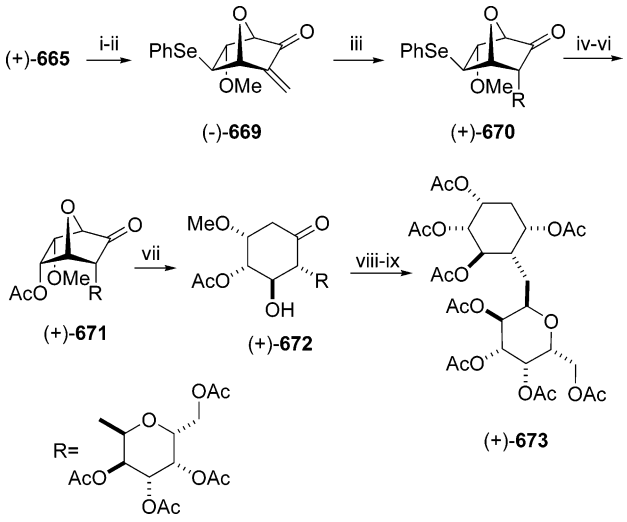
[a] Reagents: (i) $NaBH_4$, $CeCl_3$, CH_2Cl_2; (ii) 4-ethyl-7-hydroxycoumarin, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF; (iii) H_2, Pd−C; (iv) HF, $PhCH_3$, CH_3CN, 39% overall.

pure derivatives (+)-**664** and (−)-**664** can be obtained through ZnI_2- or $ZnBr_2$-catalyzed Diels−Alder addition of furan to (−)-1-cyanovinyl (1*S*)-camphanate and from (+)-1-cyanovinyl (1*R*)-camphanate, respectively. Subsequent saponification and treatment with formaline provides enantiomerically pure (+)-**665** and (−)-**665**. Enantiomerically pure cyano-acetate (+)-**663** can be obtained by crystallization of the corresponding racemic cyanohydrins with 0.5 equiv of brucine, followed by treatment with acetic anhydride.[296] Also, racemic (±)-**665** can be resolved by formation of aminals derived from (*R,R*)-1,2-diphenylethylenediamine.[297] Other methods to obtain enantiomerically pure derivatives have been proposed.[298] A total synthesis of cyclophellitol (**9**) from compound **663** has been performed by Vogel's group.[299] This approach has been recently reviewed.[300]

Vogel and co-workers[83,301] also reported the synthesis of carbaxylopyranosides [(+)-**84** and (−)-**84**] with D- and L-xylose configurations, from (+)-**665** and (−)-**665**, respectively (Scheme 98). Compound (+)-**665** was conveniently converted to **666**, which, upon base treatment, as previously reported by the authors,[302] underwent oxa-bridge opening, leading, after protecting group manipulations, to **667**. Reduction of the latter and reaction with a 4-ethyl-7-hydroxycoumarin in the presence of 1,1′-(azodicarbonyl)dipiperidine and $(n\text{-}Bu)_3P$ furnished silyl derivative (+)-**668**, which, after deprotection, led to (+)-**84**. The corresponding carba-L-xyloside [(−)-**84**] was obtained in a similar manner starting from (−)-**665**. The 5a-carba-β-D-xyloside [(+)-**84**] was an orally active antithrombotic agent in the rat (venous Wessler's test) but less active than racemic **84**.

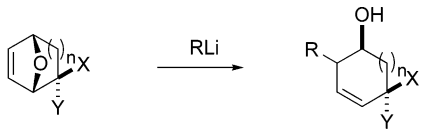
The photoinduced single electron transfer from Et_3N onto (+)-**665** has been applied to the synthesis of α-*C*-galactosides of carbapentopyranoses (+)-**673** as disaccharide mimics[303] (Scheme 99). The synthesis started from (+)-**665**, which adds to PhSeCl in the presence of $HC(OMe)_3$/MeOH to give, after treatment of the lithium enolate with the Eschenmoser's salt, the enone (−)-**669**. Radical *C*-glycosylation and subsequent stereoselective reduction of the tertiary radical onto its *exo* face gave the *endo*-*C*-galactoside (+)-**670**. Oxidation of the selenide followed by a seleno-Pummerer rearrangement and radical deselenation led stereoselectively to (+)-**671**. Irradiation of ketone (+)-**671** in the presence of Et_3N in ^{i}PrOH promoted the 7-oxa ring opening and the formation of β-hydroxy ketone (+)-**672**. Reduction of (+)-**672** followed by acetylation provided the α-*C*-galactoside (+)-**673**.

Scheme 99. Synthesis of (+)-673[a]



[a] Reagents: (i) PhSeCl, MeOH, $HC(OMe)_3$; (ii) LHMDS, THF, $CH_2{=}NMe_2I$, 75%; (iii) n-Bu_3SnH, AIBN, α-acetobromogalactose, 74%; (iv) MCPBA; (v) Ac_2O, NaOAc, 82%; (vi) n-Bu_3SnH, AIBN, 97%; (vii) $NaBH_4$; (viii) irradiation, Et_3N, MeOH; (ix) Ac_2O, py, DMAP, three steps, 46%.

Scheme 100. Regioselectivity in the Opening of 7-Oxanorbornene Systems with Organolithium Reagents



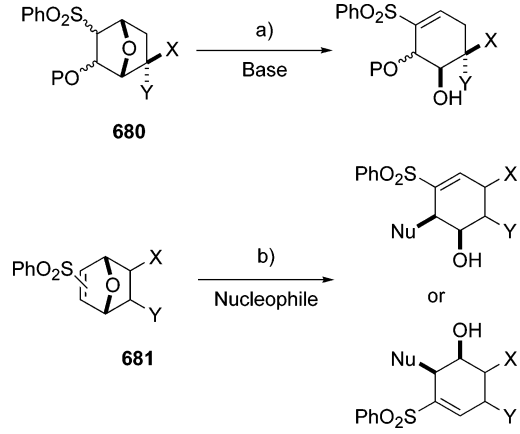
674, n=1; X=H, alkyl, vinyl, aryl, allyl; Y=OH
675, n=1; X=OH; Y=alkyl, vinyl, aryl, allyl
676, n=2; X=Me; Y=OH

677, R= alkyl, vinyl, aryl, allyl
678, R= alkyl, vinyl, aryl, allyl
679, R= t-Bu

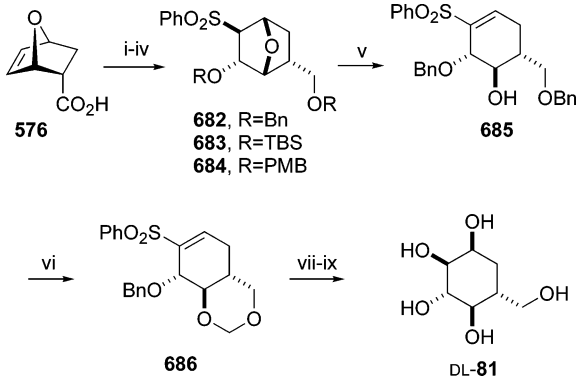
However, in the case of the related protected alcohols or hydroxymethyl derivatives, this reaction displayed a dramatic decrease in regioselectivity which, in some cases, disappeared completely.[307] In order to make this transformation synthetically useful, Arjona, Plumet, and co-workers incorporated a phenylsulfonyl functionality to the oxabicyclic system.[308] In this way, bicyclic compounds such as **680** and **681** (Scheme 101) were able to react with organolithium compounds by application of two different methodologies: (a) base-induced ethereal bridge opening, applied to compounds **680**, and (b) a Michael addition ring-opening sequence applied to compounds **681**.[309]

Implementation of methodology a, using **576** as the starting material, led to 5a-carba-α-DL-glucopyranose (**81**) (Scheme 102).[310] Regiocontrolled phenylsulfenoetherification, followed by reduction, protection of the diol, and oxidation, yielded bicyclic sulfones **682**−**684**. Strain-directed β-elimination was then achieved on **682** using ^{n}BuLi as the basic reagent, to give **685**. Reaction of **685** with dimethoxyethane

Scheme 101. Reaction of Organolithium Reagents with Phenylsulfonyl Oxabicyclic Systems

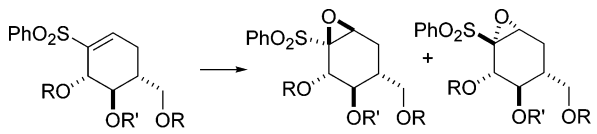


Scheme 102. Synthesis of 5a-Carba-α-DL-glucopyranose (81)[a]



[a] Reagents: (i) PhSCl, $CHCl_3$, 82%; (ii) LAH, THF, 90%; (iii) TBSCl, imidazole, DMF, 95% for **683**; BnCl, KOH, dioxane, 90% for **682**; PMBCl, KOH, dioxane, 85% for **684**; (iv) MMPP, MeOH, 97%; (v) n-BuLi, $PhCH_3$-TMEDA, 80%; (vi) $(MeO)_2CH_2$, TsOH, CH_2Cl_2, 88%; (vii) Na(Hg), MeOH, Na_2HPO_4, 75%; (viii) OsO_4, NMMO, acetone−H_2O, 95%; (ix) BF_3OEt_2, EtSH, 90%.

Scheme 103. Influence of the Protecting Groups in the Stereoselectivity of the Nucleophilic Epoxidation of Sulfones 685 and 687−689



685 R=Bn, R'=H, 92%	**690** (100%)	(0%)
687 R=TBS, R'=H, 85%	**691** (95%)	**692** (5%)
688 R=Bn, R'=TBS, 88%	**693** (10%)	**694** (90%)
689 R=R'=TBS, 80%	(0 %)	**695** (100%)

and p-TsOH afforded **686**, arising from debenzylation of the primary alcohol followed by intramolecular acetalation. Desulfonylation and debenzylation with concurrent acetal cleavage gave DL-**81**.

The stereochemistry of the nucleophilic epoxidation of sulfones **685** and **687**−**689** has been shown to depend on the nature of the protecting groups R and R′ (Scheme 103).[311]

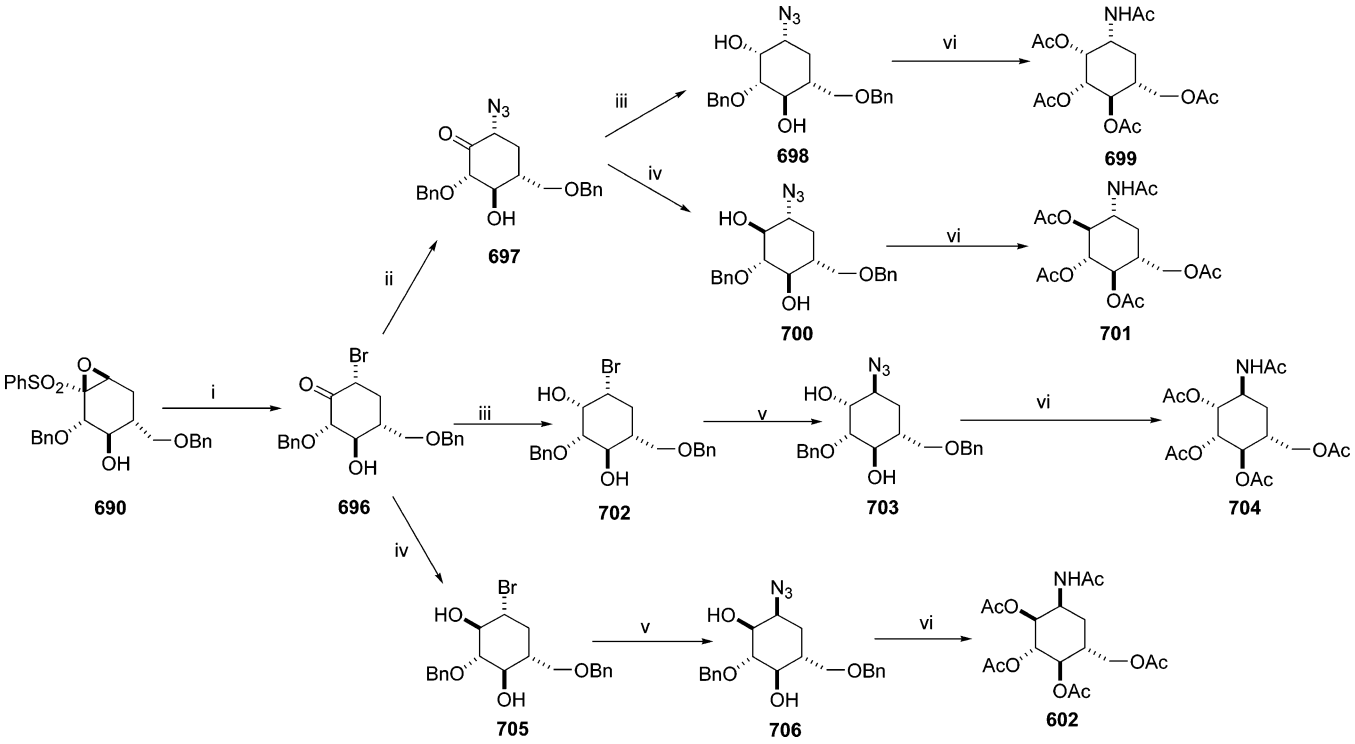
These highly distereoselective epoxidation reactions have been applied to the preparation of key intermediates in the synthesis of some carbasugar derivatives. Thus, penta-*N*,*O*-acetyl-(±) validamine (**602**) and its C_1 and C_2 stereoisomers, **699**, **701**, and **704**, have been synthesized from epoxysulfone **690** via stereoselective introduction of an amine group precursor in the epoxide cleavage (Scheme 104).[311] Reaction of **690** with $MgBr_2 \cdot OEt_2$ afforded α-bromoketone **696** along with its epimer in an 89:11 ratio. After chromatographic separation, compound **696** was transformed into the related α-azidoketone **697** with overall retention of the configuration, owing to equilibration of the product in the reaction media. Compound **697** was a precursor of **699** and **701** by stereocontrolled reduction of the carbonyl group followed by azide hydrogenation. On the other hand, bromohydrins **702** and **705**, obtained by stereocontrolled reduction of the carbonyl group of **696**, were precursors for compounds **703** and **706**, respectively, by azide displacement in each case with inversion of the configuration and subsequent reduction of azide to amine. Final functional group manipulation of compounds **703** and **706** allowed for the synthesis of **602** and **704**.

The synthesis of racemic cyclophellitol (**9**, R = H) and its unnatural diastereoisomer (1*R**6*S**)-cyclophellitol has been carried out using bromoketone **696** as the starting material.[312] In the original synthetic plan, the key step was the stereoselective epoxidation of the alcohol **708** controlled by the free hydroxy group at the allylic and/or homoallylic position regarding the double bond (Scheme 105a). Thus, reaction of **696** with $CaCO_3$ in DMF gave enone **707**. Stereoselective carbonyl reduction under Luche's conditions yielded diol **708**, which, after epoxidation controlled by the free allylic hydroxy group followed by debenzylation and acetylation, afforded **710**, the tetraacetyl derivative of (1*R**6*S**)-cyclophellitol. In order to invert the stereochemistry of the epoxidation reaction, a change of the protecting groups in **708** was necessary. However, preparation of the required diol **711** (Scheme 105b) was unsuccessful under a variety of experimental conditions. In view of the problems associated with the removal of the benzyl groups in **708**, the overall sequence had to be repeated with more labile protecting groups (Scheme 106). Thus, compound **713** (analogous to **708** with PMB rather than Bn protecting groups) was prepared from **576** in nine steps and 25% overall yield, as previously described for **708**. Silylation of **713** gave **714**, which could be cleanly deprotected to give **715**. Epoxidation then yielded **716**, which, after desilylation, yielded racemic cyclophellitol tetraacetate **717**.

The same authors carried out the synthesis of 5a-carba-β-DL-mannopyranosylamine (**720**) from α,β-epoxysulfone **695**, obtained from **689** following the same methodology (Scheme 107).[313] The key step in this route was a new transformation epoxysulfone → enaminone, via treatment with NaN_3, restricted to the use of silyl protecting groups. Thus, treatment of **695** with sodium azide afforded enaminone **718**, which, by reaction with Ac_2O−pyridine followed by catalytic hydrogenation of the resulting *N*-acetylenaminone, gave rise to the amidoketone **719**. Reduction of **719** with $NaBH_4$ and subsequent reaction with tetrabutylammonium fluoride yielded, after acetylation, compound **720**.

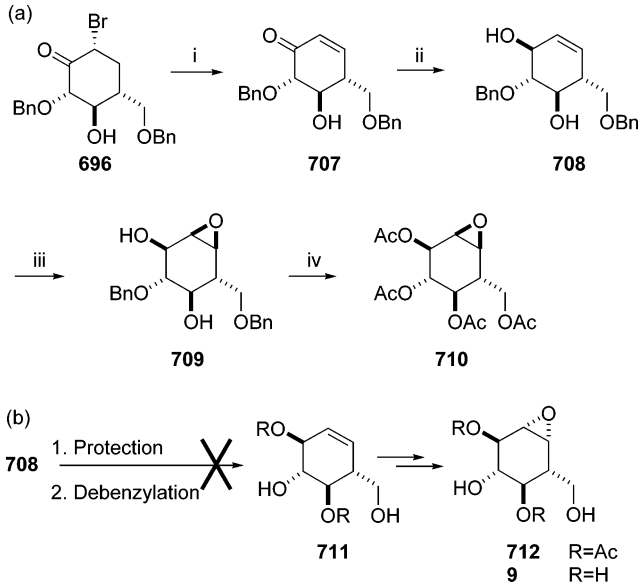
The transformation of **695** into **718** deserves some comments. A reasonable reaction path (Scheme 108) involves the attack of the nucleophilic reagent to the epoxysulfone in the normal fashion to give intermediate **721**, which would undergo desulfonylation, affording **722**. Evolution of nitrogen in **722** should give nitrene **723**, which, after a 1,2-hydrogen shift, would afford intermediate **724**. This intermediate evolves to **725** via 1,2-silyl migration of its enolic form. After the workup of the crude reaction, two sequences of keto−enol and imine−enamine tautomerism should give the final observed product **718**. This proposed mechanism was sup-

Scheme 104. Synthesis of Aminocarbasugars[a]



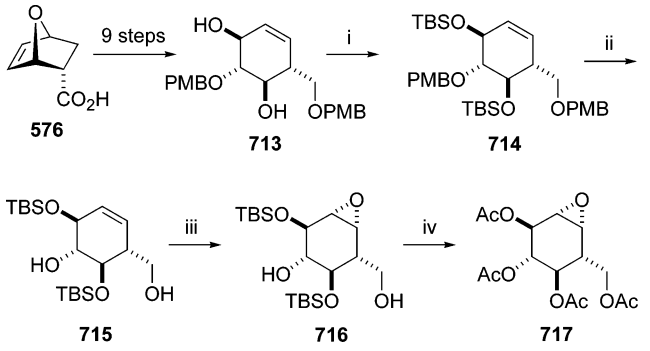
[a] Reagents: (i) $MgBr_2$, Et_2O−THF, 80%; (ii) NaN_3, DMF, 88%; (iii) $LiAl(t\text{-}BuO)_3H$, THF, −78 °C, 82% for **698**; 85% for **702**; (iv) $BH_3{\cdot}SMe_2$, THF, diastereomeric ratio for **700**, 52:48; 91% overall yield; diastereomeric ratio for **705**, 82:18; 94% overall yield; (v) NaN_3, DMF−HMPA, 150 °C, 66% for **703**, 77% for **706**; (vi) (a) H_2/Pd−C; (b) Ac_2O, py, DMPA. Yield two steps: 54% for **602**; 66% for **699**; 62% for **701**; 49% for **704**.

Scheme 105. Synthesis of (1*R6*S**)-Cyclophellitol Tetraacetate 710**[a]



[a] Reagents: (i) $CaCO_3$, DMF, 150 °C, 70%; (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, −78 °C to rt; (iii) MCPBA, CH_2Cl_2, 71%; (iv) (a) H_2, Pd/C, MeOH; (b) Ac_2O, py, DMAP, 80% two steps.

Scheme 106. Synthesis of Racemic Cyclophellitol Tetraacetate 717[a]



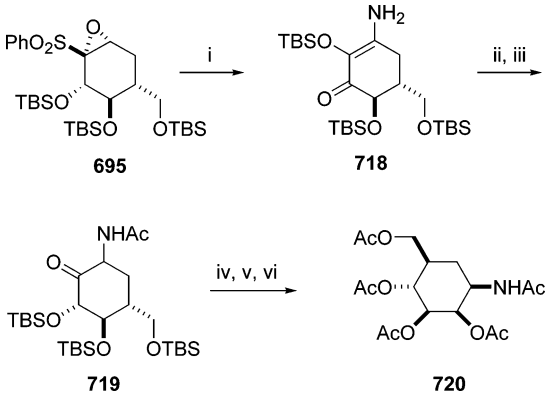
[a] Reagents: (i) TBSOTf, Et_3N, 98%; (ii) DDQ, CH_2Cl_2−H_2O, 75%; (iii) MCPBA, CH_2Cl_2, 81%; (iv) (a) TBAF, THF; (b) Ac_2O, py, DMAP, 75% two steps.

ported by the observation that both diastereomeric epoxides, **695** and **726**, were transformed into **718** under the same reaction conditions and in almost the same isolated yield.

The synthesis of new 2-deoxycarbapyranoses of the allo-**733** and galacto-**734** series and new 3-deoxycarbapyranoses of the gluco-**735** and manno-**736** series has been achieved,[314] in a divergent manner from the readily available (from compound **576**) oxanorbornenic sulfones **727** and **728**, respectively[315] (Scheme 109). The key step was the same base-induced ethereal bridge opening but effected on the reduced vinylic sulfones **729** and **730**. Further desulfonylation and bishydroxylation, followed by protection−deprotection, allowed the synthesis of the mentioned 2- or 3-deoxycarbapyranoses.

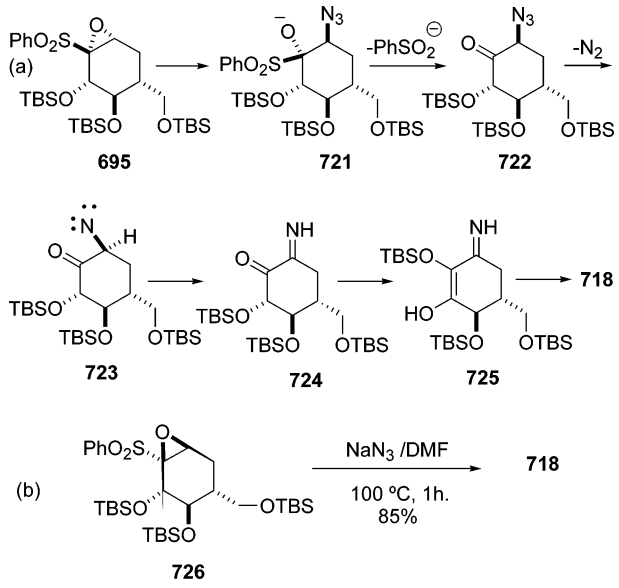
The Michael addition, ring-opening sequence (method b, Scheme 101), using lithium acetylide as alkylating reagent to the vinyl sulfone (−)-**737**, has been applied to the synthesis of three carbasugars derivatives:[316] (i) a protected carbasugar (+)-**740** related to the antibiotic Rancinamycin III;[317] (ii) a protected derivative of 5a-carba-α-D-talopyranose D-**741**, and (iii) a protected derivative of 6-deoxy-5a-carba-α-D-talopyranose D-**742** (Scheme 110). Sulfone (−)-**737** was obtained from the Diels−Alder adduct of furan and *E*-bis-phenylsulfonyl-ethylene.[318] The ring-opening reaction of (−)-**737** with lithium trimethylsilylacetylide afforded compound (−)-**738**. This compound was transformed into diene (−)-**739** by reaction with sodium methoxide in methanol in a sequence

Scheme 107. Synthesis of 5a-Carba-β-DL-mannopyranosylamine (720) from α,β-Epoxysulfone (695)[a]



[a] Reagents: (i) NaN_3, DMF, 95%; (ii) Ac_2O, py, 92%; (iii) H_2, Pd/C, MeOH, 46%; (iv) $NaBH_4$, MeOH, 100%; (v) TBAF, THF; (vi) Ac_2O, py, 70%, two steps.

Scheme 108. Proposed Mechanism for the Transformation 695 to 718



involving alkyne desilylation, alkyne−allene rearrangement, vinylsulfone isomerization, and Michael addition/protonation.[319] Sequential desulfonylation and oxidative cleavage of the exocyclic double bond gave aldehyde **740**. For the synthesis of compound **741**, a sequence aldehyde reduction and protection of the free hydroxy group and catalytic double bond hydrogenation was used. Alternatively, the sequence lithium aluminum hydride reduction and acetylation with concomitant hydrogenolysis of the primary group afforded **742**.

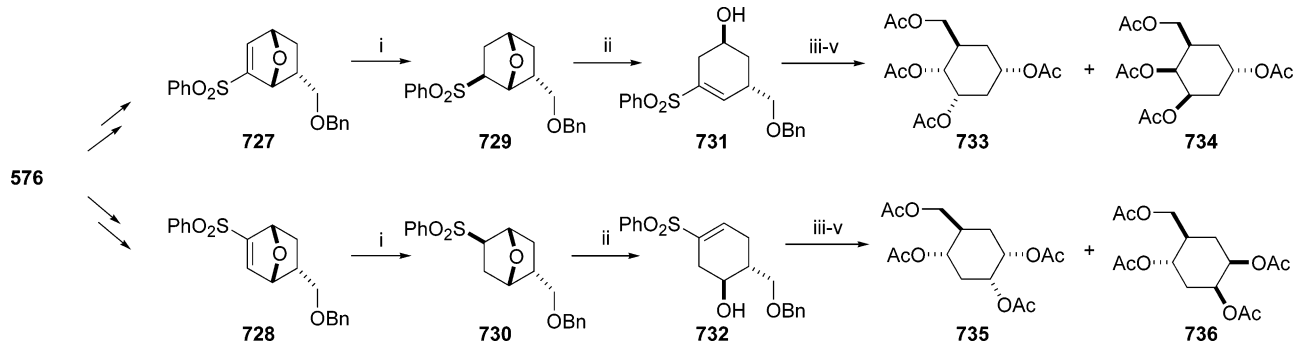
Finally, a new electrochemical ring opening of 7-oxanorbornene systems,[320] which has been applied to the synthesis of the bicyclic valienamine analogue **744**, should be mentioned. The strategy uses 3,7-dinitro-11-oxatricycloundec-9-ene (**743**)[321] as starting material (Scheme 111).

6.2.1.2. From Other Bicyclic Compounds. The C_7 framework of the bicyclo[2.2.1]heptane system has been used by Mehta and co-workers to elaborate carbasugars and "confused" carbasugars, taking advantage of the inherent regio- and stereodirecting preferences of the norbornyl system. In their approach (Scheme 112), the authors identified a 7-norbornenone system with a "locked" carbasugar in which a C_1-C_7 bond scission could lead to a C_7-carbasugar skeleton, whereas the alternative C_4-C_7 would pave the way to a "confused" carbasugar system. According to the authors, "confused" carbasugars have the same oxygenation level as carbasugars but differ in the location of the hydroxymethyl and the "para" hydroxy groups.[322]

A concise illustration of their protocol is outlined in Scheme 113 with the synthesis of 5a-carba-α-DL-talopyranose pentaacetate (**568**) and "confused" carbasugar **748**.[323] The starting 7-ketonorbornane, **745**, was prepared from *endo*-2-acetoxy-7-norbornene ketal or derivatives, with the latter having been readily obtained by Diels−Alder reaction between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and vinyl acetate, followed by reductive dehalogenation. Baeyer−Villiger oxidation of **745** led to a regioisomeric mixture of lactones **746** and **747** (13:87 ratio). The reduction of **746** followed by a deprotection−protection sequence led to 5a-carba-α-DL-talopyranose pentaacetate (**568**), and the same sequence applied to the major lactone delivered **748**.

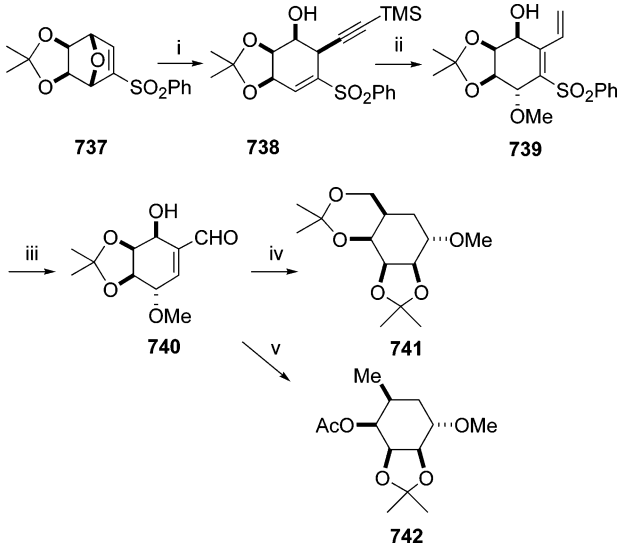
To introduce stereochemical diversity, a different strategy was developed.[322] Baeyer−Villiger oxidation of *endo*-2-acetoxy-7-norbornenone (**749**) furnished a mixture of lactones **750** and **751** (30:70 ratio) (Scheme 114a). LAH reduction of **750** led to cyclohexenetriol **752**, which underwent a stereoselective OsO_4-mediated dihydroxylation to afford, after acetylation, 5a-carba-α-DL-altropyranose pentaacetate (**753**). On the other hand, the stereoselective epoxidation (MCPBA) of **752** led to **754**, which, upon acid-catalyzed ring opening of the oxirane and acetylation, afforded 5a-carba-α-DL-mannopyranose pentaacetate (**585**), as the main product, with only traces of the regioisomeric 5a-carba-α-DL-idopyranose (**583**) (Scheme 114b). In an

Scheme 109. Synthesis of 2- and 3-Deoxy Carbasugars[a]



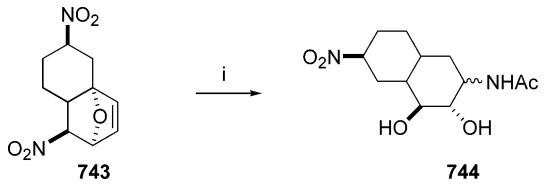
[a] Reagents: (i) $NaBH_4$, MeOH, 78% for **729**; 71% for **730**; (ii) n-BuLi, THF, 93% for **731**; 72% for **732**; (iii) Na−Hg, Na_2HPO_4, MeOH, 60%; (iv) OsO_4, NMMO, $NaHCO_3$, t-BuOH−THF−H_2O, 92%, Ac_2O, py/DMAP, 80%; (v) BF_3·OEt_2, EtSH, Ac_2O, py/DMAP, 60%; (vi) Ac_2O, py/DMAP, 82%; (vii) BF_3·OEt_2, EtSH, Ac_2O, py/DMAP, 65%.

Scheme 110. Syntheses of Carbasugar Derivatives 740−742[a]



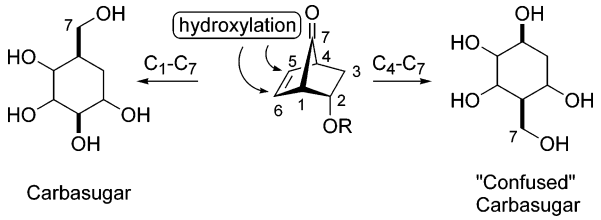
[a] Reagents: (i) lithium trimethylsilyl acetylide, $PhCH_3$, 63%; (ii) Na/MeOH, 71%; (iii) (a) Na−Hg, Na_2HPO_4; (b) $NaIO_4$; (c) $RuCl_3 \cdot H_2O$, 40% (three steps); (iv) (a) LAH, THF; (b) $Me_2C(OMe)_2$, TsOH; (c) H_2, Pd/C, MeOH, 32% (three steps); (v) (a) LAH, THF; (b) Ac_2O, py/DMAP; (c) H_2, Pd−C, MeOH, 36% (three steps).

Scheme 111. Electrochemical Synthesis of Bicyclic Valienamine Analogue 744[a]



[a] Reagents: (i) CH_3CN, $LiClO_4$, platinum electrode, $E = 2.5$ V (ecs).

Scheme 112. Mehta's Approach to Carbasugars from 7-Norbornenones Based on Baeyer−Villiger-Induced C_1-C_7 or C_4-C_7 Bond Cleavage

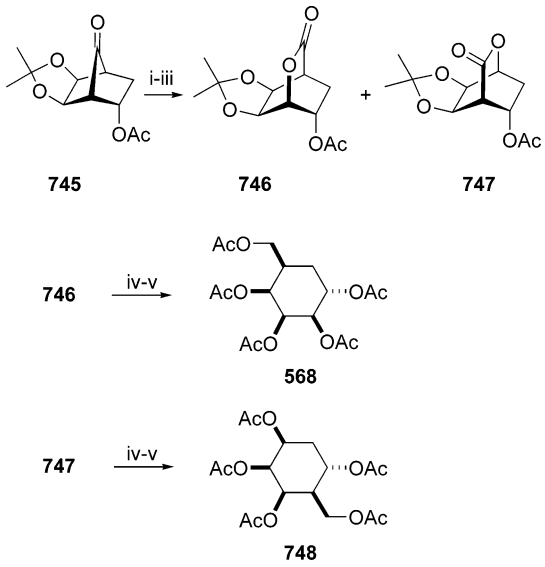


analogous manner, the major lactone **751** was transformed in the "confused" carbasugars **756** and **757** (Scheme 114c).

A different fragmentation process in the norbornyl system, a sodium methoxide-mediated Grob-like "top to bottom" fragmentation implying C_7-C_1 bond cleavage (**A** → **B** → **C**, Scheme 115), was used by Mehta and co-workers to develop new access to carbasugars.[324] Accordingly, reaction of keto-tosylate **758** with NaOMe resulted in a C_7-C_1 bond cleavage to furnish the cyclohexene methyl ester **759** as a single product (Scheme 116). Further transformations of **759** delivered the desired targets, 5a-carba-α-DL-galactopyranose (**570**), 5a-carba-β-DL-galactopyranose (**760**), and 5a-carba-α-DL-talopyranose (**568**) as pentaacetates and 5a-carba-α-DL-fucopyranose (**762**) (Scheme 116).

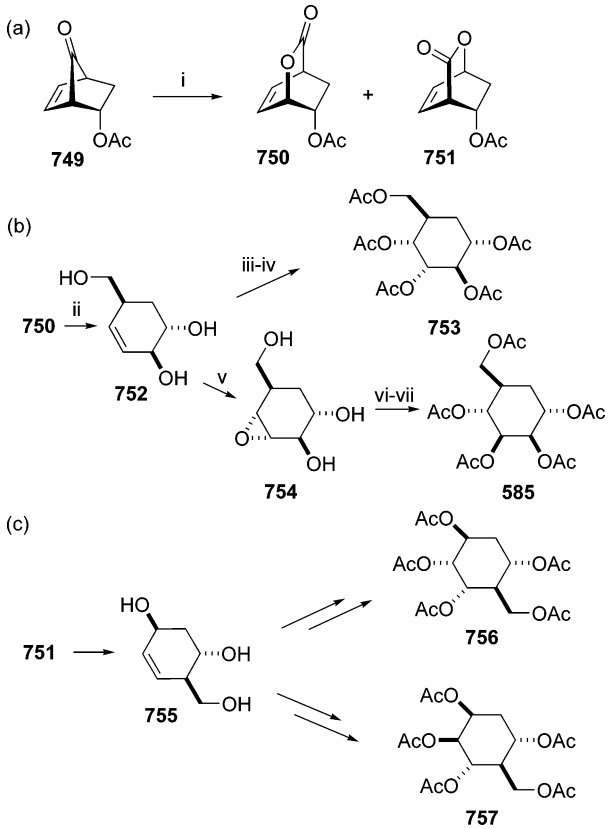
From the same starting material, Mehta and co-workers were able to prepare 6-aminocarbagalactopyranose (**766**), carbagalactovalidamine (**767**), new 2-deoxy-2-aminocarbagalactopyranose (**768**), and a range of "confused" amino carbasugars, **764**, **770**, **773**, and **774** (Scheme 117).[325]

Scheme 113. Mehta's Approach to Carbasugars from 7-Norbornenones[a]



[a] Reagents: (i) OsO_4, NMMO, acetone−H_2O, 80%; (ii) Amberlyst-15, acetone, 70%; (iii) MCPBA, $NaHCO_3$, CH_2Cl_2, quant; (iv) LAH, THF, 70%; (v) (a) Amberlyst-15, aq MeOH; (b) Ac_2O, py, 72%.

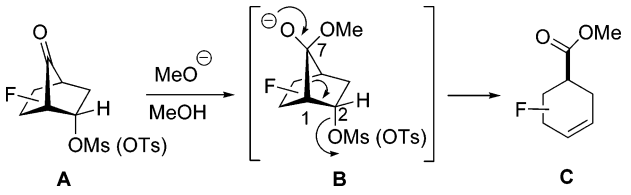
Scheme 114. Mehta's Syntheses of 5a-Carba-α-DL-altropyranose and 5a-Carba-α-DL-mannopyranose Pentaacetates (753 and 585) and Confused Carbasugars 756 and 757[a]



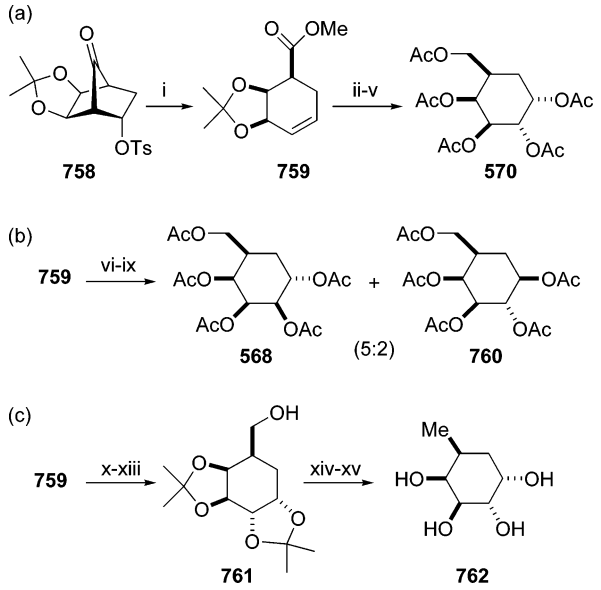
[a] Reagents: (i) MCPBA, CH_2Cl_2, 94%; (ii) LAH, THF, 70%; (iii) OsO_4, NMMO, acetone-H_2O; (iv) Ac_2O, py, two steps, 78%; (v) MCPBA, H_2O, 75%; (vi) $HClO_4$, H_2O; (vii) Ac_2O, py, 73%.

Mehta et al. also reported the synthesis of new bicyclic analogues of carbasugars, which they named "annulated carbasugars", of types **A** and **B**.[326] The synthesis of polyhydroxylated hydrindanes (+)-**778** and (−)-**779** was carried

Scheme 115. Mehta's Grob-like Fragmentation of Norbornyl Systems Leading to Carbasugar Precursor C



Scheme 116. Mehta's Syntheses of 5a-Carba-α-DL-galacto- (570), 5a-Carba-β-DL-galacto- (760), and 5a-Carba-α-DL-talo- (568) Pyranose Pentaacetates and 5a-Carba-α-DL-fucopyranose (762) via Grob-like Fragmentation[a]



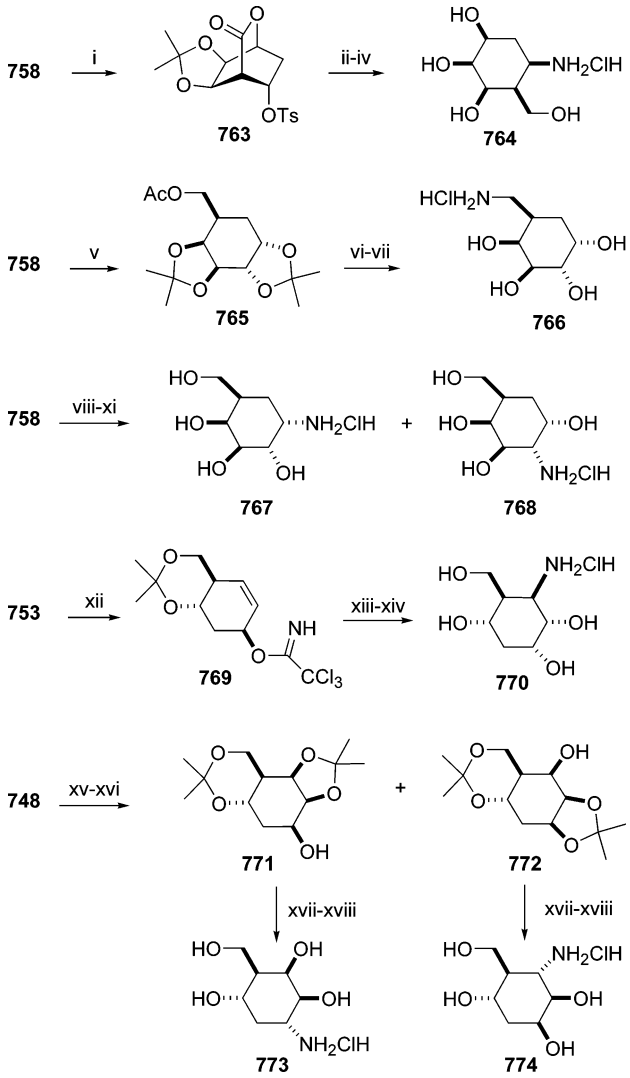
[a] Reagents: (i) NaOMe, MeOH, 70%; (ii) OsO_4, NMMO, 95%; (iii) LAH, THF, 88%; (iv) Amberlyst-15, aq MeOH; (v) Ac_2O, py, 74% (two steps); (vi) LAH, THF, 90%, Ac_2O, DMAP, 95%; (vii) MCPBA, Na_2CO_3, 65%; (viii) cat $HClO_4$, H_2O; (ix) Ac_2O, py, 67% (two steps); (x) OsO_4, NMMO, 95%; (xi) Amberlyst-15, acetone, 85%; (xii) LAH, THF, 82%; (xiii) TsCl, py, 94%; (xiv) $NaBH_4$, DMSO, 72%; (xv) Amberlyst-15, MeOH, 75%.

out from *endo* allylic alcohol (+)-**777**, readily available from racemic **775** by kinetic enzymatic acylation.[327] Polyhydroxylated decahydronaphthalene **781**, prepared from norbornenyl derivative **780**,[326b] was found to be a potent and selective α-glucosidase inhibitor (k_i = 12 μM, compared to deoxynojirimycin k_i = 25.4 μM), although it showed no significant inhibitory activity against β-glucosidases at millimolar concentrations (Scheme 118).

Afarinkia and Mahmood[328] also used bicyclic lactones in the synthesis of racemic 2-epi-validamine (**704**). The key step in their methodology is the Diels−Alder cycloaddition of appropriately substituted 2-pyrones with electronically matched dienophiles. Accordingly, bicyclic lactone **784**, obtained as the major *endo* isomer (*endo*:*exo* 6:1) from the Diels−Alder reaction of ethyl cumalate **782** and vinylene carbonate **783** (Scheme 119), was submitted to hydrogenation and ammonolysis to afford amide **785**. Hofmann rearrangement and reduction led to 2-epi-validamine, which was characterized as its pentaacetate, **704**.

6.2.1.3. From Aromatics. The microbial oxidation of arenes to cyclohexadiene diols has also been prevalent in carbasugar synthesis.[260] In particular, the use of *Pseudomonas putida* is one of the most valuable tools in this field,

Scheme 117. Mehta's Synthesis of Aminocarbapyranoses and "Confused" Aminocarbapyranoses[a]



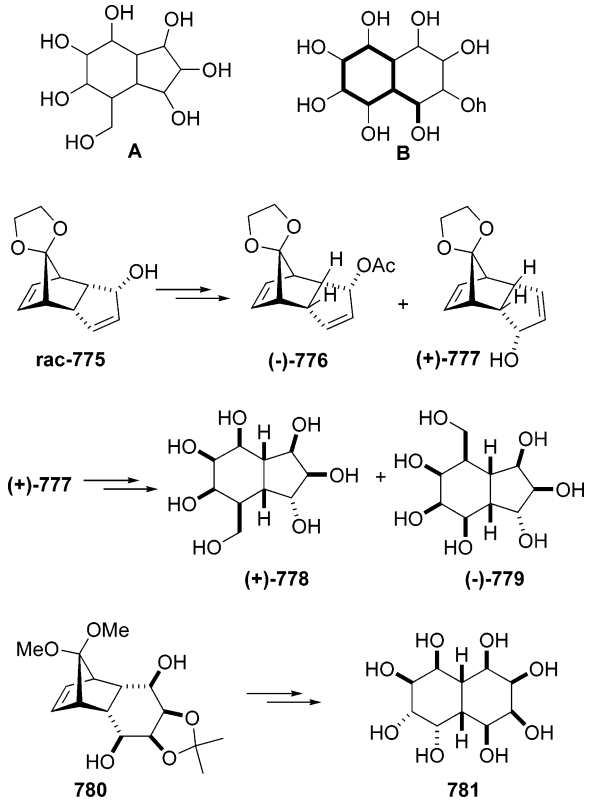
[a] Reagents: (i) MCPBA, CH_2Cl_2, 85% (87:13); (ii) LAH, THF, 85%, Ac_2O, DMAP, 92%; (iii) NaN_3, DMF, 82%; (iv) H_2, Pd−$CaCO_3$, 80%, HCl, 90%; (v) NaI, acetone, 92%, NaN_3, DMF, 92%; (vi) H_2, Pd−$CaCO_3$, Ac_2O, DMAP, 62%; (vii) HCl, 92%; (viii) LAH, THF, 90%, Ac_2O, DMAP, 95%; (ix) Chloramine T, OsO_4, 70% (4:1); (x) Ac_2O, DMAP, Na-naphtalenide, DME; (xi) HCl, 56% for **767**, 42% for **768**; (xii) Amberlyst-15, acetone, 81%, CCl_3CN, DBU, 93%; (xiii) K_2CO_3, p-xylene, 70%; (xiv) OsO_4, NMMO, 92%, HCl, quant; (xv) LAH, THF, 70%; (xvi) Amberlyst-15, acetone, 78% (47:43); (xvii) MsCl, py, NaN_3, DMF, 65% for **771**, 70% for **772**; (xviii) H_2, Pd−$CaCO_3$, HCl, 80% for **773**, 85% for **774**.

facilitating sequential oxygen introduction and leaving the introduction of the exocyclic carbon atom as the key step.

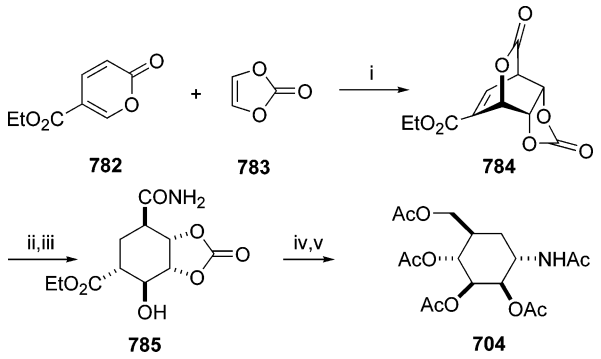
Ley and co-workers[329] described the synthesis of 5a-carba-α-D-glucopyranose (**81**), using the microbial metabolite *meso*-cyclohexa-3,5-diene-1,2-diol (**787**) as starting material (Scheme 120). The diol **787** was then converted into the epoxide **788**, following previous work by the authors,[330] and treated with lithium acetylide ethylene diamine complex to yield alkyne **789**. The latter was deoxygenated, via Super-Hydride reduction of the derived triflate, and transformed into **81** by Lindlar reduction, reductive ozonolysis, and deprotection.

In their protocol for the synthesis of carbapyranoses, Vandewalle and co-workers described a chemoenzymatic conversion of **787** to the hydroxyl ester (+)-**792** (Scheme

Scheme 118. Mehta's Group Approaches to Polyhydroxylated Hydrindanes and Decahydronaphthalenes as New Families of "Annulated" Carbasugars



Scheme 119. Synthesis of 2-Epi-validamine Pentaacetate (704)[a]

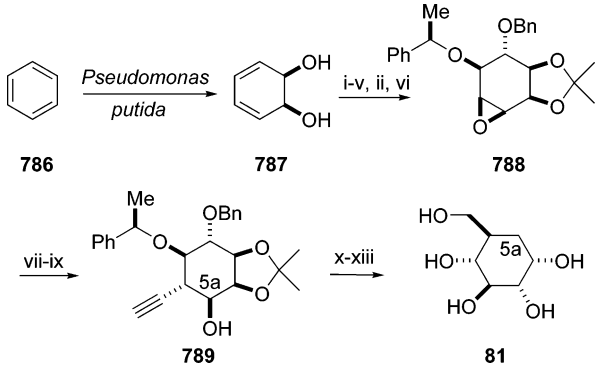


[a] Reagents: (i) sealed tube, 110 °C, 81%; (ii) H_2, Pd/C, EtOAc, quant; (iii) NH_3, 1,4-dioxane, 91%; (iv) $PhI(OCOCF_3)_2$, $MeCN-H_2O$, aq HCl, 92%; (v) LAH, THF, Ac_2O, py, 88%.

121).[331] Their strategy demanded the incorporation of a functionalized one-carbon substituent on one of the sp^2-carbon atoms of (+)-**792**. Their first key intermediate, (bromomethyl)silyl ether **793**, was transformed into the cyclic silyl ether **794** by radical cyclization. Cyclic silyl ether **794** was subsequently oxidized, deprotected, and acetylated to lead to 5a-carba-β-L-gulopyranose pentaacetate (**795**). The corresponding α-anomer, 5a-carba-α-L-gulopyranose pentaacetate (**797**), was obtained from **794** via an oxidation−reduction sequence involving ketone **796**. For the synthesis of α- and β-D-talopyranoses, D-**568** and D-**800**, respectively, a similar protocol starting from **798**, readily prepared by Mitsunobu inversion of (+)-**792**, was used.[332]

For the synthesis of 5a-carba-manno- and -allopyranoses, Vandewalle and co-workers employed a 2,3-Wittig rearrangement, rather than a radical cyclization, for the introduction of the hydroxymethyl group (Scheme 122). The allylic alcohol (+)-**792** was transformed, by inversion of the configuration in one of the allylic oxy substituents, into stannane **801**, from which a 2,3-Wittig rearrangement led to alkene **802** (Scheme 122). The latter, after hydroboration, hydroxyl deprotection, and peracetylation, yielded 5a-carba-α-D-mannopyranose pentaacetate (D-**585**). On the other hand, hydroboration of **802** followed by an oxidation−reduction sequence led to epimeric 5a-carba-β-D-mannopyranose pentaacetate (**657**). For the preparation of the carbasugars with the allo configuration, the authors interchanged the protection of the allylic oxy groups in (+)-**792** to obtain **805**. From this compound, and in essentially the same way as above, they prepared carbasugar derivative **807** and, thence, 5a-carba-β-D-allo- and 5a-carba-α-D-allopyranose pentaacetates (**808** and **809**), respectively.[333]

Scheme 120. Synthesis of 5a-Carba-α-D-glucopyranose (81)[a]



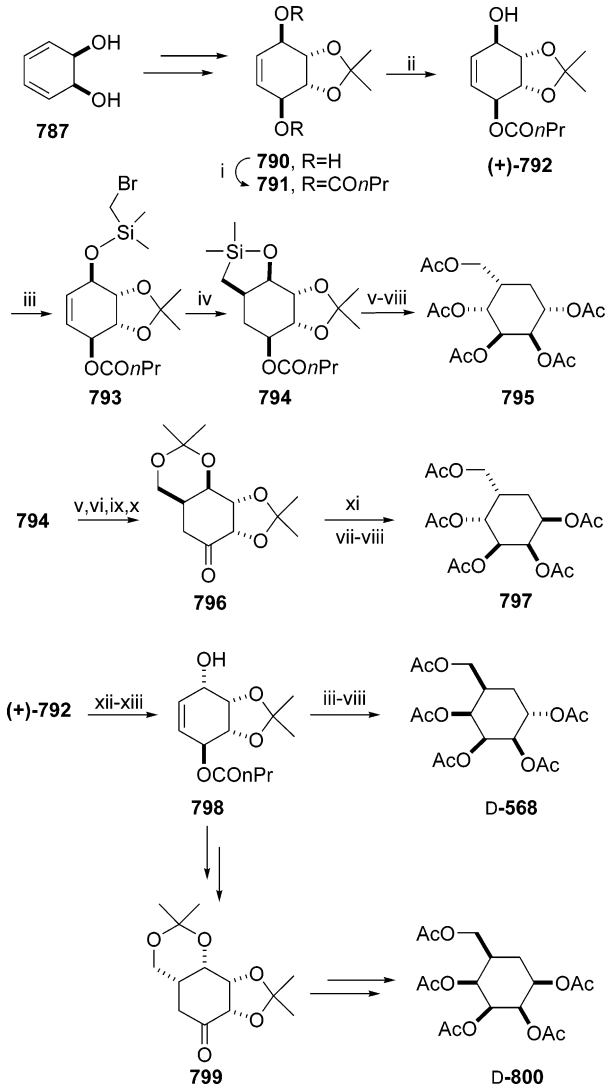
[a] Reagents: (i) NaOMe, $(MeO)_2CO$; (ii) MCPBA, CH_2Cl_2; 47% two steps; (iii) (*R*)-(+)-*sec*-phenetyl alcohol, $HBF_4 \cdot OEt_2$, 67%; (iv) BnBr, Ag_2O, DMF, quant; (v) Et_3N, MeOH, H_2O, 99%; (vi) DMP, CSA, CH_2Cl_2, 77%; (vii) HCCLi-EDA, DMPU, 60%; (viii) Tf_2O, py, 76%; (ix) SuperHydride, 93%; (x) H_2, Lindlar catalyst, 93%; (xi) O_3, $MeOH/NaBH_4$, 93%; (xii) Amberlyst IR-120$^+$, MeOH, 79%; (xiii) H_2, Pd−C, quant.

1-Iodocyclohexa-1,3-diene-5,6-diol (**811**), obtained by whole cell fermentation of iodobenzene **810** with *Pseudomonas putida*, has been used by Entwistle and Hudlicky, in the synthesis of 5a-carba-β-D-altropyranose pentaacetate (D-**586**) (Scheme 123).[334] The diol **811** was converted, in several steps, to the diacetonide **812**. Halogen lithium exchange, with ^{t}BuLi, followed by quenching with carbon dioxide and esterification, furnished α,β-unsaturated ester **813**. Hydrogenation of the alkene, reduction of the ester, deprotection, and peracetylation gave 5a-carba-β-D-altropyranose pentaacetate (D-**586**).

Carless and Malik[335] described a direct route to 5a-carba-α-L-fucopyranose (L-**762**) from *cis*-cyclohexadienediol (**815**), available in enantiopure (1*S*,2*R*) form by microbial oxidation of toluene using *Pseudomonas putida* (Scheme 124). Isopropylidenation of **815**, followed by dihydroxylation, led to diol **816**. Hydrogenation of **816** resulted in the formation of 5a-carba-α-L-fucopyranose derivative **817** along with 6-deoxy-5a-carba-β-D-altropyranose derivative **818** as a minor component. Acid hydrolysis of **817** yielded 5a-carba-α-L-fucopyranose (L-**762**).

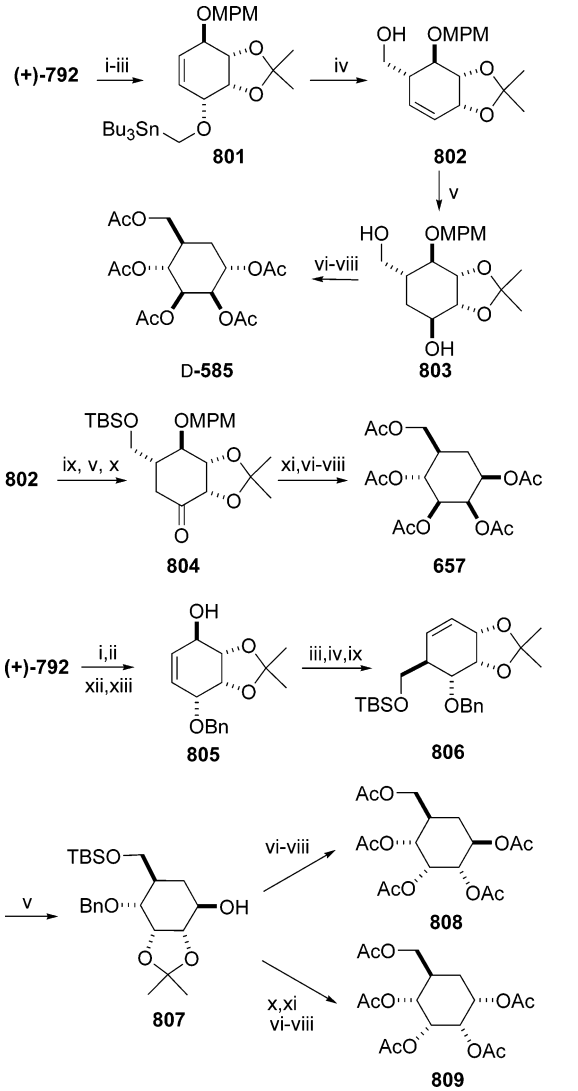
Crout and co-workers[336] reported the synthesis of 5a-carba-α-L-fucopyranose (L-**762**) and 6-deoxy-5a-carba-β-D-altropyranose (**823**) using the microbial metabolite **819** as the homochiral starting material. This metabolite was produced by biotransformation of cyanobenzene using a recombinant toluene dioxygenase expressed in *Escherichia coli*[337] (Scheme 125). Aldehyde **821** was prepared in four steps from the cyanodiol **819**. Reduction and protection to allylic acetate

Scheme 121. Vandewalle's Group Approach to Carbapyranoses Based on Radical Cyclization[a]



[a] Reagents: (i) n-PrCOCl, Et_3N, DMAP, CH_2Cl_2, quant; (ii) PGL, pH = 7, NaOH, 83%; (iii) (bromomethyl)chlorodimethyl silane, Et_3N, DMAP, CH_2Cl_2; (iv) n-Bu_3SnH, AIBN, $PhCH_3$, reflux; (v) KF, $KHCO_3$, H_2O_2, THF/MeOH, Na_2SO_3, 71% from (+)-**792**; (vi) $KHCO_3$, MeOH; (vii) TsOH, MeOH; (viii) Ac_2O, 75% (three steps); (ix) 2,2-dimethoxypropane, DMF, PPTS; (x) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, 96%; (xi) $NaBH_4$, THF−MeOH, 84%; (xii) p-$NO_2PhCOOH$, Ph_3P, DEAD, THF; (xiii) $KHCO_3$, MeOH, 94%, two steps.

Scheme 122. Vandewalle's Group Approach to Carbapyranoses Based on 2,3-Wittig Rearrangement[a]



[a] Reagents: (i) (a) MPMOC(=NH)CCl_3, CSA, CH_2Cl_2; (b) MeOH, $KHCO_3$, 98% two steps; (ii) (a) $PhCO_2H$, Ph_3P, DEAD, THF; (b) MeOH, $KHCO_3$, 97% two steps; (iii) KH, ICH_2SnBu_3, THF, 76%; (iv) n-BuLi, THF, 92% for **802**, 72% for **805**; (v) BH_3, THF, then H_2O_2, NaOH, 89% for **803**, 95% for **807**; (vi) H_2, Pd−C, MeOH; (vii) TsOH, MeOH; (viii) Ac_2O, py, 87% for **808**, 98% for **809** overall; (ix) TBSCl, imidazole, DMF, 92% for **804**, 76% for **806**; (x) oxalylchloride, DMSO, Et_3N; (xi) $NaBH_4$, MeOH, 92% for **804**, 72% for **809**; (xii) NaH, THF, TBAI, BnBr, 98%; (xiii) DDQ, CH_2Cl_2, H_2O, 91%.

822 was followed by hydrogenolysis, which proceeded with simultaneous removal of the allylic acetate function and saturation of the double bond to yield isomeric carbasugars L-**762** and **823**.

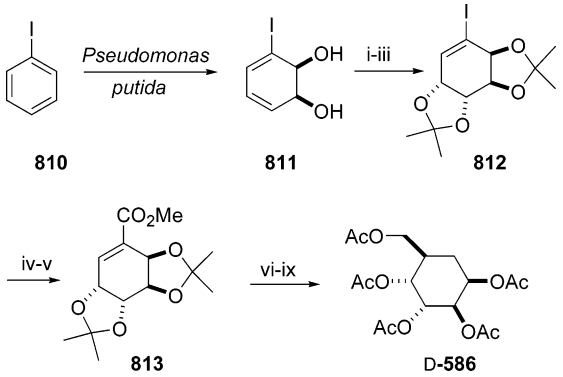
Landais and co-workers employed the desymmetrization of cyclohexadienylsilane **825** as an access to carbasugars, carba-*C*-disaccharides, and aminocarbasugars.[338] The "controlled" Birch reduction of (*tert*-butyldimethylsilyl)benzene (**824**) furnished cyclohexadienylsilane **825** (Scheme 126). Differentiation of the enantiotopic double bonds of **825** was accomplished by Sharpless asymmetric dihydroxylation, and the ensuing diol (71% ee) was then protected as its bis-benzylether **826**.[339] The CH_2OH group at C_5 was stereoselectively introduced by an electrophile-mediated cyclopropane ring opening from **827** to either **828** or **829**. Iodide **828** was converted to (phenyldimethyl)silyl derivative **830**, and from it, a sequence of transformations involving catalytic osmylation, oxidation of the silyl group, acetylation, debenzylation, and complete acetylation led to 5a-carba-β-L-altropyranose pentaacetate (L-**586**).[340]

Halogenated intermediates **828** and **829** were used for the synthesis of 6-deoxy-5a-carba-β-L-altropyranose (L-**823**) and 1-oxy-carba-*fructo*pyranose derivative **835** as illustrated in Scheme 127.[340]

In a complementary approach, the CH_2OH moiety was introduced through a [2,3]-Wittig sigmatropic rearrangement. Thus, the authors transformed the silicon group, in **836**, into a OH group using the Tamao−Kumada conditions,[341] and the ensuing allylic alcohol, **837**, was transformed into the tin-containing precursor **838** (Scheme 128) by alkylation. This sequence was applied to the synthesis of 5a-carba-α-D-galactopyranose pentaacetate (D-**570**).[340]

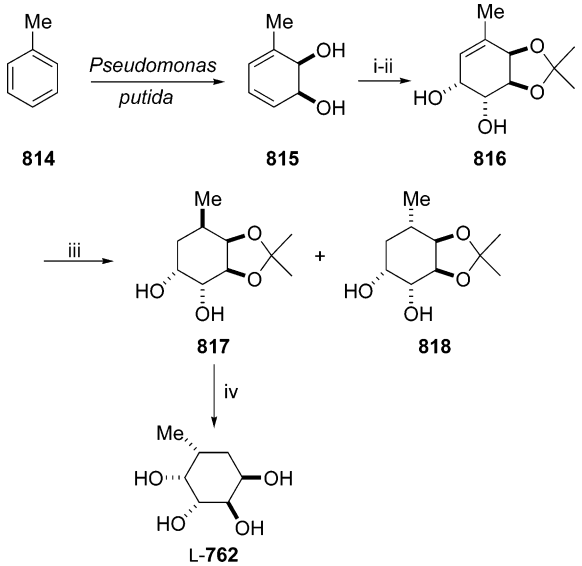
Landais' group[342] also followed their approach for the synthesis of carba-*C*-disaccharide **843** (Scheme 129). The implementation of the protocol involved cyclopropanation

Scheme 123. Synthesis of 5a-Carba-β-D-altropyranose Pentaacetate (D-539) by Microbial Oxidation of Iodobencene[a]



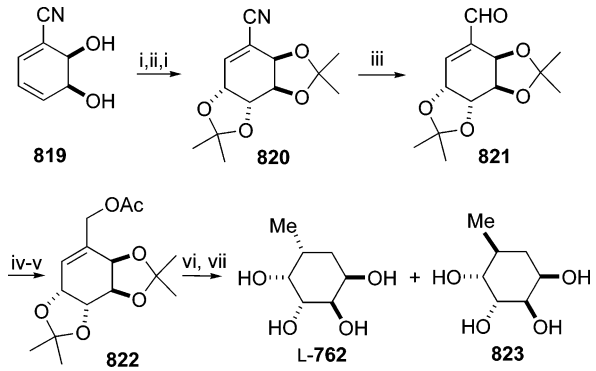
[a] Reagents: (i) DMP, TsOH; (ii) OsO_4, NMMO, t-BuOH, H_2O; (iii) DMP, TsOH, 75% from **811**; (iv) t-BuLi, Et_2O, CO_2; (v) MeI, K_2CO_3, acetone, 90% two steps; (vi) H_2, Pd−C, EtOAc, EtOH, 92%; (vii) DIBAL-H, PhMeI, 74%; (viii) Amberlyst-15, MeOH, H_2O; (ix) Ac_2O, py, DMAP, 89% (two steps).

Scheme 124. Synthesis of 5a-Carba-α-L-fucopyranose (L-716) by Microbial Oxidation of Toluene[a]



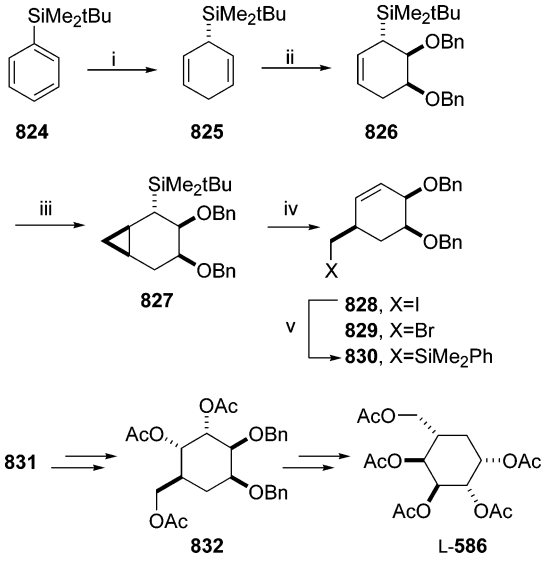
[a] Reagents: (i) DMP, acetone, CF_3CO_2H, 86%; (ii) OsO_4, NMMO, acetone, H_2O, 30%; (iii) H_2, PtO_2, 58% for **818**; 12% for L-**762**; (iv) AcOH, H_2O, 96%.

Scheme 125. Synthesis of Carbasugars by Microbial Oxidation of Cyanobenzene[a]



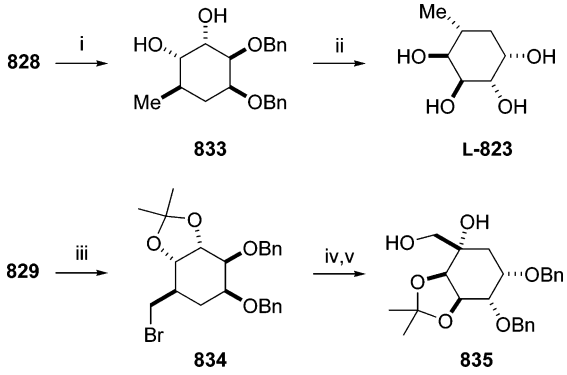
[a] Reagents: (i) 2,2-dimethoxypropane/H^+; (ii) cat. OsO_4, NMMO, 52%; (iii) DIBAL, THF, 39%; (iv) DIBAL-H, THF, 82%; (v) Ac_2O, py, 90%; (vi) H_2, Pd−C, EtOH; (vii) HCl, MeOH, H_2O, 40% for L-**762**, 40% for **823**.

Scheme 126. Synthesis of 5a-Carba-β-L-altropyranose Pentaacetate (L-586) by Desymmetrization of Dienylsilanes (825)[a]



[a] Reagents: (i) NH_3, Li, THF, t-BuOH, 94%; (ii) $K_2OsO_2(OH)_4$, $(DHQ)_2py$, t-BuOH−H_2O, K_2CO_3, $K_3Fe(CN)_6$, NaH, BnBr, 76%; (iii) $ZnEt_2$, CH_2I_2, $ClCH_2CH_2Cl$, 88%; (iv) NIS, MeCN, 82% for **828**, NBS, MeCN, 70% for **831**; (v) t-BuLi, $PhMe_2SiCl$, 80%.

Scheme 127. Landais' Group Synthesis of 6-Deoxy-5a-carba-β-L-altropyranose (L-823) and 1-oxycarbafructopyranose (835)[a]

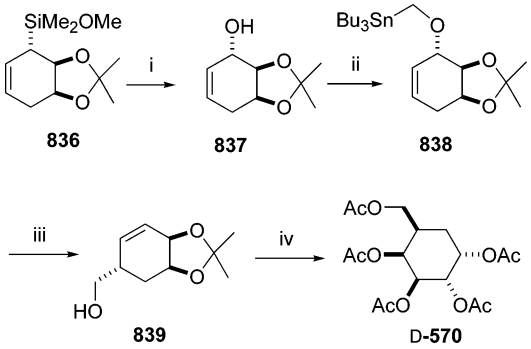


[a] Reagents: (i) n-BuLi, THF, OsO_4, NMMO, THF, 60%; (ii) H_2, Pd−C, EtOH, 64%; (iii) OsO_4, NMMO, THF, DMP, TsOH, 95%; (iv) phosphazen-Et; (v) THF, OsO_4, NMMO, THF, 36% (82:18 ratio).

of allylsilane **826** (71% ee), using Cu(I)OTf-Schiff-base and ethyl diazoacetate, and treatment of the ensuing cyclopropane with CsF in acetonitrile, producing the olefin **841**. Osmylation of the double bond, protection of the resulting diol, reduction of the ester, and Swern oxidation afforded the aldehyde **842**. Reaction of the latter with 2-deoxyglucosyllithium took place with retention of the configuration of the anomeric center and led to an 80:5 mixture of the two aldol epimers at C_7, which was subsequently oxidized to the ketone **843**. The formation of a third aldol product, arising from the minor enantiomer of the carbasugar precursor **842**, was also observed (15%).

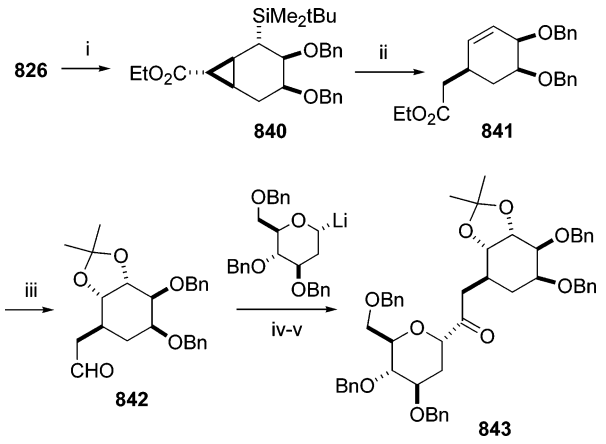
Aminocarbasugar derivative **848** (Scheme 130)[343] was prepared from cyclohexadienylsilane derivative **844**.[344] Sharpless asymmetric aminohydroxylation provided **845**,[345] with complete regio- and diastereocontrol, that after oxidation of the C−Si bond and protection led to **846**. Tin-mediated 5-*exo*-*trig* radical cyclization of the (bromomethyl)silyl ether **847**, as previously described by Vandewalle et al.,[332] led to

Scheme 128. Synthesis of 5a-Carba-α-D-galactopyranose Pentaacetate (D-570)



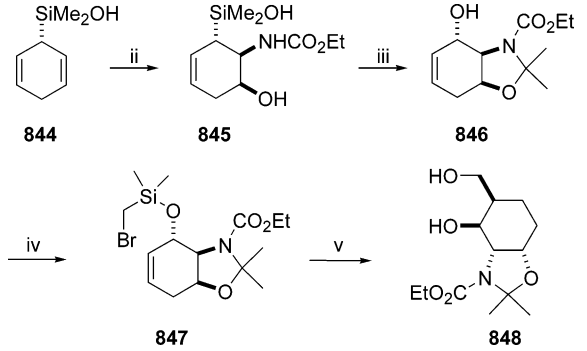
[a] Reagents: (i) H_2O_2, KF, $KHCO_3$, DMF, 75%; (ii) KH, THF, Bu_3SnCH_2I, 82%; (iii) n-BuLi, THF, 51%; (iv) (a) Ac_2O, py, OsO_4, NMMO, THF; (b) $AcOH-H_2O$; (c) Ac_2O, py, 92% (four steps).

Scheme 129. Landais' Group Approach to Carba-*C*-disaccharides[a]



[a] Reagents: (i) ethyldiazoacetate, CuOTf, 82%; (ii) CsF, DMF, 83%; (iii) (1) OsO_4, NMMO, acetone-H_2O; (2) $Me_2C(OMe)_2$, TsOH; (3) LAH, Et_2O, 0 °C, 1 h; (4) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −20 °C, 84% (four steps); (iv) 2-deoxyglucosyl lithium, THF, 82%; (v) PDC, CH_2Cl_2, 54%.

Scheme 130. Synthesis of Aminocarbasugar Derivative 848[a]



[a] Reagents: (i) $K_2OsO_2(OH)_4$, $(DHQ)_2py$, t-BuOCl, NaOH, EtO_2CNH_2, n-PrOH−H_2O, 98%; (ii) H_2O_2, KF, $KHCO_3$, DMF, 70%; (iii) $Me_2C(OMe)_2$, 75%; (iv) $BrCH_2SiMe_2Cl$, Et_3N, Et_2O, 94%; (v) (a) n-Bu_3SnH, PhH; (b) H_2O_2, KF, $KHCO_3$, DMF, 74%.

the formation of amino carbasugar derivative **848**, after the oxidation of the C−Si bond.

6.2.1.4. Miscellaneous. Casiraghi and co-workers extended the strategy previously used by them for the preparation of carbafuranoses (see Figure 45) to the synthesis of carbapyranoses and derivatives. The new protocol is outlined in Figure 48.[175]

Along this line, the synthesis[176,346] of 5a-carba-β-D-gulopyranose (D-**5**) and 5a-carba-β-D-allopyranose (**853**)

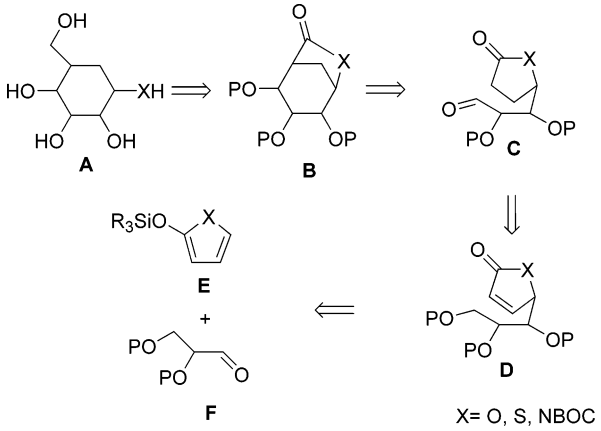
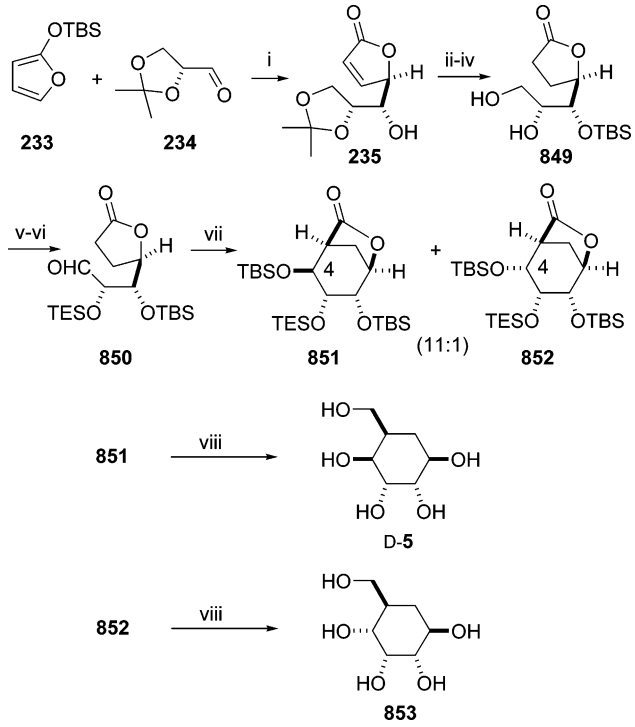


Figure 48. Casiraghi's approach for carbapyranose synthesis.

Scheme 131. Synthesis of 5a-Carba-β-D-gulopyranose (D-5) and 5a-Carba-β-D-allopyranose (853)[a]

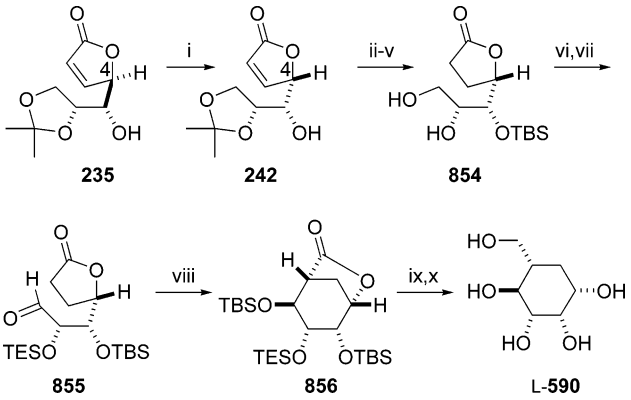


[a] Reagents: (i) $BF_3{\cdot}Et_2O$, 75%; (ii) $NiCl_2$, $NaBH_4$, quant; (iii) TBSOTf, 90%; (iv) aq AcOH, 96%; (v) TESOTf, py, DMAP, 95%; (vi) $(COCl_2)_2$, DMSO, Et_3N, 98%; (vii) TBSOTf, DIPEA, 69% for **851**, 6% for **852**; (viii) $LiBH_4$, aq HCl, 81% for D-**5**, 80% for **853**.

(Scheme 131) started with unsaturated lactone **235**, prepared by the vinylogous cross-aldolization of furan-based silyloxy diene **233** and glyceraldehyde derivative **234**. Hydrogenation, followed by protection and deprotection steps, led to lactone **849**. Silylation of the free hydroxyl groups was followed by chemoselective Swern oxidation at the primary silyl group to give aldehyde **850**. The cycloaldolization reaction furnished bicyclooctane **851** (69%) accompanied by small quantities (6%) of its C_4 epimer, **852**. Reduction with $LiBH_4$ followed by removal of the protecting groups yielded the desired carbapyranoses D-**5** and **853**.

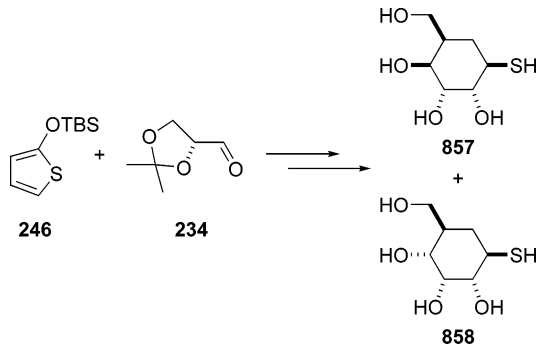
The same approach was also used for the synthesis of 5a-carba-β-L-mannopyranose (L-**590**)[346] (Scheme 132) but using lactone **242**, the C_4 epimer of **235**, obtained after equilibration with Et_3N.[177] Accordingly, the synthesis of 5a-carba-β-L-mannopyranose (L-**590**) from **242** took place in five steps and 30% yield.

Scheme 132. Synthesis of 5a-Carba-β-L-mannopyranose (L-590)[a]



[a] Reagents: (i) Et_3N, 80%, three equilibration cycles; (ii) $BF_3 \cdot Et_2O$; (iii) $NiCl_2$, $NaBH_4$, quant; (iv) TBSOTf, 84% (three steps); (v) aq AcOH; (vi) TESOTf, py, DMAP, 68% (two steps); (vii) $(COCl)_2$, DMSO, Et_3N, 70%; (viii) TBSOTf, DIPEA, 74%; (ix) $LiBH_4$; (x) aq HCl, THF, MeOH, 59% (two steps).

Scheme 133. Rassu-Casiraghi's Strategy for the Synthesis of 1-Thio-5a-carbahexopyranoses



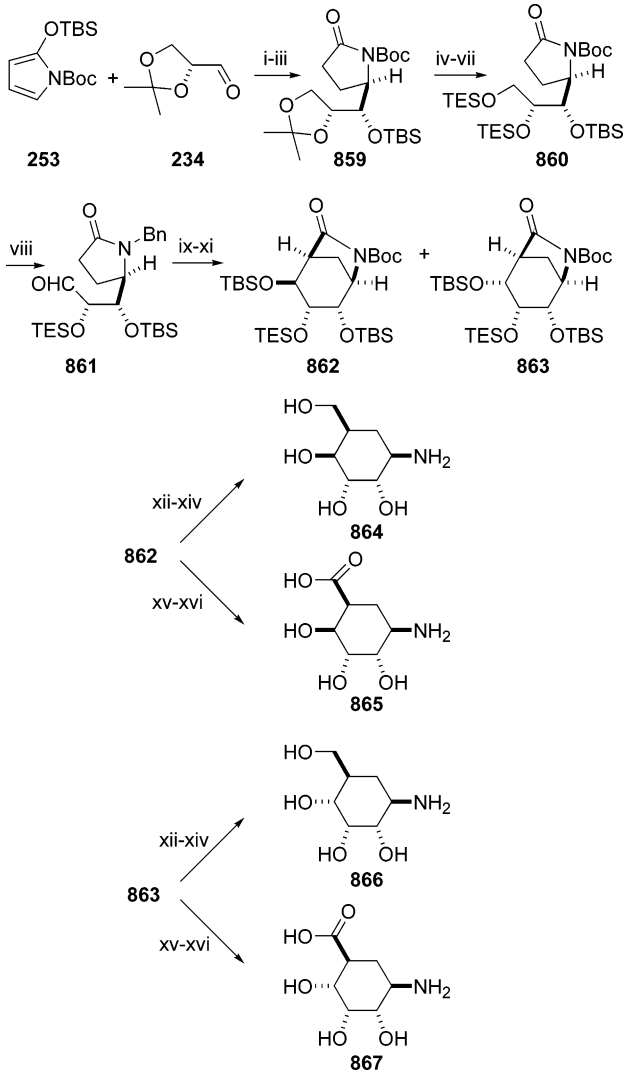
An analogous strategy using silyloxy thiophene **246** (Scheme 133) and aldehyde **234** was used by Casiraghi's group for the preparation of carbapyranose derivatives containing a thiol, rather than a hydroxyl group, at C_1.[346] In this manner, 1-thio-5a-carba-β-D-gulopyranose (**857**) and 1-thio-5a-carba-β-D-allopyranose (**858**) were obtained in nine steps and 11% and 12% overall yields, respectively.

This protocol was extended to aminocarbasugar derivatives by using silyloxy pyrrole **253** as the starting material (Scheme 134).[178,347] In this manner, the divergent syntheses of (5a-carba-β-D-gulopyranosyl)amine (**864**), (5a-carba-β-D-allopyranosyl)amine (**865**), (5a-carba-β-D-gulopyranuronyl)amine (**866**), and (5a-carba-β-D-allopyranuronyl)amine (**867**) were efficiently achieved.

A very short and efficient synthesis of valienamine (**11**) has been described by Trost and co-workers[348] (Scheme 135). The key aspect of the strategy involves the use of a new palladium-based *cis*-hydroxyamination reaction of the allylic epoxide **869** (Scheme 135c). The required oxirane **869** was prepared in racemic form by Diels−Alder reaction of ethyl propiolate and 1-sililoxy-1,3-butadiene followed by epoxidation, whereas the asymmetric synthesis made use of an asymmetric palladium-catalyzed hydroxycarbonylation[349] reaction (Scheme 135a,b).

Van der Eycken and co-workers[350] have described the synthesis of 6a-carba-β-D-fructopyranose (**80**) and 6a-carba-α-D-fructopyranose (**880**), from the enzymatically resolved homochiral building block 1(*R*)-**875**, in 36% and 20% overall yield, respectively (Scheme 136).

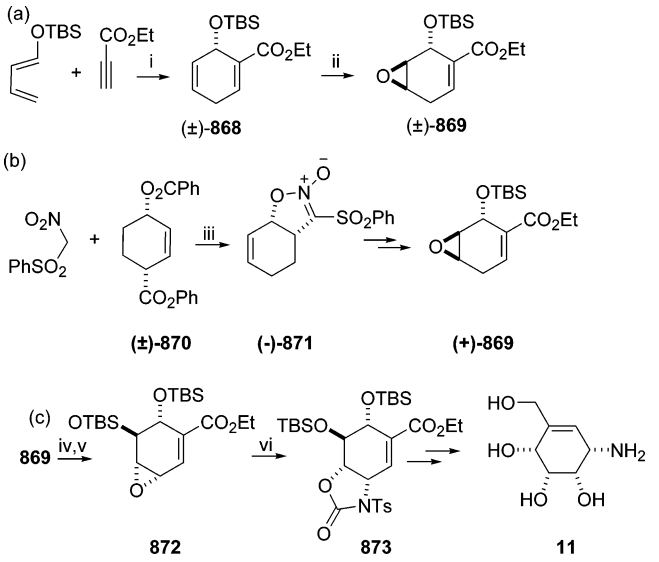
Scheme 134. Rassu-Casiraghi's Strategy for the Synthesis of 1-Amino-5a-carbahexopyranoses[a]



[a] Reagents: (i) $SnCl_4$, 80%; (ii) $NiCl_2$, $NaBH_4$; (iii) TBSOTf, 93% two steps; (iv) TBSOTf, DIPEA; (v) BnCl, KH, 79% two steps; (vi) aq AcOH, 95%; (vii) TESOTf, py, DMAP, 98%; (viii) Swern oxidation, 98%; (ix) TBSOTf, DIPEA, 84%; (x) Na, liq NH_3; (xi) Boc_2O, 66% for **862**, 28% for **863**; (xii) $NaBH_4$, THF, 85% for **864**, 74% for **866**; (xiii) aq HCl; (xiv) DOWEX H^+, 97% for **864**, 95% for **862**; (xv) aq LiOH, THF, 80% for **865**, 90% for **867**; (xvi) (a) aq HCl; (b) DOWEX H^+, 96% for **865**, 98% for **867**.

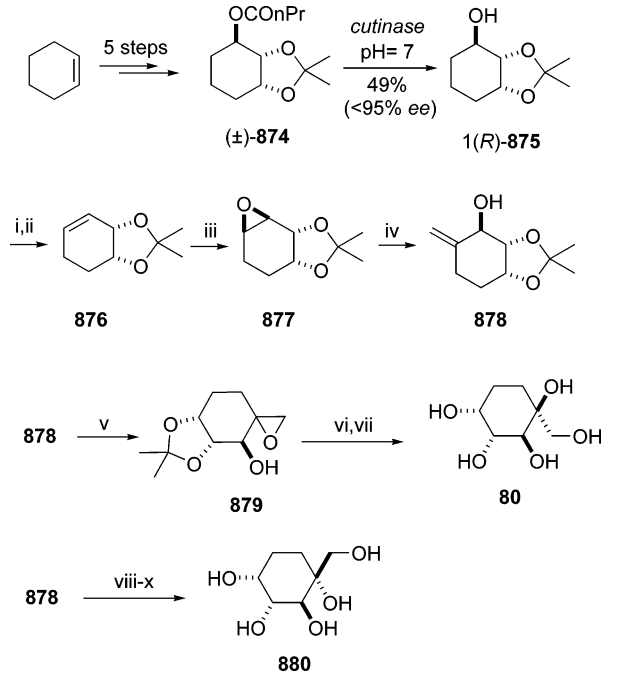
More recently, Yu and Chung have described a new protocol for the synthesis of 5a-carba-β-D-altropyranose derivatives (e.g., D-**881**, Scheme 137) from (±)-3-cyclohexene-1-carboxylic acid [(±)-**883**].[351] The retrosynthesis, outlined in Scheme 137a, is based on the transformation of (±)-**883** into homochiral diol D-**882** and, thence, on to D-**881**. Enzymatic resolution of hydroxy ester (±)-**884**, readily prepared from (±)-**883**, allowed access to hydroxy esters D-**885** and L-**886** (Scheme 137b). The former was then reduced to diol D-**882** and transformed into the 5a-carba-β-D-altropyranose derivative D-**881** by a series of transformations (Scheme 137c) in which the key step was the transformation of an epoxide to an allyl alcohol. The authors extended this strategy, first, to the synthesis of 5a-carba-β-D-manno-, β-D-ido-, and β-D-talopyranosides (D-**889**, D-**890**, and D-**891**, respectively; Scheme 137d) from 5a-carba-β-D-altropyranose (D-**881**),[351] by procedures involving regioselective benzoylation and stereoselective oxidation/reduction at C_3 and C_4. More recently, they have reported the

Scheme 135. Trost's Synthesis of Valienamine[a]



[a] Reagents: (i) 80 °C, neat, 91%; (ii) MCPBA, $NaHCO_3$, PhH, 80%; (iii) π-allylpalladium dimer, (1*S*,2*S*)-bis[(diphenylphosphino)benzamido]cyclohexane, $NaHCO_3$, THF, H_2O, then (dibenzylideneacetone)palladium, PPh_3, 60 °C, 87%; (iv) DBU, DMAP, TBDMSCl, CH_2Cl_2, 76%; (v) MCPBA, $NaHCO_3$, 86%; (vi) 2,2′-(pentane-2,4-diylbis(oxy))bis(4,6-dimethyl-1,3,2-dioxaphosphinane), $Pd(OAc)_2$, TsNCO, Me_3SnOAc, THF, 70%.

Scheme 136. Synthesis of 6a-Carba-β-D-fructopyranose (80) and 6a-Carba-α-D-fructopyranose (880)[a]

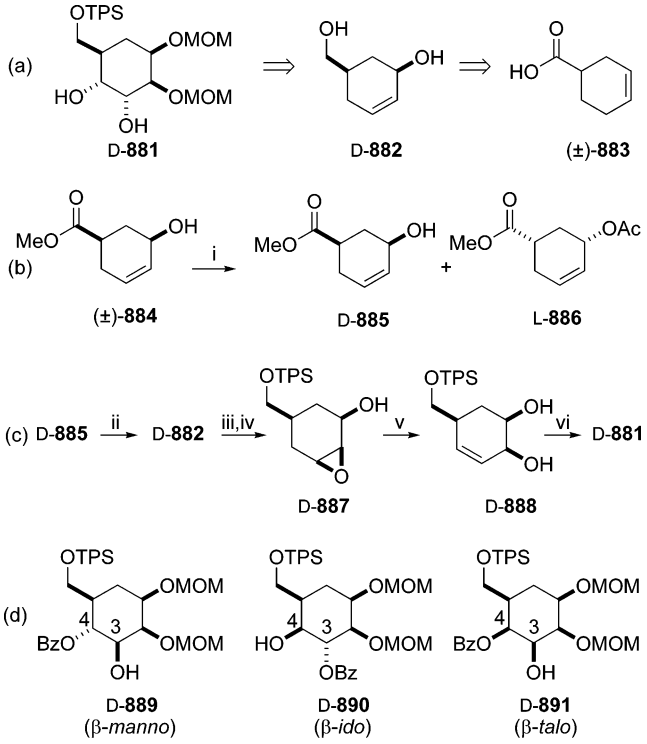


[a] Reagents: (i) $MeSO_2Cl$, Et_3N, 98%; (ii) DBU; (iii) MCPBA, 72% two steps; (iv) $Me_3S^+I^-$, n-BuLi, 45%; (v) MCPBA, 74%; (vi) NaOH, 81%; (vii) Amberlyst-15, MeOH, 77%; (viii) OsO_4, NMMO, 97%; (ix) $HClO_4$, acetone, 93%; (x) Amberlyst-15, MeOH, 80%.

preparation of the remaining α-D isomers and on to the α- and β-D-allo-, -gluco-, -gulo-, and -galactopyranoses, thus completing the synthesis of all 16 carbasugar stereoisomers.[352]

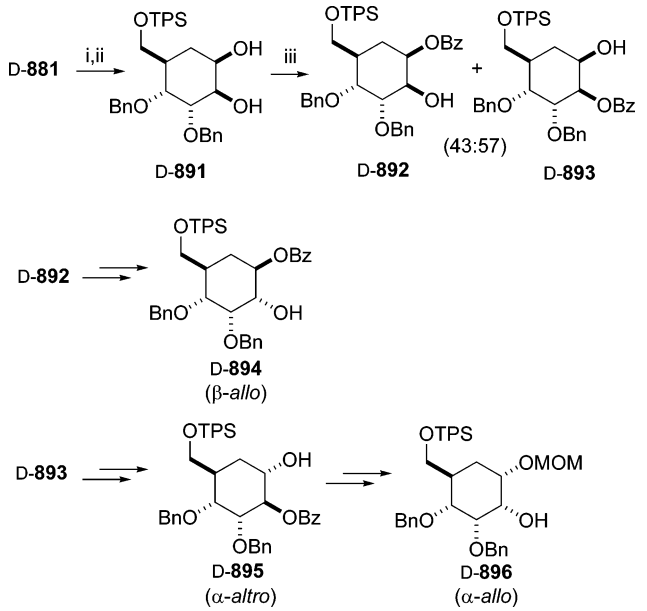
Protecting group manipulations in the altro derivative D-**881** permitted the preparation of diol D-**891**, which was monobenzoylated to a give a mixture of benzoates D-**892** and D-**893**. These compounds were submitted to stereoselective oxidation/reduction processes at C_1 and C_2, to give

Scheme 137. Yu and Chung's Synthesis of 5a-Carba-β-D-manno-, -β-D-ido-, and -β-D-talopyranose Derivatives[a]



[a] Reagents: (i) Novozym 435, vinyl acetate, t-BuOMe, 48% D-**885** (90−95% ee), 52% L-**886** (80−85% ee); (ii) LAH, THF, crystallization, 75%, 100% ee; (iii) t-butydiphenyl silyl chloride (TPSCl), imidazole, 70%; (iv) MCPBA, CH_2Cl_2, 96%; (v) (a) BzCl, py, 98%; (b) TMSBr; (c) DBU; (d) 1 N HCl, 78%; (vi) (a) MOMCI, (i-Pr)$_2$NEt, 99%; (b) OsO_4, NMMO, 99%.

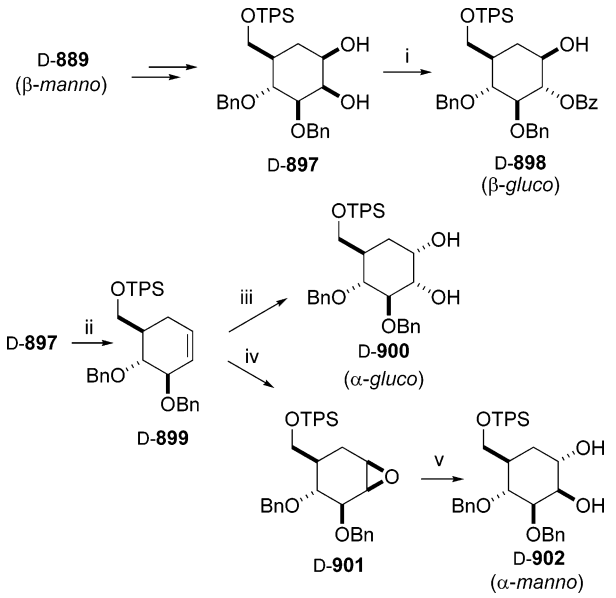
Scheme 138. Synthesis of 5a-Carba-β-D-allo-, -α-D-altro-, and -α-D-allopyranose Derivatives from D-881[a]



[a] Reagents: (i) NaH, BnBr, TBAI, THF, 90%; (ii) TMSBr, CH_2Cl_2, 64%; (iii) (a) $(EtO)_3CPh$, TsOH, CH_2Cl_2; (b) 80% aq AcOH, 95%.

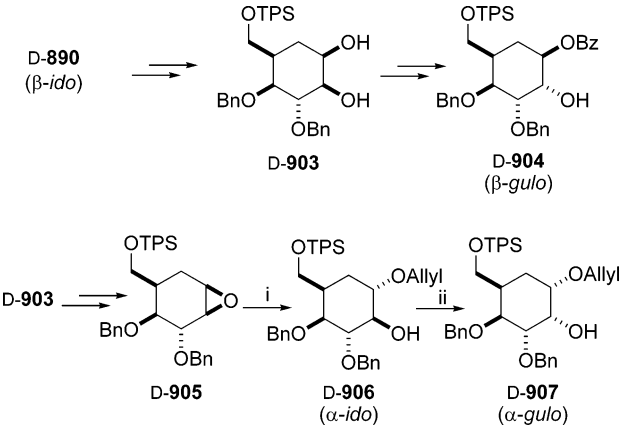
5a-carba-β-D-allose (D-**894**), 5a-carba-β-D-altrose (D-**895**), and 5a-carba-α-D-allose (D-**896**) (Scheme 138). β-D-Manno derivative D-**889** was converted to diol D-**897** and thence to 5a-carba-β-D-glucose derivative D-**898**, 5a-carba-α-D-glucose derivative D-**900**, and 5a-carba-α-D-mannose derivative D-**902** according to the transformations depicted in Scheme 139.

Scheme 139. Synthesis of 5a-Carba-β-D-gluco-, -α-D-gluco-, and -α-D−mannopyranose Derivatives from D-889[a]



[a] Reagents: (i) PPh_3, DEAD, PhCOOH, $PhCH_3$, 63%; (ii) PPh_3, imidazole, I_2, $PhCH_3$, 90%; (iii) OsO_4, NMMO, 100%; (iv) MCPBA (minor isomer); (v) $HClO_4$, acetone, 95%.

Scheme 140. Synthesis of 5a-Carba-β-D-gulo-, -α-D-ido-, and -α-D-gulopyranose Derivatives from D-890[a]



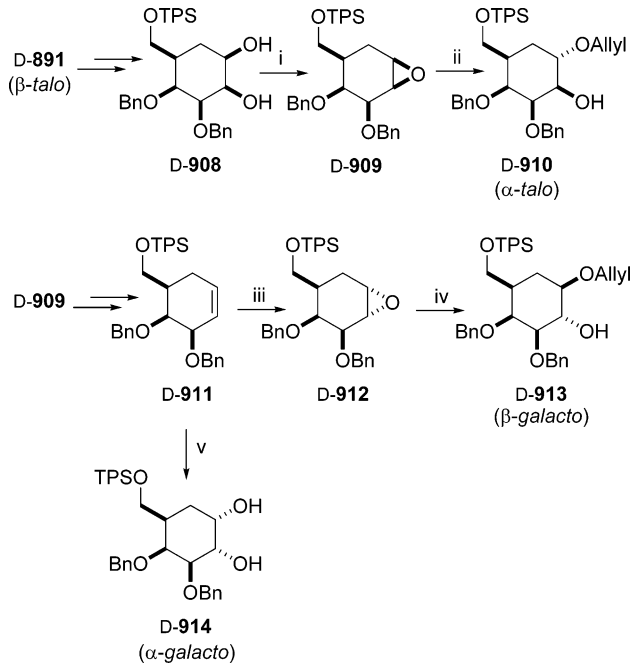
[a] Reagents: (i) TsOH, allyl alcohol, 73%; (ii) (a) PCC, molecular sieves, 99%; (b) L-Selectride, THF, 73%.

β-D-Ido derivative D-**890** was likewise transformed to diol D-**903**, and from this intermediate 5a-carba-β-D-gulose (D-**904**), 5a-carba-α-D-idose (D-**906**), and 5a-carba-α-D-gulose (D-**907**) were prepared (Scheme 140). In an analogous manner, β-D-talo derivative D-**891** was converted to diol D-**908**, which, by appropriate manipulations at C_1 and C_2, was transformed into 5a-carba-α-D-talose (D-**910**), 5a-carba-β-D-galactose (D-**913**), and 5a-carba-α-D-galactose (D-**914**) (Scheme 141).

6.2.2. Synthesis from Carbohydrate Precursors

As mentioned earlier, carbasugars were initially postulated as carbohydrate mimics of enhanced stability. However, the first, and more generally used to date, approach to carbasugars did not involve the use of carbohydrates as starting materials. It was clear, however, that the use of carbohydrates will provide important advantages to the preparation of their carbocyclic analogues. On the one hand, the hydroxyl groups could be maintained thorough the synthetic sequence, with

Scheme 141. Synthesis of 5a-Carba-α-D-talo-, -β-D-galacto-, and -α-D-galactopyranose Derivatives from D-891[a]



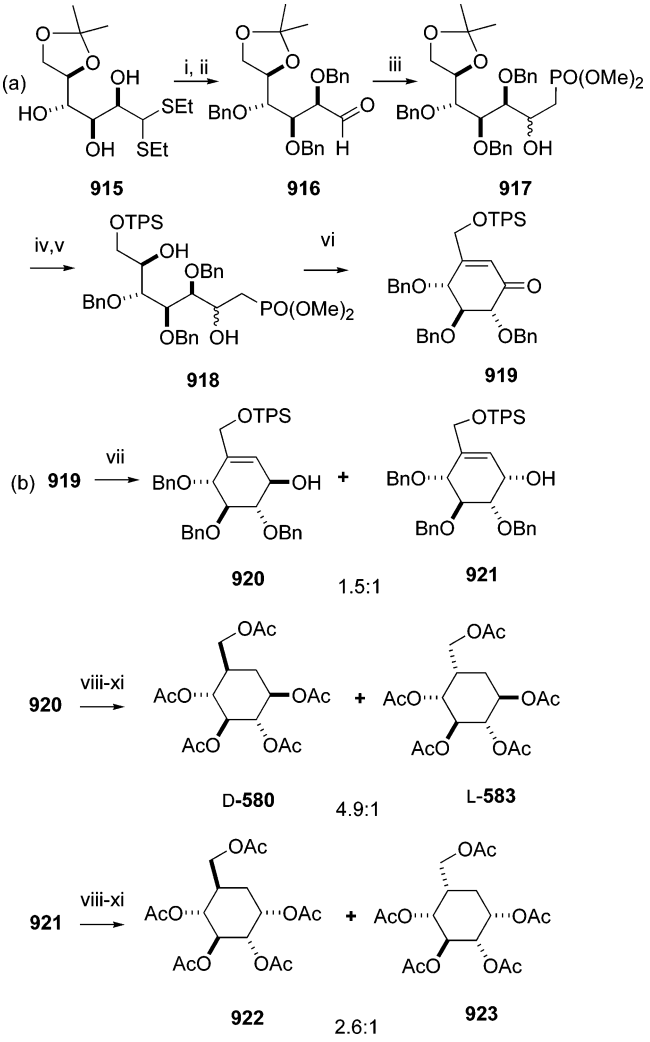
[a] Reagents: (i) (a) $(CH_3O)_3CCH_3$, PPTS, CH_2Cl_2; (b) AcBr, Et_3N; (c) NaOMe, MeOH, 99%; (ii) TsOH, allyl alcohol, 68%; (iii) MCPBA, CH_2Cl_2, both isomers; (iv) TSA, allyl alcohol, 54% (also other isomer, 23%); (v) OsO_4, NMMO, 91%.

no need for "hydroxylation" reactions, and the enantiomeric purity of the target carbasugars will be guaranteed. The challenges in these types of approaches lie in two main areas: (a) the homologation step, because the *carbasugar* contains one more carbon atom than the parent carbohydrate, and (b) the cyclization reaction. The methods for the preparation of carbasugars described in this section have been classified according to the type of ring-closing reaction.

6.2.2.1. Nucleophilic Cyclization. Most methods for the preparation of carbapyranoses from carbohydrates involved intramolecular nucleophilic additions of simple carbanions to aldehyde or ketone groups. These reactions are treated in this section according to the nature of the stabilization, and carbanions adjacent to either phosporous atoms or carbonyl or nitro groups are considered. In addition, intramolecular nucleophilic displacement reactions of carbanions at saturated carbon centers of carbohydrate derivatives which originated carbasugar precursors are also included in this section. The Ferrier (II) reaction is also included in this section since it can be considered formally as the cyclization of a mercury enolate onto an aldehyde.

6.2.2.1.1. Cyclization of Phosphorus-Stabilized Carbanions. Cyclization of carbanions, which are stabilized both by phosphonate and carbonyl neighboring groups, have been of particular value in the synthesis of carbapyranoses from carbohydrates. In this context, Paulsen et al. paid special attention to the intramolecular Horner−Emmons olefination (Scheme 142).[353] The reaction of aldehyde **916**, prepared from D-glucose diethyl dithioacetal **915**, with lithium dimethyl methyl phosphonate yielded the adduct **917**. Manipulation of protecting groups in **917** followed by Swern oxidation resulted in the formation of enone **919**, which furnished alcohols **920** and **921** by sodium borohydride reduction. *O*-Desilylation, catalytic hydrogenation, *O*-debenzylation, and acetylation converted **920** into 5a-carba-β-D-glucopyra-

Scheme 142. Synthesis of Carbasugars by Intramolecular Horner−Emmons Olefination[a]

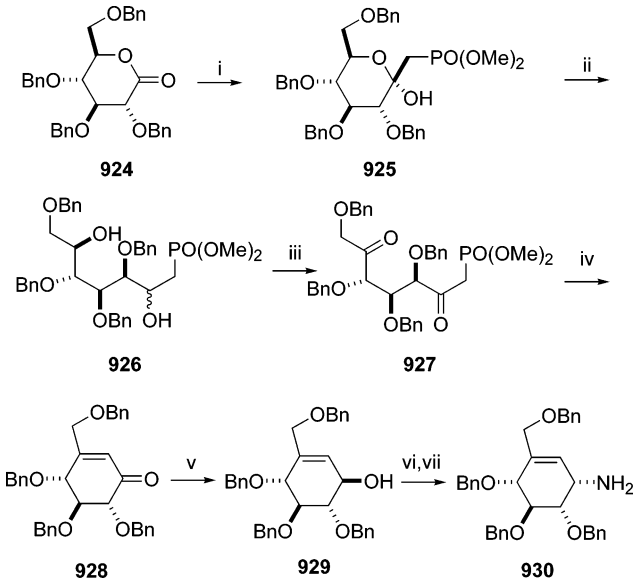


[a] Reagents: (i) HNa, BnBr, DMF, 93%; (ii) $HgCl_2$, HgO, CH_3CN, 71%; (iii) n-BuLi, $MePO(OMe)_2$, −78 °C; (iv) AcOH, 60 °C; (v) TPSCl, imidazole, 85% from **917**; (vi) $(COCl)_2$, DMSO, Et_3N, 50%; (vii) $NaBH_4$, 87%; (viii) TBAF, THF; (ix) Ra−Ni, dioxane; (x) H_2, Pd/C, MeOH; (xi) Ac_2O, py; (a) 54% from **920**; (b) 46% from **921**.

nose pentaacetate (D-**580**) and 5a-carba-α-L-idopyranose pentaacetate (L-**583**). Similarly, **921** was transformed into 5a-carba-α-D-glucopyranose pentaacetate (**922**) and 5a-carba-*β*-L-idopyranose pentaacetate (**923**).[353]

Fukase and co-workers also used the intramolecular Horner−Emmons reaction starting from tetra-*O*-benzyl-D-glucono-1,5-lactone (**924**), readily available from D-glucose, in their synthesis of tetra-*O*-benzylvalienamine (**930**) (Scheme 143).[354] Lactone **924** was treated with 2 equiv of lithium dimethyl methyl phosphonate to yield dimethoxyphosphoryl heptulospyranose derivative **925**. Direct oxidation of the C_6 hydroxyl group of **925** proved to be difficult because the hydroxyl group is blocked by the pyranose ring formation. Therefore, the pyranose ring was reductively opened with sodium borohydride to give the heptitol derivative **926**, in which the 2-OH and 6-OH groups were oxidized with a reagent combination of DMSO, trifluoroacetic anhydride, and triethylamine. The intramolecular cyclization reaction of the resulting 2,6-heptodiulose derivative **927** was accomplished with potassium carbonate in the presence of 18-crown-6 to give the branched unsaturated inososе derivative **928**. Next, the oxo group of **928** was reduced stereoselectively to an

Scheme 143. Synthesis of Tetra-*O*-benzylvalienamine (930)[a]



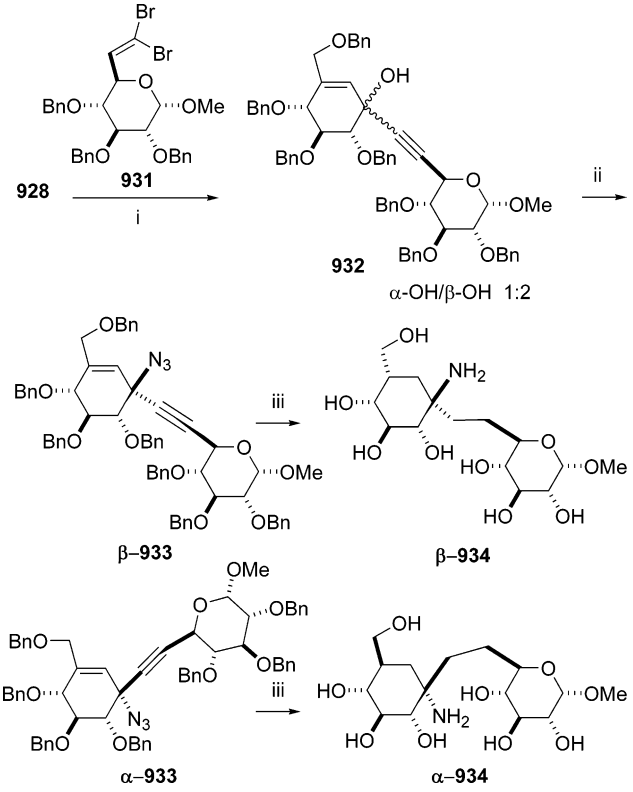
[a] Reagents: (i) n-BuLi, $MePO(OMe)_2$, −78 °C, 95%; (ii) $NaBH_4$, 94%; (iii) DMSO, TFA, Et_3N, CH_2Cl_2, −78 °C, 94%; (iv) K_2CO_3, 18-crown-6, $PhCH_3$, 76%; (v) $NaBH_4$, $CeCl_3$, EtOH, −78 °C, 75%; (vi) phthalimide, Ph_3P, DEAD, THF, 52%; (vii) H_2N-NH_2, MeOH, THF, 74%; (viii) liq NH_3, 62%.

allylic equatorial hydroxyl group with $NaBH_4-CeCl_3$ in ethanol. The resulting alcohol **929** was then converted to an axial amino group employing a Mitsunobu reaction to afford tetra-*O*-benzylvalienamine (**930**).

The value of this intramolecular Horner−Emmons approach was further illustrated with the synthesis of the first carba-*C*-disaccharide from ketone **928** (Scheme 144).[355] The ketone **928** was reacted with the lithium acetylide generated by treatment of dibromide **931** with BuLi to give two stereomeric alcohols **932** from which pseudo-glycosyl azides **933** were prepared employing BF_3Et_2O and $TMSN_3$. Finally, the two diastereomeric azides (α-**933** and *β*-**933**) were independently hydrogenated with palladium on charcoal as catalyst to give carbasugar-*C*-glycosides with the L-ido- and D-gluco configurations, α-**934** and *β*-**934**, respectively. The stereoselectivity in the reaction was explained in relation to the presence of the bulky *C*-glycoside substituent, which directs the hydrogenation of the double bond from the less hindered face.

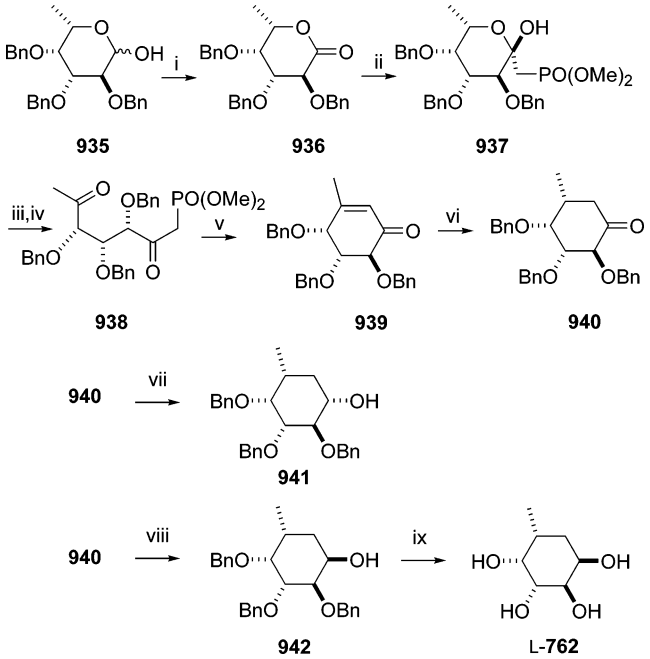
Finally, Toyokuni et al. utilized the intramolecular Horner−Emmons reaction for the conversion of L-fucose to its carbocyclic analogue L-**762** (Scheme 145).[87] The synthesis started from benzylated L-fucose **935**. Oxidation to the 1,5-lactone **936** followed by a nucleophilic substitution reaction with the carbanion derived from dimethyl methyl phosphonate afforded the heptulopyranose **937** as a single isomer. Reductive ring opening of **937** with $NaBH_4$ and subsequent Swern oxidation yielded the unstable dioxo phosphonate **938**. The ensuing intramolecular olefination occurred by treatment with NaH in diglyme to give the unsaturated inososе **939**. The copper(I) hydride hexamer allowed the stereoselective conjugate reduction of **939**, yielding the inososе **940** as the only diastereomer. The $NaBH_4-CeCl_3$ reduction in MeOH produced an almost quantitative conversion of **940** to the equatorial alcohol **941**, which is a protected form of carba-*β*-L-fucopyranose. In the absence of $CeCl_3$, the same reduction resulted in poor selectivity, giving a mixture of **941** and its epimeric alcohol **942** in a 1.3:1 ratio. Hydrogenolysis of **942** yielded 5a-carba-α-L-fucopyranose (L-**762**).[87]

Scheme 144. Synthesis of a Carbasugar-*C*-disaccharide[a]



[a] Reagents: (i) n-BuLi, THF, −50 °C, 59%; (ii) $TMSN_3$, $BF_3{\cdot}Et_2O$, 37%; (iii) Pd/C, H_2, HCl, EtOH; (a) 66% for β-N_3; (b) 100% for α-N_3.

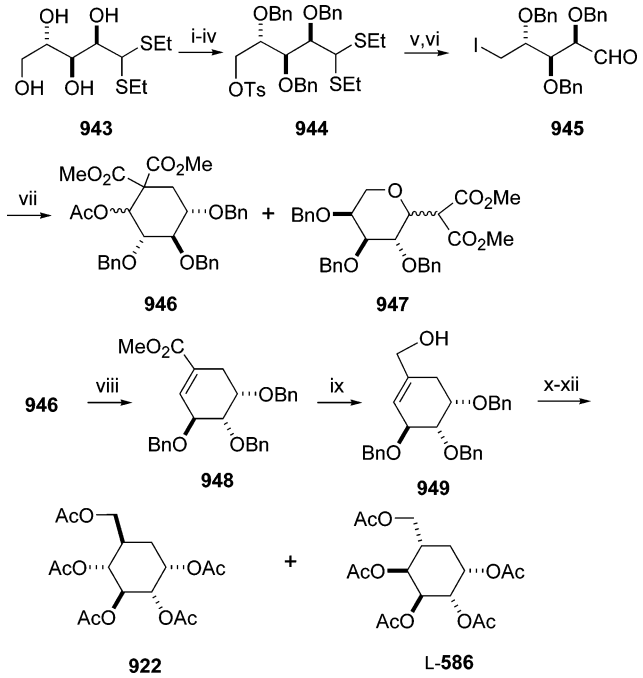
Scheme 145. Synthesis of 5a-Carba-α-L-fucopyranose (L-762)[a]



[a] Reagents: (i) DMSO, Ac_2O, 84%; (ii) n-BuLi, $MePO(OMe)_2$, −78 °C, 91%; (iii) $NaBH_4$, 93%; (iv) DMSO, TFA, Et_3N, 82%; (v) NaH, diglime, 65 °C, 94%; (vi) $(Ph_3PCuH)_6$, THF, 93%; (vii) $NaBH_4$, $CeCl_3$, MeOH, 99%; (viii) $NaBH_4$, EtOH, 98%; (ix) H_2, Pd/C, 67%.

6.2.2.1.2. Cyclization of Carbonyl-Stabilized Carbanions. Cyclizations involving either intramolecular nucleophilic displacement or aldol condensations have been of particular value in the synthesis of carbahexopyranoses. In the course of their extensive work in this area, Suami, Tadano, and co-

Scheme 146. Synthesis of 5a-Carba-α-D-glucopyranose Pentaacetate (922) and 5a-Carba-β-L-altropyranose Pentaacetate (L-586)[a]

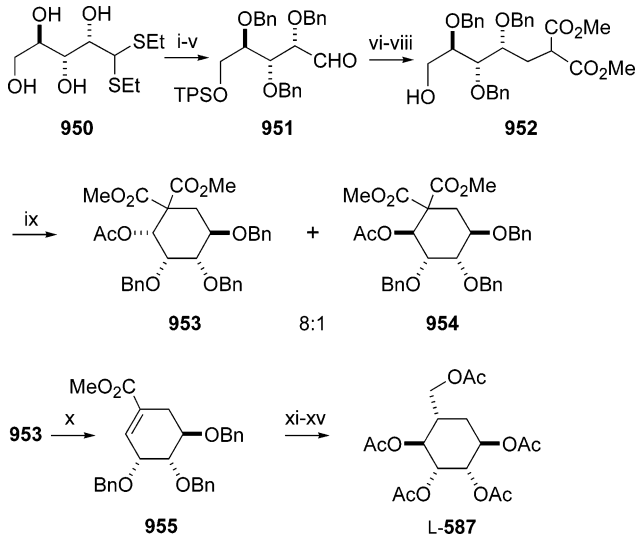


[a] Reagents: (i) TrCl, py, DMAP, 85%; (ii) HNa, BnBr; (iii) TsOH, MeOH, 79%, two steps; (iv) TsCl, py; (v) $HgCl_2$, $CaCO_3$; (vi) NaI, acetone, reflux, 54% three steps; (vii) dimethyl malonate, NaH, DMF, then Ac_2O, 76%; (viii) DMSO, NaCl, 170 °C, 75%; (ix) LAH, −15 °C, 83%; (x) B_2H_6, then H_2O_2, NaOH; (xi) Ac_2O, py, 69% two steps; (xii) Na, liq NH_3, then Ac_2O, py, 49% **922**, 31% L-**586**.

workers converted L-arabinose diethyl dithioacetal **943** to compound **944** by successive *O*-tritylation, *O*-benzylation, *O*-detritylation, and *O*-tosylation (Scheme 146).[356,357] The parent aldehyde was regenerated from **944** with $HgCl_2$ and $CaCO_3$, and substitution with sodium iodide gave the iodo compound **945**. Cyclization of **945** with dimethyl malonate and sodium hydride, followed by acetylation, provided cyclohexane derivative **946** and a secondary pyranose derivative **947** in the ratio of 1.3:1. The hydroxyl group generated in the addition of the malonate anion onto the aldehyde may attack the iodine-containing carbon atom, giving the pyranose **947**. Krapcho decarboxylation of **946** provided the cyclohexene derivative **948**, which gave compound **949** by lithium aluminum hydride reduction. Hydroboration−oxidation of **949**, followed by acetylation, deprotection, and final peracetylation, gave a mixture of 5a-carba-α-D-glucopyranose pentaacetate (**922**) and 5a-carba-β-L-altropyranose pentaacetate (L-**586**).[356,357]

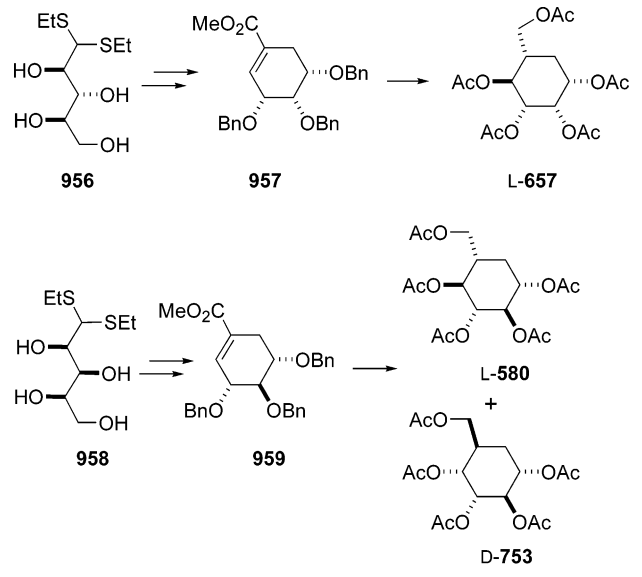
This reaction, as seen above, suffers from the competitive formation of tetrahydropyranes, e.g., **947**, and in order to overcome that, a stepwise procedure was adopted for the synthesis of 5a-carba-α-L-mannopyranose pentaacetate (L-**587**) (Scheme 147).[207b] D-Arabinose diethyl dithioacetal **950** was converted into compound **951** by sequential tritylation, benzylation, detritylation, *O*-silylation, and regeneration of the parent aldehyde group. Knoevenagel reaction of **951** with dimethyl malonate and pyridine provided compound **952** after catalytic hydrogenation and desilylation. The crucial cyclization of **952** was accomplished by oxidation with PCC, providing two cyclohexane derivatives **953** and **954** in the ratio of 10:1. Thermal demethoxycarbonylation of **953** accompanied by β-elimination of the acetoxy group gave protected methyl shikimate **955**. Diisobutyl aluminum hy-

Scheme 147. Synthesis of 5a-Carba-α-L-mannopyranose Pentaacetate (L-587)[a]



[a] Reagents: (i) TrCl, py, DMAP; (ii) HNa, BnBr; (iii) p-TsOH, MeOH; (iv) TPSCl, imidazole, DMF; (v) $HgCl_2$, $CaCO_3$; (vi) dimethyl malonate, py, Ac_2O; (vii) H_2, Ra−Ni, EtOH, NaH; (viii) TBAF, THF, 37% from **950**; (ix) PCC, then Ac_2O, py, 53%; (x) DMSO, NaCl, 170 °C, 46%; (xi) DIBAL-H, 93%; (xii) B_2H_6, then H_2O_2, NaOH; (xiii) Ac_2O, py; (xiv) Na, liq NH_3; (xv) Ac_2O, py, 66% from **955**.

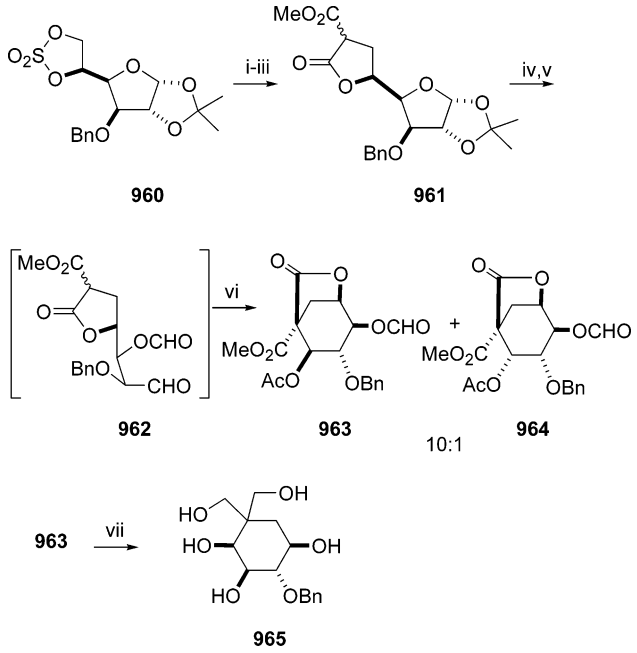
Scheme 148. Synthesis of 5a-Carba-β-L-mannopyranose Pentaacetate (L-657), 5a-Carba-β-L-glucopyranose Pentaacetate (L-580), and 5a-Carba-α-D-altropyranose Pentaacetate (D-753)



dride reduction followed by hydroboration and successive oxidation permitted access, after *O*-debenzylation and acetylation, to 5a-carba-α-L-mannopyranose pentaacetate (L-**587**).

This strategy has been extended to different carbasugars (Scheme 148). D-Ribose diethyl dithioacetal **956** was converted to cyclohexene **957** (C_1 epimer of **955**), from which 5a-carba-β-DL-mannopyranose pentaacetate (L-**657**) was stereoselectively obtained (Scheme 148a).[207a] On the other hand, D-xylose diethyl dithioacetal **958** was transformed to cyclohexene **959**, which was used in the preparation of 5a-carba-β-L-glucopyranose pentaacetate (L-**580**) and 5a-carba-α-D-altropyranose pentaacetate (D-**753**) (Scheme 148b).[207]

Scheme 149. Synthesis of Carbasugar Derivative 965[a]



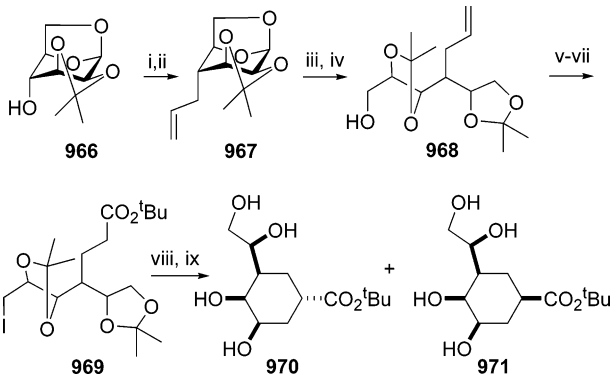
[a] Reagents: (i) dimethyl malonate, NaH, DMF; (ii) aq H_2SO_4; (iii) 0.1 M MeONa, MeOH, 67% from **960**; (iv) Dowex 50(H^+); (v) $NaIO_4$, aq dioxane; (vi) py, Ac_2O, 38% from **961**; (vii) LAH, 79%.

Hrebabecky and Holy disclosed a related strategy to carba analogues of 5-C-(hydroxymethyl)hexopyranoses via nucleophilic attack of the malonyl ester carbanion on the carbonyl group of an aldehyde (Scheme 149).[358] Treatment of cyclic sulfate **960** with the sodium salt of dimethyl malonate afforded, after hydrolysis with aqueous sulfuric acid, lactone **961** as an equimolecular mixture of diastereomers. Deketalization of the anomeric position in **961** followed by oxidative cleavage with $NaIO_4$ gave an intermediate aldehyde, **962**, which was immediately cyclized, by treatment with acetic anhydride (only the 3*S* isomer was able to react), to give the bicyclic derivatives **963** and **964**. Reduction and hydrogenolysis of **963** gave the corresponding bis(hydroxymethyl) derivative **965**, which was considered as a useful intermediate in carbanucleoside synthesis.

A similar strategy has been used by Samuelsson et al. to gain access to the carba analogue of the Gram-negative bacterial polysaccharide component KDO (Scheme 150).[359] 1,6-Anhydro-D-mannose derivative **966** was converted into the branched chain derivative **967** in high diastereomeric excess employing a free radical carbon−carbon bond-forming reaction. Acetolysis of **967** followed by deacetylation, reduction, and isopropylidenation gave the *C*-allyl-mannitol derivative **968**, which was subjected to iodination, and hydroboration followed oxidative workup. Final oxidation with pyridinium dichromate/acetic anhydride yielded ester **969**, which was cyclized by treatment with LDA to a 3:1 epimeric mixture of compounds which upon separation and deprotection yielded **970** and **971**. These compounds were screened for *in vitro* biological activity. Compound **970** showed a weak inhibitory effect toward CMP−KDO synthetase but no antibacterial effect, whereas compound **971** was inactive.

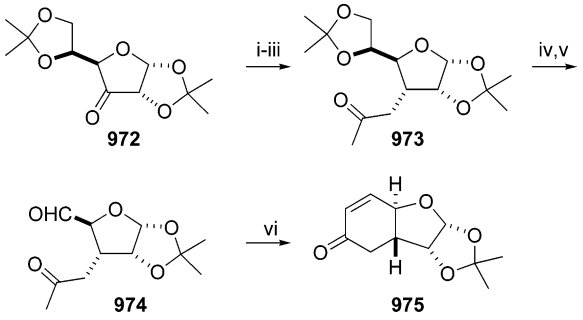
Tadano et al. have used aldol cyclizations of carbohydrate precursors with carbonyl-containing, extended or branched, chains in a different approach to carbasugars. The protocol features an efficient intramolecular aldol cyclization leading to the chiral synthon **975** and a subsequent stereoselective

Scheme 150. Synthesis of Carbasugar Analogues of KDO[a]



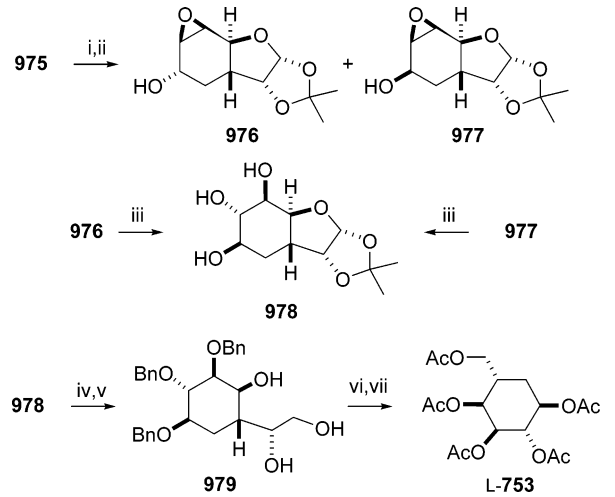
[a] Reagents: (i) phenylchlorothionoformate, py, 94%; (ii) allyltributylstannane, *hv*; 85 °C; (iii) Ac_2O, TFA, 71% two steps; (iv) NaOMe, MeOH, then $NaBH_4$, then 2,2-dimethoxypropane, acetone, $CuSO_4$, 73%; (v) Ph_3P, imidazole, I_2, $PhCH_3$, reflux; (vi) BH_3-SMe_2, then NaOH, H_2O_2, H_2O; (vii) PDC, Ac_2O, t-BuOH, 65%; (viii) LDA, −75 °C, 90%; (ix) TFA, H_2O, 96%.

Scheme 151. Synthesis of Key Intermediate 975 by Intramolecular Aldol Cyclization[a]



[a] Reagents: (i) (acetylmethylene)triphenylphosphorane, PhH, reflux; (ii) H_2, Ra−Ni, MeOH; (iii) PCC, CH_2Cl_2, 88% from **972**; (iv) AcOH, H_2O; (v) $NaIO_4$, H_2O, MeOH; (vi) DBU, PhH, reflux, then py, Ac_2O, 43% from **973**.

Scheme 152. Synthesis of 5a-Carba-α-L-altropyranose Pentaacetate (L-753) from Key Intermediate 975[a]



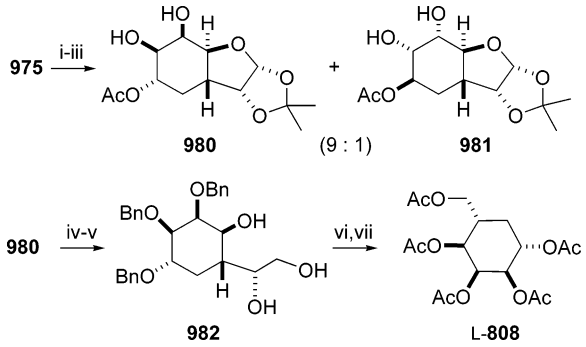
[a] Reagents: (i) H_2O_2, NaOH, MeOH, 96%; (ii) $NaBH_4$, EtOH, 84%; (iii) 2-methoxyethanol, H_2O, NaOAc, 73% from **976**, 81% from **977**; (iv) NaH, $BrCH_2Ph$, DMF; (v) AcOH, H_2O, 1,4-dioxane, reflux, then $NaBH_4$, MeOH; (vi) $NaIO_4$, MeOH, H_2O, then $NaBH_4$, MeOH; (vii) Ac_2O, py, 48% from **978**.

introduction of a triol system on this aldol product (Schemes 151 and 152).[360,361] 1,2:5,6-Di-*O*-isopropylidene-α-D-ribo-hexofuranos-3-ulose (**972**) was subjected to Wittig olefination with acetylmethylenetriphenylphosphorane in refluxing benzene to give a 3:1 mixture of *E/Z* diastereomers. Hydrogenation of the mixture, from the β-face, and reoxidation with PCC provided ketone **973**. Chemoselective hydrolysis of the 5,6-*O*-isopropylidene group, followed by periodic acid oxidation, yielded aldehyde **974**, which was subjected to the aldol cyclization by refluxing in benzene in the presence of DBU. A subsequent elimination with acetic anhydride and pyridine furnished compound **975** (Scheme 151), the key intermediate in the synthesis of carbasugars of the α-L-altro, β-D-gluco, β-L-allo, and α-D-manno series.[360]

In order to introduce oxygen functionalities in the 2-cyclohexenone ring, epoxidation of **975** was carried out with hydrogen peroxide to give one very major β-epoxide which was reduced with sodium borohydride to give epoxy alcohols **976** and **977** in a 5:1 ratio (Scheme 152). *Trans*-diaxial opening of the oxirane ring in **977** by hydroxide anion provided triol **978**. On the other hand, nucleophilic ring opening of the isomeric epoxide **976** also produced triol **978**, by way of a migration of the epoxide and subsequent hydroxide ring opening in a diaxial manner. Benzylation of the free alcohols in **978**, acid hydrolysis of the acetal moiety, and successive sodium borohydride reduction of the released aldehyde provided a protected form of 5a-carba-heptopyranose **979**. Glycol cleavage in **979**, reduction, removal of the protecting groups, and final acetylation furnished 5a-carba-α-L-altropyranose pentaacetate (L-**753**).[361]

In another set of experiments, enone **975** was reduced with DIBAL-H to give an inseparable mixture of allylic alcohols which were acetylated and treated with osmium tetroxide to give, stereoselectively, diols **980** and **981** (53% and 6% yield, respectively). *O*-Deacetylation of **980**, successive benzylation, hydrolysis of the acetal moiety, and reduction with $NaBH_4$ gave carbaheptopyranose **982**. The glycol cleavage on **982** with sodium periodate, followed by reduction of the resulting aldehyde and acetylation, paved the way to 5a-carba-β-L-allopyranose pentaacetate (L-**808**) (Scheme 153).[362]

Scheme 153. Synthesis of 5a-Carba-β-L-allopyranose Pentaacetate (L-808)[a]

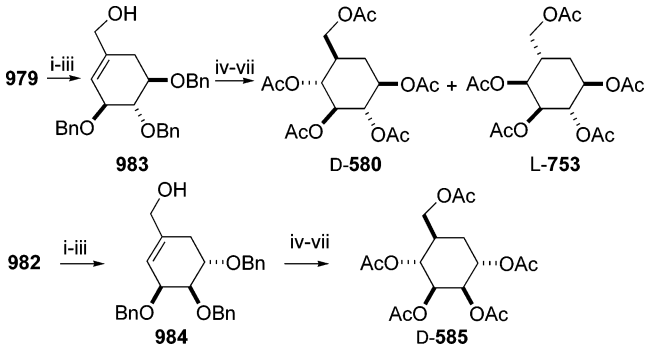


[a] Reagents: (i) DIBAL-H, CH_2Cl_2, −78 °C, 69% (7:1 mixture of epimers); (ii) Ac_2O, py, 96%; (iii) OsO_4, t-BuOH, H_2O_2, 59%; (iv) NaOMe, MeOH, then NaH, $BrCH_2Ph$, DMF, 88%; (v) AcOH, H_2O, 1,4-dioxane, reflux, then $NaBH_4$, MeOH, 56%; (vi) $NaIO_4$, MeOH, H_2O, then $NaBH_4$, MeOH; (vii) Ac_2O, py, 85% from **982**.

In another set of experiments, enone **975** was reduced with DIBAL-H to give an inseparable mixture of allylic alcohols which were acetylated and treated with osmium tetroxide to give, stereoselectively, diols **980** and **981** (53% and 6% yield, respectively). *O*-Deacetylation of **980**, successive benzylation, hydrolysis of the acetal moiety, and reduction with $NaBH_4$ gave carbaheptopyranose **982**. The glycol cleavage on **982** with sodium periodate, followed by reduction of the resulting aldehyde and acetylation, paved the way to 5a-carba-β-L-allopyranose pentaacetate (L-**808**) (Scheme 153).[362]

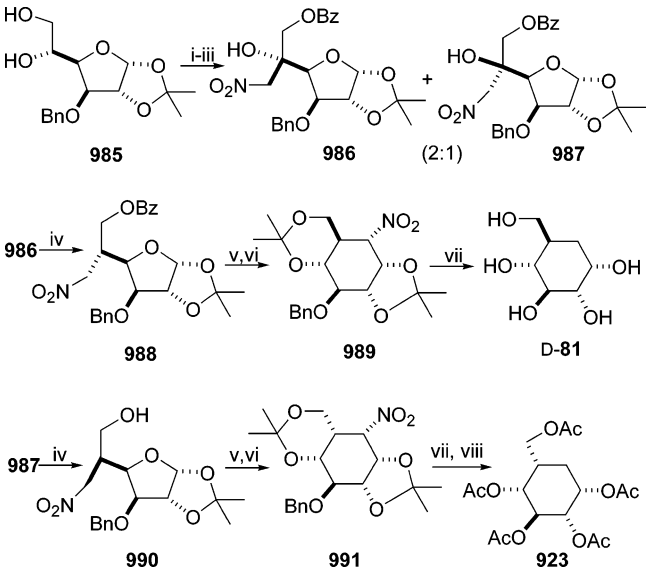
Alternatively, the inversion of the configuration at the branched carbon could be carried out by hydroboration−oxidation on unsaturated cyclohexane intermediates (Scheme 154). Thus, treatment of triols **979** or **982** with sodium periodate and then an excess of methanesulfonyl chloride in pyridine gave the corresponding cyclohexanecarbaldehydes, which were reduced to afford the allylic alcohols **983** and **984**, respectively. Hydroboration of **983** with borane−THF complex and oxidative workup, followed by *O*-debenzylation

Scheme 154. Synthesis of Carbasugars of the L-Altro, D-Gluco, and D-Manno Series (L-753, D-580, and D-585)[a]



[a] Reagents: (i) $NaIO_4$, MeOH, H_2O; (ii) MsCl, py; (iii) LAH, THF, 22% overall for **983**, 37% overall for **984**; (iv) borane−THF complex, then NaOH, H_2O_2; (v) Ac_2O, py; (vi) H_2, Pd black; (vii) Ac_2O, py, 62% overall yield for D-**580**, 11% overall for L-**753**, and 56% overall for D-**585**.

Scheme 155. Synthesis of Carbasugars D-81 and 923[a]

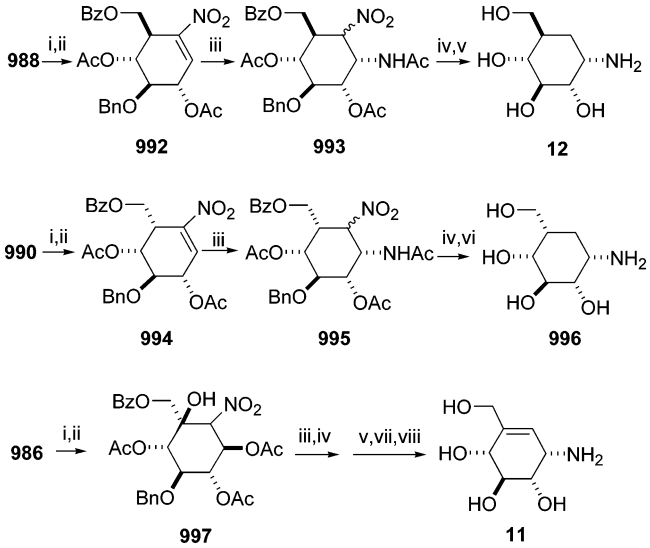


[a] Reagents: (i) BzCl, py, CH_2Cl_2; (ii) DMSO, $(COCl)_2$, Et_3N; (iii) CH_3NO_2, NaH, 15-crown-5, DMF, 61% from **985**; (iv) Ac_2O, TsOH, $NaBH_4$, EtOH, 69%; (v) 80% aq AcOH, 80 °C; (vi) (a) KF, 18-crown-6, DMF, then NaOMe/MeOH; b) 2,2-dimethoxypropane, TsOH, $CuSO_4$, 60% from **986**, 62% from **987**; (vii) (a) n-Bu_3SnH, AIBN, PhH, 80 °C; (b) aq AcOH; (c) Na, liq NH_3; 30% from **989**; (viii) Ac_2O, py, 20% from **991**.

and successive acetylation, gave a mixture of 5a-carba-β-D-glucopyranose and 5a-carba-α-L-altropyranose pentaacetates (D-**580** and L-**753**), respectively (6:1 ratio).[361] Likewise, analogous treatment of allylic alcohol **984** permitted the preparation of 5a-carba-α-D-mannopyranose (D-**585**).[361,362]

6.2.2.1.3. Cyclization of Nitro-Stabilized Carbanions. Kitagawa et al. showed that reactions involving cyclization of nitrosugars are useful processes in the enantioselective preparation of carbapyranoses (Scheme 155). Initially, they developed a method which comprised (a) addition of nitromethane to a furanose derivative and (b) subsequent cyclization as the key reactions. Accordingly, 1,2-isopropylidene-α-D-glucofuranose (**985**) was converted to nitrofuranoses **986** and **987** by treatment of the corresponding 5-keto derivative with nitromethane in the presence of KF and 18-crown-6. The reductive deacetoxylation, on **986** and **987**, with $NaBH_4$ proceeded stereoselectively to provide S_N2-type reaction products **988** and **990**, respectively. Removal of the isopropylidene groups in these compounds and treatment with KF in the presence of 18-crown-6 followed by introduction

Scheme 156. Synthesis of Validamine (12), 5-Epi-validamine (996), and Valienamine (11)[a]



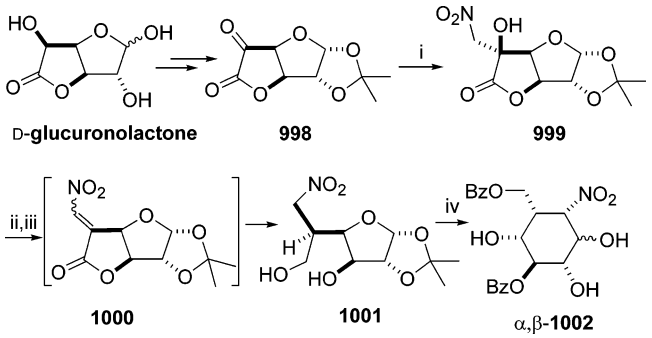
[a] Reagents: (i) 80% aq AcOH, 80 °C; (ii) KF, 18-crown-6, DMF, then Ac_2O, TsOH; (iii) liq NH_3, THF, −78 °C, then Ac_2O, py; (iv) n-Bu_3SnH, AIBN, PhH, 80 °C, 56%; (v) (a) NaOH, MeOH; (b) Na, liq NH_3; (c) Ac_2O, py, NaOMe, MeOH; (d) aq NH_2NH_2; (vi) (a) NaOH, MeOH; (b) Na, liq NH_3; (c) aq NH_2NH_2; (vii) $SOCl_2$, py; (viii) aq NH_2NH_2.

of the isopropylidene groups yielded nitro derivatives **989** and **991**, respectively. Finally, radical-mediated denitration and protecting group operations yielded 5a-carba-α-D-glucopyranose (D-**81**) and 5a-carba-β-L-idopyranose pentaacetate (**923**).[363]

The same key nitrofuranose intermediates **988** and **990** were used for the synthesis of carba-aminosugars, validamine (**12**) and 5-epi-validamine (**996**) (Scheme 156).[364] Accordingly, isopropylidene hydrolisis of **988** and **990** followed by cyclization and subsequent acetylation yielded nitroolefines **992** and **994**, which were then subjected to a Michael-type addition reaction with liq NH_3 to introduce the "anomeric" amino group. Radical elimination of the nitro group in **993** and **995** with tributyltin hydride followed by removal of protecting groups provided validamine (**12**) and 5-epi-validamine (**996**), respectively. On the other hand, reaction of nitrofuranose derivative **986** paved the way to valienamine (**11**). The incorporation of the amino group took place by treatment of the carba-nitrosugar **997** with liq NH_3, via a substitution reaction at the acetoxyl group at the β-position of the nitro group. Subsequent acetylation, radical elimination of the nitro group, and final dehydration with $SOCl_2$ furnished valienamine (**11**).

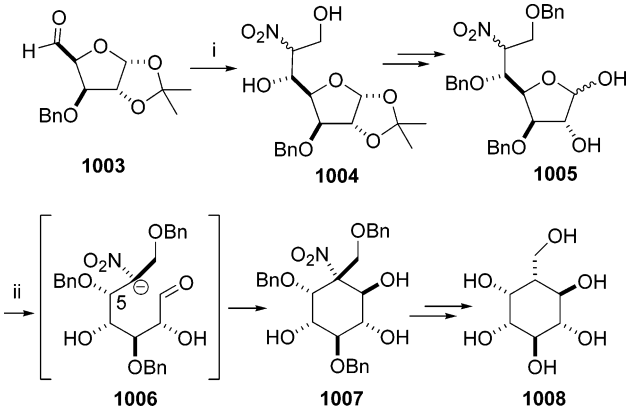
In subsequent work, Yoshikawa et al. have developed a more efficient entry to the key nitrofuranose intermediates (i.e., **988**, **990**).[365] Treatment of D-glucuronolactone derivative **998** with nitromethane in the presence of KF gave nitro compound **999**, which was subsequently subjected to ethoxyethylation and reduction with $NaBH_4$ in isopropanol to give stereoselectively and in high yield a single product, **1001**. This transformation (**999** → **1001**) is believed to proceed in three steps including elimination of the ethoxyethoxyl moiety to produce a intermediate nitroolefine (**1000**), followed by reduction with hydride from the less hindered α-face and final reduction of the 6,3-lactone ring (Scheme 157). Cyclization of **1001** gave nitrocarbasugar derivatives α,β-**1002** (2:1 mixture of diastereomers) which were converted to 5a-carba-α-D-glucopyranose, 5a-carba-β-D-glucopyranose, and validamine, using previously described transformations.[366]

Scheme 157. Synthesis of Key Intermediate 1002[a]



[a] Reagents: (i) CH_3NO_2, KF, 86%; (ii) ethyl vinyl ether, CSA, 79%; (iii) $NaBH_4$, i-PrOH, 83%; (iv) (a) BzCl, py; (b) aq TFA; (c) CsF, DMF.

Scheme 158. Synthesis of a 5a-Hydroxycarbasugar by the Henry Reaction[a]

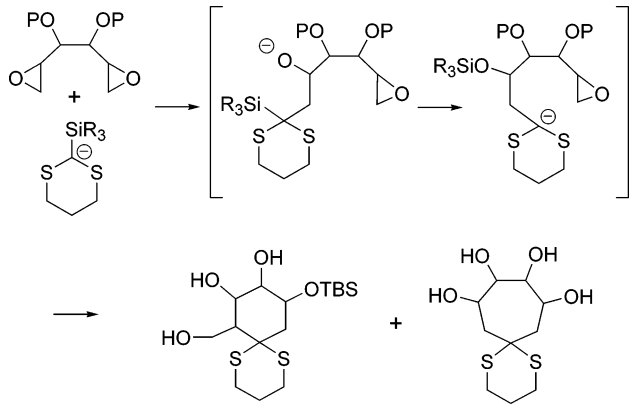


[a] Reagents: (i) nitroethanol, TBAF, 75%; (ii) aq $NaCO_3H$, MeOH, 53%.

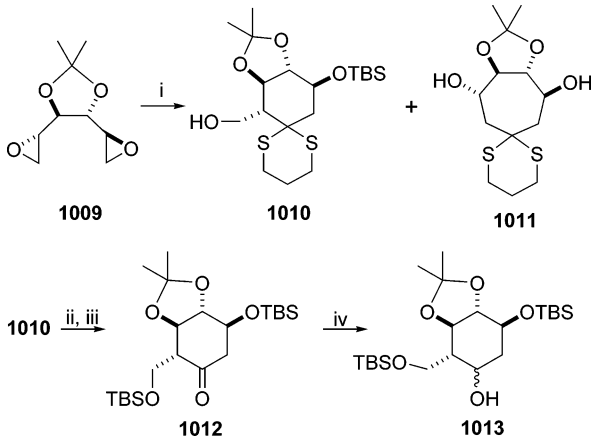
More recently, Estévez and co-workers have reported a completely stereoselective intramolecular nitroaldol condensation, using nitroethanol, leading to a 5a-hydroxycarbasugar derivative **1008** (Scheme 158).[367] The authors used two nitroaldol reactions to convert D-glucose derivative **1003** to intermediate **1007**. An intermolecular version of the reaction first yielded nitro derivatives **1004** (3:2 mixture), which after being processed to hemiacetal **1005** underwent a second, intramolecular, nitroaldol condensation leading, with complete stereoselection, to **1007**. Removal of the nitro group with tribuyltin hydride was also stereoselective and produced, after protecting group manipulations, compound **1008** as a single isomer. The authors rationalized the complete stereoselection in the second Henry reaction based on the reversibility of the condensations and considering the higher stability of **1006** when compared with its C_6 epimer, in which the bulky groups at C_5 and C_6 would be *cis* to each other.

6.2.2.1.4. Cyclization of Sulfur-Stabilized Carbanions. Cyclizations involving intramolecular nucleophilic displacement of a sulfur-stabilized carbanion in carbohydrate derivatives have recently proved to be useful in the synthesis of carbasugar analogues. Both Le Merrer's[368−370] and Schaumann's[371] groups have undertaken the key carbocyclization step leading to carbasugars by a silicon-induced domino reaction[372] of C_2-symmetrical *bis*-epoxides (Scheme 159). The reaction proceeds via a 1,4-Brook rearrangement after nucleophilic attack of the silyl-substituted sulfur-stabilized carbanion on the first epoxide followed by intramolecular opening of the second epoxide at the either more (6-*exo*-*tet*) or less (7-*endo*-*tet*) substituted side to give enantiopure six- or seven-membered carbasugars and cyclitols.

Scheme 159. Silicon-Induced Domino Cyclization Leading to Carbasugars



Scheme 160. Synthesis of Carbasugar Derivative 1013[a]



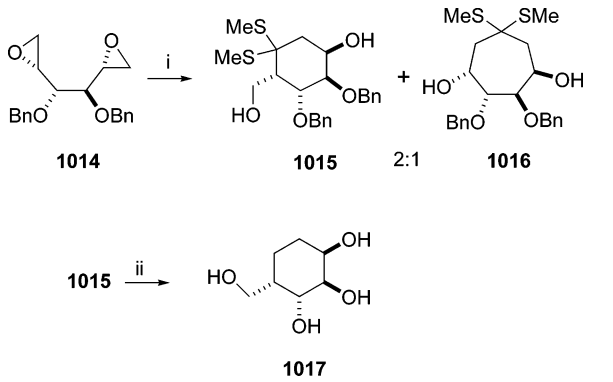
[a] Reagents: (i) t-BuLi, 2-*tert*-butyldimethylsilyl-1,3-dithiane, THF: HMPA, −30 °C, 72%; (ii) TBSCI, imidazole, DMF, quant; (iii) NBS, acetone, H_2O, −50 °C, (iv) $NaBH_4$, EtOH, −78 °C, 80% from **1012**.

Le Merrer et al. found that the mode of cyclization (*exo* or *endo*) could be directed to the formation of six- or seven-membered carbocycles by proper choice of the *O*-protecting groups in the *bis*-epoxides.[368] Thus, for 3,4-*O*-isopropylidene *bis*-epoxide **1009**, the reaction with the lithium salt of 2-*tert*-butyldimethylsilyl-1,3-dithiane afforded mainly cyclohexane **1010** along with 15% of cycloheptane **1011** (Scheme 160). Protection of the primary alcohol function in **1010** and dithioketal hydrolysis then gave the cyclohexanone **1012**, which was submitted to reduction to give carbasugar analogue **1013**.

A similar reaction was applied by Schaumann and co-workers to *bis*-epoxide **1014** to yield cyclohexane **1015** (along with cycloheptane **1016**), which was later converted to 4-epi-validatol (**1017**) (Scheme 161).[371]

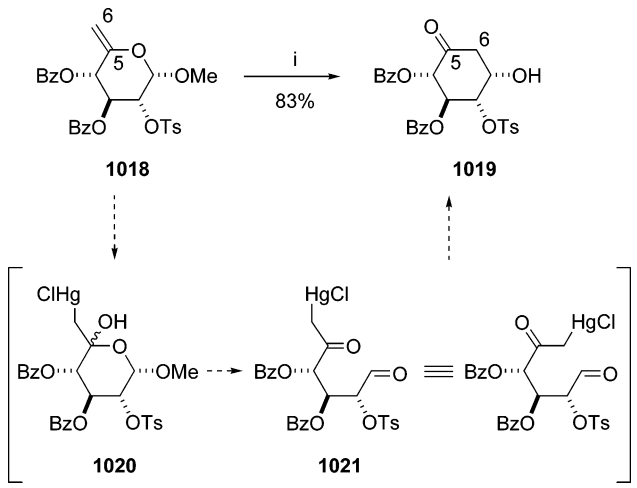
6.2.2.1.5 Cyclization of Organomercury Intermediates: Ferrier Carbocyclization Reaction or Ferrier (II) Reaction. In 1979, Ferrier described the transformation of hex-5-enopyranoside (**1018**) into substituted cyclohexanone **1019**, mediated by mercury(II) salts (Scheme 162).[373] This transformation has since proven to be a very useful synthetic tool in carbohydrate chemistry and has indeed found some application in the preparation of carbapyranoses. The reaction course for this transformation (Scheme 162) involves regiospecific hydroxymercuration of the vinyl ether moiety of **1018** to give the unstable hemiacetal **1020**, which loses methanol to afford dicarbonyl intermediate **1021**. The latter then takes part in an aldol-like, intramolecular cyclization

Scheme 161. Synthesis of Epi-validatol (1017)[a]



[a] Reagents: (i) n-BuLi, $(MeS)_2CHSiMe_3$, THF, −80 °C, 46%; (ii) Ra/Ni, 68%.

Scheme 162. Ferrier Carbocyclization, or Ferrier(II), Reaction[a]



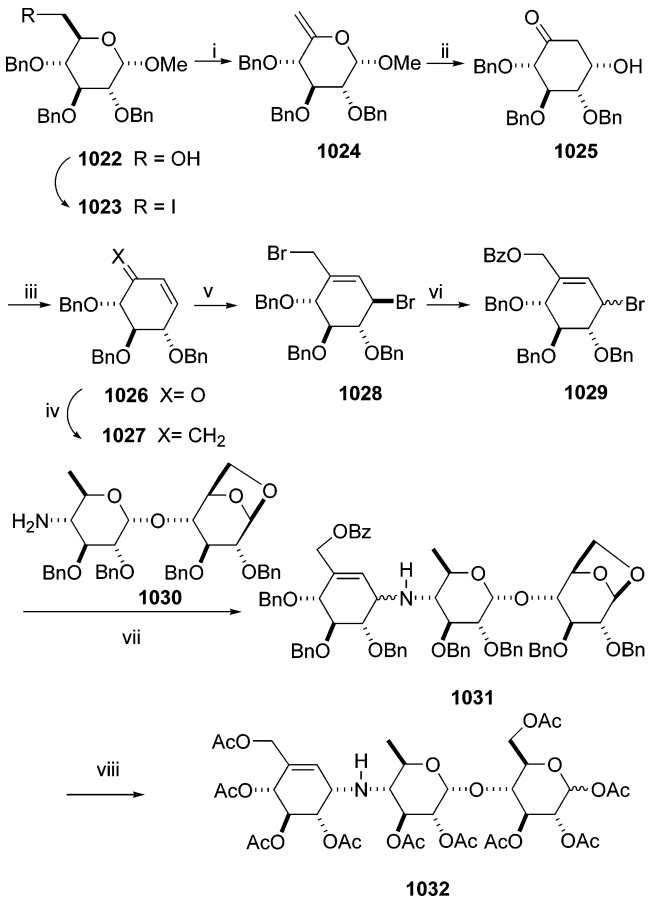
[a] Reagents: (i) $HgCl_2$, H_2O−acetone, reflux.

to give cyclohexanone **1019**. Unlike most methods described in this section, the Ferrier carbocyclization reaction cannot be applied to the preparation of carbafuranoses since treatment of pent-4-enofuranosides with mercury(II) salts does not give cyclopentanone derivatives.[374]

The first implementation of this approach, for the synthesis of a carbasugar derivative, was reported in 1982 with the preparation of a carbatrisaccharide component of amilostatins (Scheme 163).[375] Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**1022**)[376] was transformed into 6-deoxy-6-iodo derivative **1023** via the corresponding mesylate. Treatment of **1023** with DBU gave 6-deoxy-5-enohexopyranoside (**1024**), which upon treatment with mercury(II) chloride gave hydroxy ketone **1025**. The key intermediate, diene **1027**, was then prepared by Wittig reaction of enone **1026**, readily available from **1025**. 1,4-Bromination of **1027**, modeled after a similar reaction reported by Ogawa et al.,[271a] furnished dibromide **1028**. Selective substitution of the primary bromide with benzoate anion gave a mixture of epimeric bromides **1029**. Finally, coupling of aminodisaccharide **1030** with bromides **1029** furnished carbatrisaccharide **1031**. Acetylation and separation of the anomers followed by acetolysis of the desired isomer gave α-anomer **1032**, identical with an authentic specimen derived from the culture filtrate of an amylostatin-producing microorganism.

Lukacs and co-workers realized that catalytic amounts of mercury(II) sulfate in 1,4-dioxane were sufficient to effect

Scheme 163. Synthesis of a Carbatrisaccharide Component of Amylostatins[a]

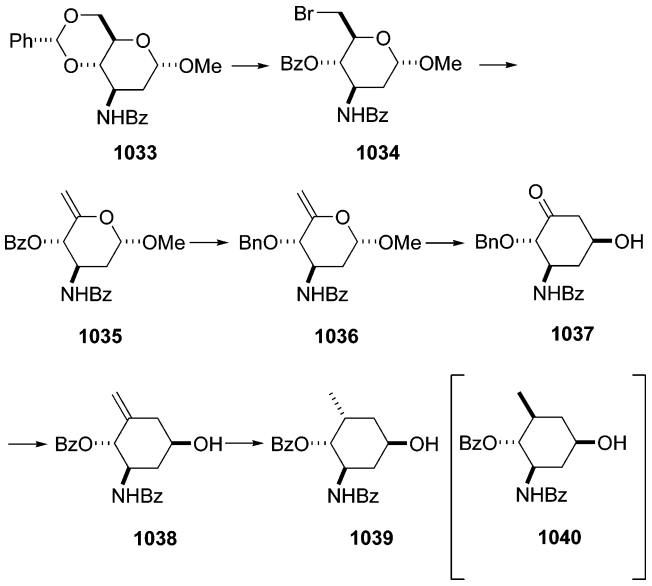


[a] Reagents: (i) DBU, THF, reflux, 79%; (ii) $HgCl_2$, acetone, H_2O, 84%; (iii) MsCl, py, 91%; (iv) Ph_3PCH_3Br, n-BuLi, 77%; (v) Br_2, CH_2Cl_2, 84%; (vi) NaOBz, DMF, 63%; (vii) NaI, DMF, 13%; (viii) Na, liq NH_3, then Ac_2O, py, 79%.

the Ferrier carbocyclization reaction,[377] and they applied their modification to the preparation of the carbocyclic analogue of daunosamine (**1039**) (Scheme 164).[378] Methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-ribohexopyranoside(**1033**)[379,380] was transformed using a methodology developed by Horton and Weckerle[381] via the bromo and the unsaturated compounds **1034** and **1035** into hex-5-enopyranoside **1036**. The latter was submitted to the catalytic modification of the Ferrier reaction to give hydroxy ketone **1037**, which upon Wittig reaction with methylenetriphenylphosphorane gave methylene cyclohexane **1038**. Finally, a hydroxy group-directed homogeneous alkene hydrogenation of the latter was completely stereoselective to yield carbocyclic daunosamine analogue **1039**. It is noteworthy that heterogeneous hydrogenation (Pd/C) of **1038** had furnished a 2:8 mixture of **1039** and its 5-epimer **1040**.

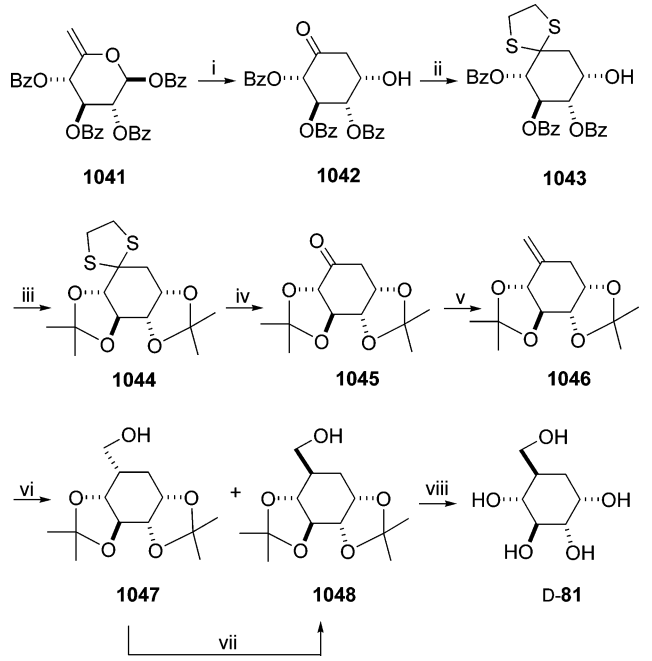
Blattner and Ferrier reported the preparation of 5a-carba-α-D-glucopyranose (D-**81**) (Scheme 165).[382] 1,2,3,4-Tetra-*O*-benzoyl-6-deoxy-β-D-xylohex-5-enopyranose (**1041**)[383,384] was converted to deoxyinosose **1042** by treatment with mercury(II) acetate. Protection of the ketone as a dithiane (**1043**) was followed by manipulation of the hydroxyl protecting groups to give di-*O*-isopropylidene analogue **1044**. Removal of the thioacetal group was followed by reaction of the ensuing ketone (**1045**) with the Lombardo methylenating reagent[385] to yield methylenecyclohexane derivative **1046**. Hydroboration of the latter afforded a mixture of 5a-carba-β-L-idopyranose derivative **1047** (81% yield) and

Scheme 164. Lukacs' Synthesis of the Carbasugar Analogue of Daunosamine, 1039



[a] Reagents: (i) NBS, CCl_4, reflux; (ii) DBU, HMPT; (iii) NaOMe; (iv) NaH, BnBr, 80%, four steps; (v) acetone, H_2SO_4, H_2O, quant; (vi) Ph_3PCH_3Br, n-BuLi, 70%; (vii) Rh[nbd(diphos-4)]BF_4, H_2, quant.

Scheme 165. Ferrier and Blattner's Synthesis of 5a-Carba-α-D-glucopyranose (D-81)[a]

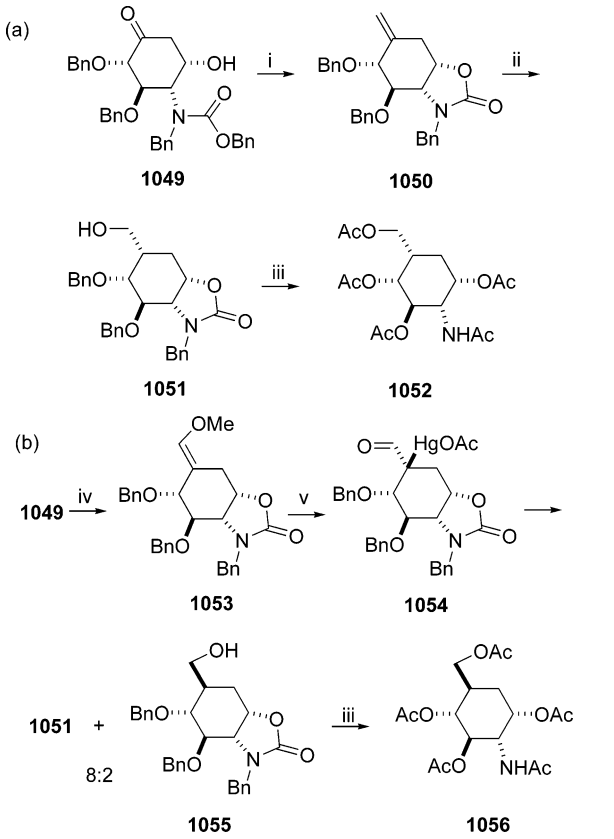


[a] Reagents: (i) $Hg(OAc)_2$, acetone, H_2O; (ii−iii) several steps not shown, 78% overall; (iv) NBS, H_2O, CH_3CN, $CdCO_3$, quant; (v) CH_2Br_2, Zn, THF, $TiCl_4$, 95%; (vi) hydroboration, 81%; (vii) (a) PDC, CH_2Cl_2, DMF; (b) Et_3N, MeOH, K_2CO_3; (c) $NaBH_4$, 36% overall; (viii) HCl, MeOH, 96%.

isomeric 5a-carba-α-D-glucopyranose derivative **1048** (4% yield). The thermodynamically preferred minor product was obtainable from the major product by an oxidation−epimerization−reduction sequence. Finally, hydrolysis of the diacetal **1048** gave 5a-carba-α-D-glucopyranose (D-**81**).

Almost simultaneously to the reports of Lukacs and Ferrier, Quiclet-Sire and co-workers reported the synthesis of the carbocyclic analogues of D-glucosamine (**1056**) and L-idosamine (**1052**) from D-glucosamine (Scheme 166).[386] The authors devised two synthetic routes from cyclohexanone

Scheme 166. Quiclet-Sire's Approach to 5a-Carba-L-idosamine and -D-Glucosamine[a]

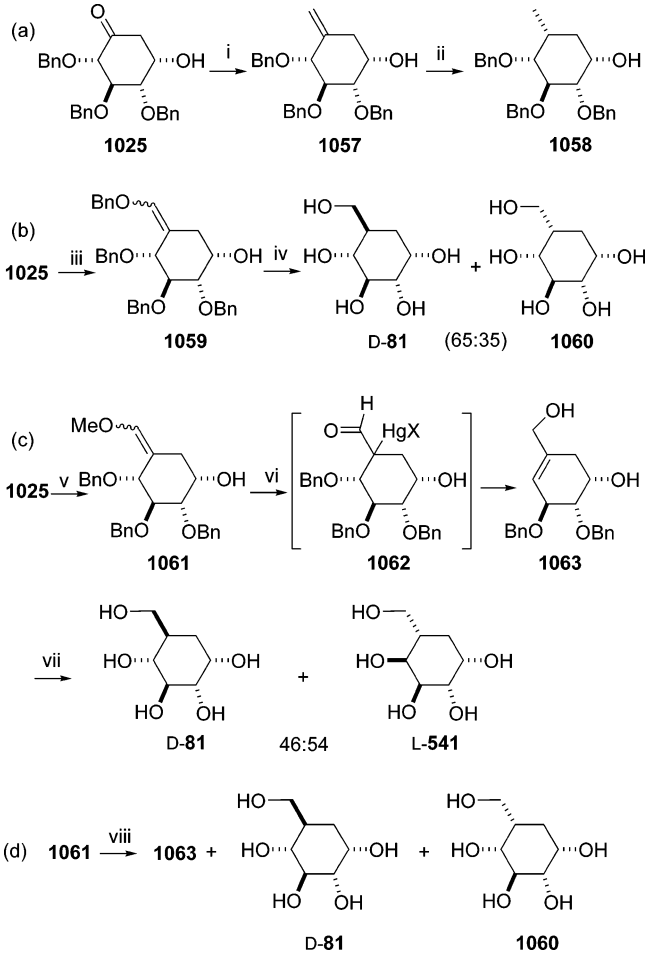


[a] Reagents: (i) $Ph_3P{=}CH_2$, dimethoxyethane, −5 to 10 °C, 67%; (ii) borane·THF, then NaOH, H_2O_2, 60%; (iii) (a) NaOH, EtOH, reflux; (b) H_2, Pd/C, (c) Ac_2O, py, 63% for **1052**, 65% for **1056**; (iv) $Ph_3P{=}CHOMe$, −5 to 10 °C, 67%; (v) $Hg(OAc)_2$, CH_3CN, H_2O; (vi) KI, H_2O, $NaBH_4$, yields not given.

1049, previously obtained from D-glucosamine by Ferrier carbocyclization.[387] The routes differed on the Wittig reagent employed, for the homologation of the ketone, and the manipulation of the ensuing exocyclic olefins. The first route (Scheme 166a) resulted in a completely stereoselective synthesis of 5a-carba-β-L-idosamine (**1052**). Accordingly, Wittig reaction of **1049** with methylenetriphenylphosphorane yield exocyclic alkene **1050**, in which formation of an oxazolidone ring had also taken place. Hydroboration followed by oxidative workup led exclusively to carbasugar derivative **1051**. The complete stereoselectivity of the hydroboration process was ascribed by the authors to the presence of the bulky oxazolidone ring. Alcohol **1051** was then deprotected and peracetylated to yield 5a-carba-β-L-idosamine pentaacetate (**1052**). The second route (Scheme 166b) made use of methoxymethylenetriphenylphosphorane as the Wittig reagent and led to vinyl ether oxazolidone **1053**. Oxymercuration of the latter afforded a 8:2 mixture of D-gluco (**1055**) and L-ido (**1051**) isomers. According to the authors, it seems likely that the oxymercuration, in analogy to the hydroboration, occurs from the β-face to give **1054**. However, since the reduction of the carbon−mercury bond by borohydride proceeds by a radical pathway, epimerization at C_5 is possible, producing the two possible alcohols, with the more stable being preponderant. Finally, deprotection and peracetylation of **1055** furnished 5a-carba-α-D-glucosamine pentaacetate (**1056**).

The same group also reported the stereodivergent preparation of α-D-gluco-, β-L-ido-, 6-deoxy-β-L-ido-, and β-L-

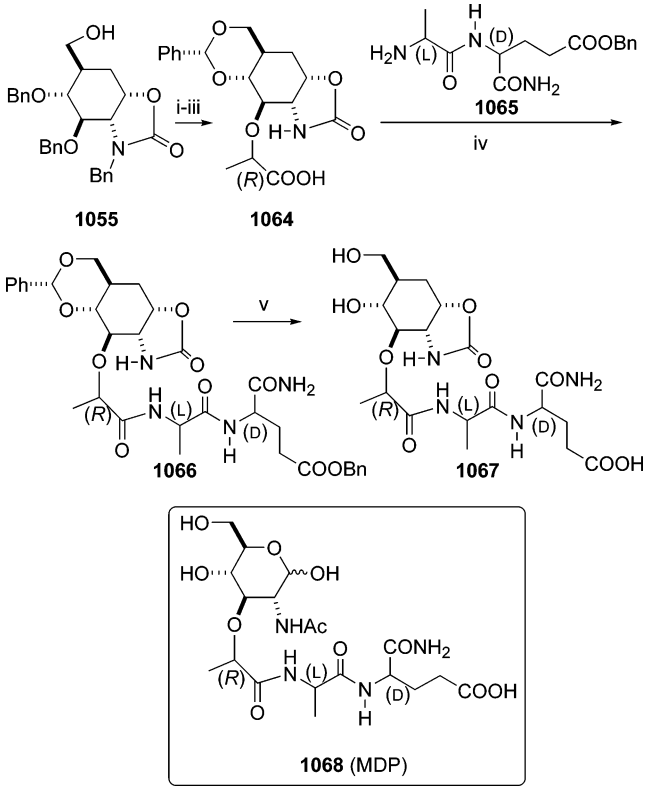
Scheme 167. Synthesis of α-D-Gluco-D-81, β-L-Ido-1060, and β-L-Altro-L-541 Carbapyranoses[a]



[a] Reagents: (i) $Ph_3P{=}CH_2$; (ii) Pd/C, H_2, MeOH, yield not given; (iii) $BnOCH_2Cl$, PPh_3, $PhCH_3$, reflux, 90%, then n-BuLi, $PhCH_3$, −35 °C, 55%; (iv) H_2, Pd/C, MeOH, 75%; (v) $MeOCHPPh_3$, dimethoxyethane, 0 °C, yield not given; (vi) $HgNO_3$, then $NaBH_4$, 85%; (vii) borane·THF, then NaOH, H_2O_2, 78%; (viii) $Hg(OAc)_2$, then $NaBH_4$, 86%.

altrocarbapyranoses from a single cyclohexanone precursor (**1025**)[388] previously prepared by Ferrier carbocyclization of a D-glucose derivative[389] (Scheme 167). Wittig reaction of **1025** with methylenetriphenylphosphorane afforded methylenecyclohexane **1057**, which, upon catalytic hydrogenation, afforded almost exclusively 5a-carba-6-deoxy-β-L-idopyranose derivative **1058** (Scheme 167a). Wittig reaction of **1025** with benzyloxymethylenetriphenylphosphorane afforded benzyloxy-vinyl ether **1059**, which was submitted to catalytic hydrogenation to afford a 65:35 ratio (75% yield) of 5a-carba-α-D-glucopyranose (D-**81**) and 5a-carba-β-L-idopyranose (**1060**) (Scheme 167b). Wittig reaction of **1025** with methoxymethylenetriphenylphosphorane yielded vinyl ether **1061** as a mixture of *E/Z* diastereomers. Treatment of **1061** with mercury(II) nitrate followed by sodium borohydride reduction yielded exclusively the unsaturated alcohol **1063**, by β-elimination from the mercurial intermediate **1062**. Hydroboration of **1063** with diborane followed by oxidative workup of the resulting organoborane afforded a 46:54 mixture (78% yield) of α-D-gluco- and β-L-altro-dibenzyl derivatives which were hydrogenolyzed to yield D-**81** and 5a-carba-β-L-altropyranose (L-**541**) (Scheme 167c). Oxymercuration of **1061** with mercury(II) acetate yielded a mixture of three products in 86% yield: α,β-unsaturated alcohol **1063** (52%) and two minor tri-*O*-benzyl diastereoisomers (6.8% α-D-gluco and 27.2% β-L-ido), which were hydrogenolyzed to yield 5a-carba-α-D-glucopyranose (D-**81**) and 5a-carba-β-L-idopyranose (**1060**) (Scheme 167d).

Scheme 168. Synthesis of the Carbasugar Analogue of *N*-Acetylmurarnyl-L-alanyl-D-isoglutamine (MDP) (1068)[a]



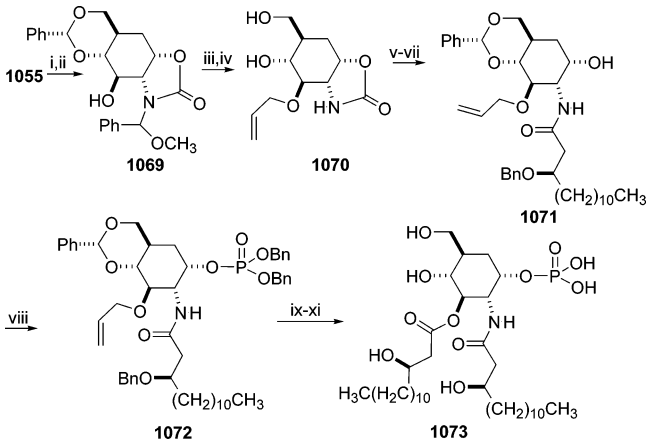
[a] Reagents: (i) Li, liq NH_3, THF, −78 °C, then t-BuOH, EtOH; (ii) PhCHO, $ZnCl_2$, 60%, two steps; (iii) NaH, DMF, 0 °C, then (*S*)-α-chloropropionic acid, then resin IRN 77 H^+, 72%; (iv) *N*-hydroxysuccinimide, DCC, DMF, 12 h, then **1065**, 78%; (v) H_2, Pd/C, EtOH, 80%.

Carbamate **1055** was also used in the preparation of carbasugar analogues of *N*-acetylmuramyl-L-alanyl-D-isoglutamine (MDP, **1068**)[390] and Lipid X[391] (Scheme 168). Carbamate **1055** was hydrogenolyzed to give a triol which was protected as a benzylidene derivative and etherified with (*S*)-α-chloropropionic acid to yield acid **1064**, which was condensed with L-Ala-D-isoglutamine benzyl ester (**1065**) to give **1066**. Hydrogenolysis of **1066** over palladium on charcoal removed the benzyl and benzylidene groups to furnish **1067**, the carbasugar analogue of MDP (**1068**).

The synthesis of the carbocyclic analogue of Lipid X (**1073**) used carbamate **1069** as the key intermediate (Scheme 169). Allylation of alcohol **1069** was followed by removal of the benzylidene and aminal groups to afford diol **1070**. Cleavage of the oxazolidinone ring followed by *N*-acylation with *N*-(*R*)-3-benzyloxytetradecanoyloxysuccinimide and 4,6-*O*-benzylidenation furnished **1071**, which was converted to dibenzylphosphono derivative **1072**. Cleavage of the allyl group, acylation at 3-OH by (*R*)-3-benzoyloxytetradecanoic acid, and catalytic hydrogenation, to remove the benzyl and benzylidene groups, yielded the carbasugar analogue of Lipid X (**1073**).[391]

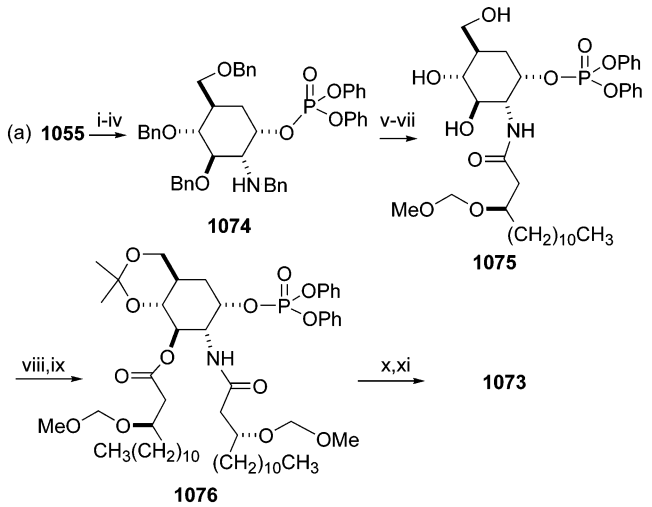
Lewis and co-workers followed the synthetic sequence developed by Quiclet-Sire and co-workers for the preparation of glucosamine derivative **1055** and reported two different routes to the carbasugar analogue of Lipid X (**1073**) (Schemes 170 and 171).[392] The two sequences employed different protecting groups on the ester side chains. The

Scheme 169. Synthesis of Carbasugar Lipid X (1073)[a]



[a] Reagents: (i) Li, liq NH_3, THF, −78 °C; (ii) PhCHO, TsOH, DMF, 54%, two steps; (iii) NaH, allyl bromide, DMF, 71%; (iv) AcOH, H_2O, 95%; (v) LiOH, MeOH−H_2O, 93%; (vi) (*R*)-3-benzyloxytetradecanoylsuccinimide, DMF, 78%; (vii) $ZnCl_2$, PhCHO, 86%; (viii) *N*,*N*-ethyldiisopropyldibenzylphosphoramidite, tetrazole, CH_3CN, 73%; (ix) SeO_2, dioxane, AcOH, 100 °C, 62%; (x) (*R*)-3-benzyloxytetradecanoic acid, DMAP, DCC, CH_2Cl_2, 52%; (xi) H_2, Pd/C, THF, H_2O, 85%.

Scheme 170. Lewis and Co-workers First Synthesis of the Carbasugar Analogue of Lipid X (1073)[a]

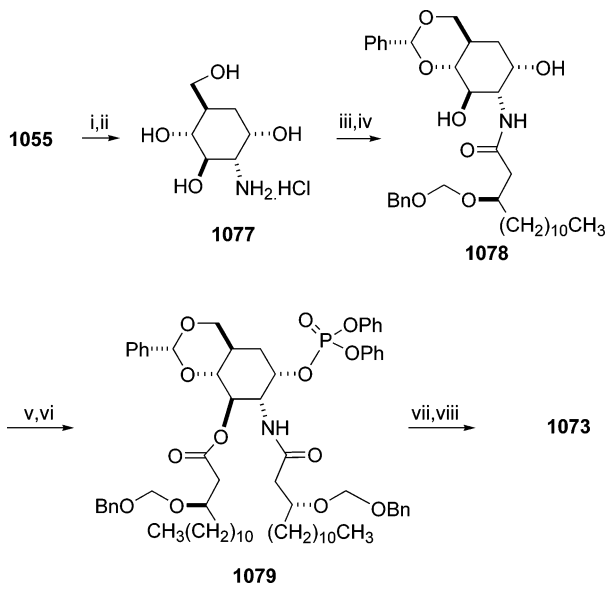


[a] Reagents: (i) NaH, BnBr, DMF, 0 °C, 67%; (ii) NaOH, EtOH, reflux, 90%; (iii) n-BuLi, THF, −78 °C; (iv) $(PhO)_2POCl$, −78 to −40 °C, 80%; (v) H_2, $Pd(OH)_2$, MeOH, 61%; (vi) (*R*)-3-methoxymethyloxytetradecanoic acid, DCC, CH_2Cl_2, 92%; (vii) H_2, $Pd(OH)_2$, THF, MeOH, 98%; (viii) DMP, CSA, DMF, 69%; (ix) (*R*)-3-methoxymethyloxytetradecanoic acid, DCC, DMAP, CH_2Cl_2, 64%; (x) HCl, MeOH, 50 °C, 97%; (xi) H_2, PtO_2, H_2O, EtOH, 90%.

second sequence, which used benzyloxymethyl protecting groups, has the advantage of not requiring acid media for the final liberation of **1073** (Scheme 171). In the first sequence (Scheme 170), benzylation of alcohol **1055** was followed by urethane removal and phosphorylation at 1-OH to yield **1074**. Chemoselective catalytic hydrogenation was possible in compound **1074** for the *N*-benzyl group and was followed by *N*-acylation with (*R*)-3-methoxymethyltetradecanoic acid and hydrogenation to yield triol **1075**. Selective protection of **1075** as a 4,6-*O*-isopropylidene acetal left the 3-OH free for acylation with (*R*)-3-methoxymethyltetradecanoic acid and resulted in the formation of **1076**. Finally, treatment with hydrochloric acid and catalytic hydrogenation led to the carbasugar analogue of Lipid X (**1073**).

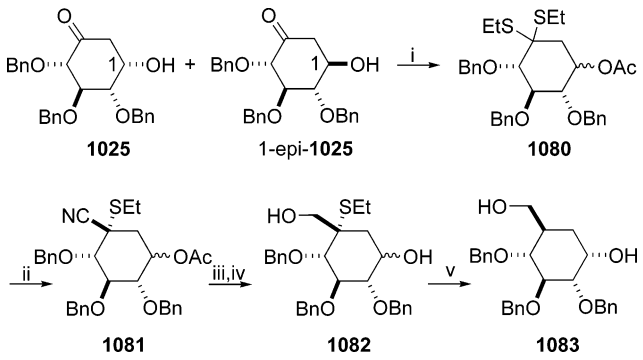
The second sequence (Scheme 171) started with the carbamate hydrolysis on **1055** followed by hydrogenolytic

Scheme 171. Lewis and Co-workers Second Synthesis of the Carbasugar Analogue of Lipid X 1073[a]



[a] Reagents: (i) NaOH, EtOH, reflux, 62%; (ii) H_2, $Pd(OH)_2$, MeOH, HCl, quant; (iii) *N*-hydroxysuccinyl (*R*)-3-methoxymethyloxytetradecanoate, DIEA, DMF, 62%; (iv) $PhCH(OMe)_2$, TsOH, DMF, 50%; (v) n-BuLi, THF, −78 °C, $(PhO)_2POCl$, 36%; (vi) (*R*)-3-methoxymethyloxytetradecanoic acid, $EtNCN(CH_2)_3NMe_2$, HCl, DMAP, CH_2Cl_2, 74%; (vii) H_2, $Pd(OH)_2$, MeOH, EtOAc, 88%; (viii) H_2, PtO_2, H_2O, EtOH, quant.

Scheme 172. Synthesis of 5a-Carba-2,3,4-tri-*O*-benzyl-α-D-Glucopyranose (1083)[a]

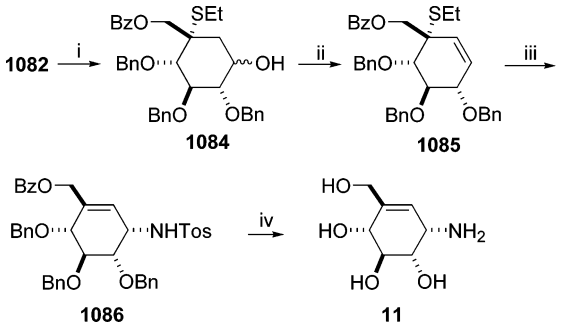


[a] Reagents: (i) EtSH, H^+, then Ac_2O, py, 86%; (ii) TMSCN, $SnCl_4$, 85%; (iii) DIBAL-H, $PhCH_3$, −70 °C, 78%; (iv) LAH, THF, 0 °C, 85%; (v) Ra-Ni, THF, 69%.

deprotection in acidic methanol to yield 5a-carba-α-D-glucosamine hydrochloride (**1077**). Selective acylation using *N*-hydroxysuccinyl (*R*)-3-benzyloxymethyltetradecanoate followed by 4,6-*O*-benzylidene formation afforded diol **1078**. Selective 1-OH phosphorylation was observed, albeit the reaction did not go to completion and was followed by acetylation at 3-OH with (*R*)-3-benzyloxymethyloxytetradecanoic acid to yield carbasugar Lipid X precursor **1079**. Sequential mild hydrogenolysis afforded **1073** with no need for acid treatment.

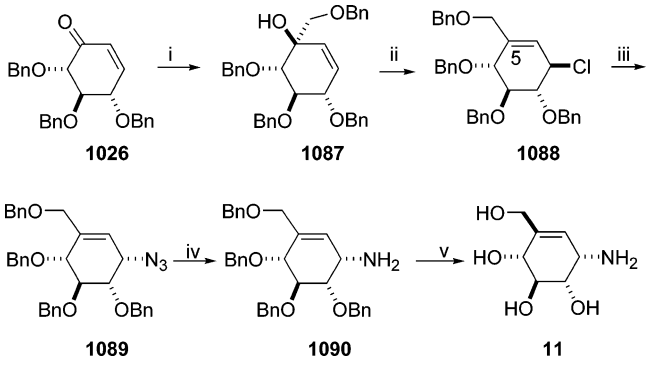
In 1987 Köhn and Schmidt explored the usefulness of cyclohexanones **1025** and 1-epi-**1025**,[389] in the synthesis of carbasugar derivatives (Scheme 172).[393] The attachment of the functionalized C_5-side chain was examined by reaction of the ketone moiety with 2-lithio-1,3-dithiane, dimethylsulfoxonium methylide, and diazomethane. Cyclohexanones **1025** and 1-epi-**1025** (4:1 mixture) were also treated with ethanothiol under acidic conditions to give, after acetylation, dithioacetal **1080**. Subsequent cyano/mercapto group ex-

Scheme 173. Synthesis of Valienamine (11) by Schmidt and Khon[a]



[a] Reagents: (i) BzCN, CH_3CN, NEt_3, −15 °C, 73%; (ii) PPh_3, DEAD, $PhCH_3$, 79%; (iii) Chloramine T, BTAC, CH_2Cl_2, 78%; (iv) Na, liq NH_3, −70 °C, 58%.

Scheme 174. Synthesis of Valienamine (11) by Panza's Group[a]



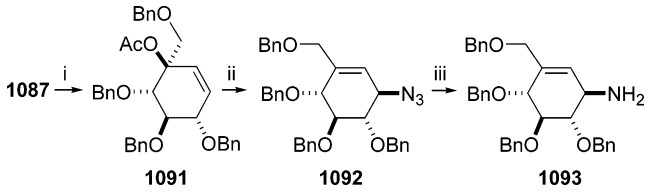
[a] Reagents: (i) $PhCH_2OCH_2Cl$, Mg, $HgCl_2$, −78 °C, then 0 °C, 75%; (ii) $SOCl_2$, Et_2O, reflux, 81%; (iii) NaN_3, DMF, 50 °C, 83%; (iv) H_2S, py, H_2O, 79%; (v) liq NH_3, 56%.

change with TMS-CN yielded branched nitrile **1081**, which was treated with DIBAL-H and lithium aluminum hydride to yield **1082** as a 4:1 epimeric mixture. The major α isomer was treated with Raney-Ni to furnish 5a-carba-2,3,4-tri-*O*-benzyl-α-D-glucopyranose (**1083**). Schmidt and Köhn also exploited this route in their approach to valienamine (**11**) (Scheme 173).[394] Accordingly, branched cyclitol **1082** was selectively benzoylated at the primary hydroxyl group to give **1084**, which upon regioselective dehydration yielded **1085**. Amination of the thioether group with chloramine T afforded directly and with complete stereoselectivity valienamine derivative **1086**. The protecting groups of **1086** were removed with sodium in liquid ammonia to give valienamine (**11**).

Panza and co-workers[395] reported a stereocontrolled synthesis of valienamine from enone **1026**[389] (Scheme 174). Reaction of **1026** with benzyloxymethylmagnesium chloride afforded regio- and stereoselectively the branched chain cyclitol **1087**. Treatment of **1087** with thionyl chloride paved the way to chloro derivative **1088**, which upon reaction with sodium azide furnished azidocyclitol **1089**. Reduction of the azido group gave perbenzylated valienamine **1090**. Debenzylation of **1090** with sodium in liquid ammonia afforded valienamine (**11**).

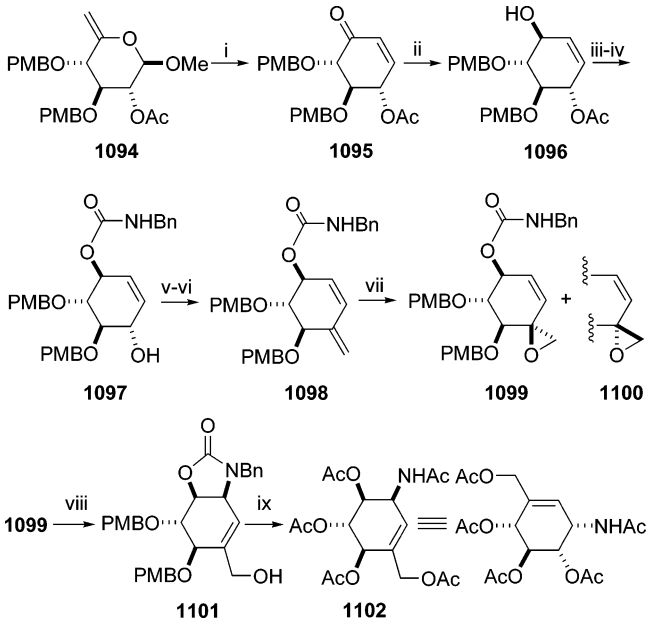
McAuliffe and Stick[396] reported some modifications to the method reported by Panza for the preparation of multigram amounts of valienamine (Scheme 175). They also reported on a novel route to 1-epi-valienamine. Acetylation of **1087** yielded an allylic acetate, **1091**, which upon treatment with sodium azide and tetrakis(triphenylphosphine)palladium(0)

Scheme 175. Synthesis of 1-Epi-valienamine (1093) by Stick's Group[a]



[a] Reagents: (i) Ac_2O, py, DMAP, 60 °C, 81%; (ii) NaN_3, $Pd(PPh_3)_4$, THF, reflux; (iii) H_2S, py, Et_3N, H_2O (4:1:1), 92%.

Scheme 176. Synthesis of Pentaacetyl Valienamine (1102) by Danishefsky and Park[a]



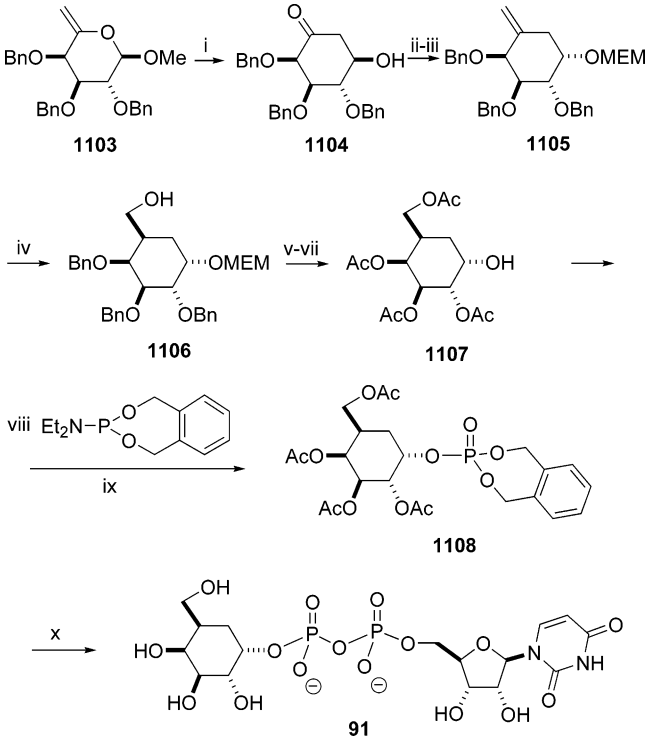
[a] Reagents: (i) $HgCl_2$, acetone, H_2O, reflux, then MsCl, DMAP, py, 72%; (ii) $NaBH_4$, $CeCl_3$, EtOH, −78 °C, 92%; (iii) benzylisocyanate, PhH, reflux, 98%; (iv) K_2CO_3, MeOH, quant; (v) PDC, AcOH, EtOAc, 85%; (vi) CH_2I_2, Zn, $TiCl_4$, THF, 45%; (vii) MCPBA, $NaHCO_3$, CH_2Cl_2, 85%; (viii) KHMDS, 18-crown-6, THF, −78 °C, 75%; (ix) (a) Na, liq NH_3, THF, −78 °C; (b) LiOH, H_2O, EtOH, reflux; (c) Ac_2O, py, 51%.

gave azide **1092**. Reduction of **1092** with hydrogen sulfide in a mixture of pyridine, triethylamine, and water gave 1-epi-valienamine derivative **1093**.

A Ferrier-based carbocyclization approach was employed by Park and Danishefsky for the synthesis of valienamine (**11**) (Scheme 176).[397] Compound **1094** served as the substrate for the Ferrier transformation. The β-aldol thus elaborated was converted to **1095** by mesylation and elimination. Reduction of the ketone gave **1096**, which was converted to carbamide **1097** through the action of benzylisocyanate followed by acetate cleavage with potassium carbonate. Oxidation of **1097** and methylenation with a modified Lombardo reagent[398] gave rise to **1098**. Epoxidation of **1098** with MCPBA led to a separable mixture of diastereomeric epoxides, with the major isomer being **1099**. Reaction of compound **1099** with KHMDS gave rise to valienamine derivative **1101**. Deprotection of the latter followed by acetylation led to pentaacetyl valienamine **1102**.

A contribution from Hindsgaul's group focused on the synthesis of uridine 5′-(5a-carba-α-D-galactopyranosyl diphosphate) (**91**), the carbocyclic analogue of UDP-galactose, as a potential inhibitor of galactosyltransferases (Scheme 177).[86] The proposed synthesis required the preparation of 5a-carba-

Scheme 177. Synthesis of Uridine 5′-(5a-Carba-α-D-galactopyranosyl Diphosphate) (91)[a]

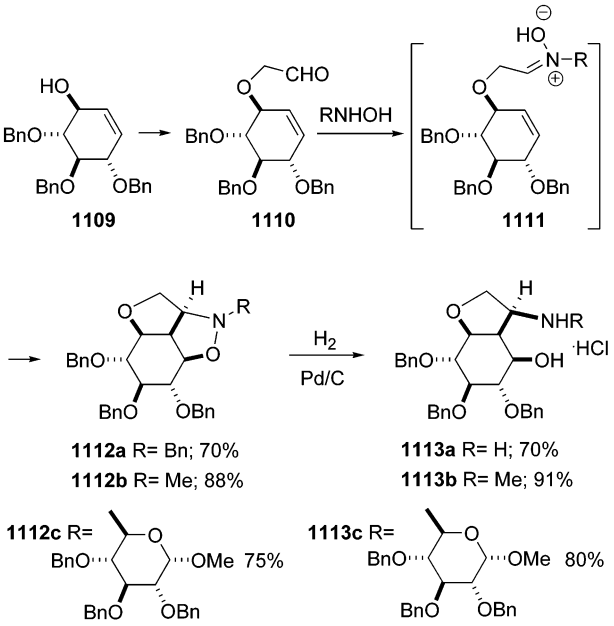


[a] Reagents: (i) $Hg(OAc)_2$, AcOH, NaCl, aq acetone; (ii) MEMCI, DIEA, CH_3CN, reflux, 55% two steps; (iii) Tebbe's reagent, 78%; (iv) borane·THF, then NaOH, H_2O_2; (v) H_2, Pd/C; (vi) Ac_2O, py, 44%, three steps; (vii) Me_2BBr, −78 °C, 95%; (viii) tetrazol; (ix) MCPBA, CH_2Cl_2, 53%, two steps; (x) (a) H_2, Pd/C; (b) 1,1′-carbonyldiimidazole; (c) UMP, DMF; (d) Et_3N, MeOH, H_2O (7:3:1), 85%.

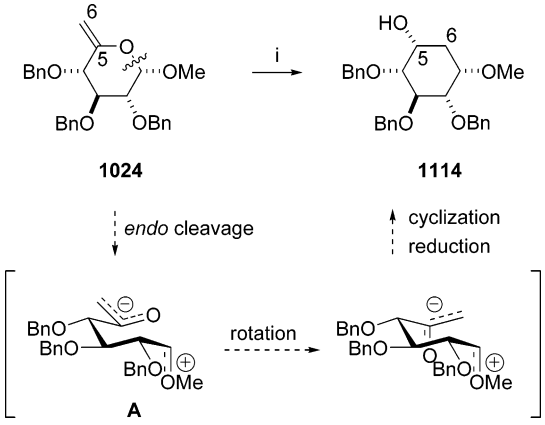
α-D-galactopyranose and its coupling to uridine diphosphate. Application of the Ferrier reaction to **1103**, obtained from methyl 2,3,4-tri-*O*-benzyl-*β*-D-galactopyranose in three steps, yielded cyclohexanone **1104**. Protection of the 1-OH as the methoxyethoxymethyl (MEM) ether and Tebbe's olefination[399] gave methylenecyclohexane **1105**. Hydroboration of **1105** gave a complex mixture from which 5a-carba-α-D-galactopyranose derivative **1106** could be obtained and transformed into **1107** by hydrogenation, acetylation, and deprotection of the MEM group. Phosphitylation followed by oxidation gave phosphate **1108**, which was subjected to removal of the benzyl esters, coupling with uridine monophosphate, and deacetylation to yield the desired compound, **91**.

Peseke and co-workers have reported an approach to fused carbasugar derivatives, also based on the Ferrier carbocyclization, in which the C_5 branch was incorporated through an intramolecular 1,3-dipolar nitrone cycloaddition (Scheme 178).[400] Cyclitol derivative **1109**, readily obtained from **1022** via **1024**,[389] was converted to aldehyde **1110** by a carbene-insertion reaction (ethyl diazocarboxylate, rhodium(II) acetate) followed by reduction (DIBAL-H) of the resulting ester. Treatment of the unstable aldehyde **1110** with either *N*-benzylhydroxylamine, *N*-methylhydroxylamine, or methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-hydroxyamino-α-D-glucopyranoside hydrochloride in toluene furnished the intermediate nitrones **1111**, that underwent spontaneous intramolecular 1,3-dipolar cycloaddition to afford tricyclic derivatives **1112**. Catalytic hydrogenation then yielded anellated carbasugars **1113**. These compounds were evaluated as glucosidase inhibitors but displayed only weak inhibition.

Scheme 178. Synthesis of Anellated Carbasugar Derivatives



Scheme 179. Sinaÿ's Rearrangement of Hex-5-enopyranosides Catalyzed by TIBAL[a]



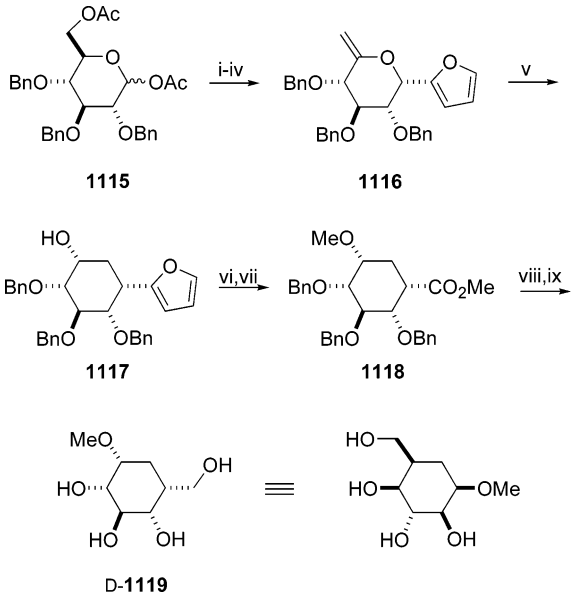
[a] Reagents: (i) TIBAL, PhMe, 40 °C, 79%.

6.2.2.2. Electrophilic Cyclizations. Even though cyclization processes which involve carbanions are very common, methods which make use of the addition of electron rich double bonds onto electrophilic centers have also proved successful in the synthesis of carbasugars.

6.2.2.2.1. Rearrangement of Hex-5-enopyranosides. Sinaÿ and co-workers reported in 1997 that carbohydrate vinyl acetals (e.g., **1024**, Scheme 179), the substrates used in Ferrier reaction, undergo reductive rearrangement[401,402] on treatment with triisobutylaluminum (TIBAL) to afford highly functionalized cyclohexanes (e.g., **1114**).[403,404] The key step in this transformation is the *endo* cleavage of the glycosidic bond leading to a stabilized carbocationic intermediate **A**, which then recycles and undergoes reduction to give the final product. This rearrangement proceeds with retention of both the aglycon moiety and its stereochemistry, due to the initial *endo*-glycosidic bond cleavage, and therefore complements the Ferrier carbocyclization reaction, which inherently requires *exo*-glycosidic cleavage to eject the aglycon.

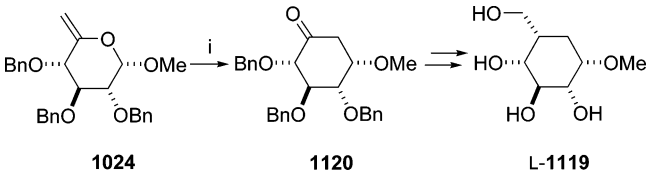
The Lewis acid $Ti(O^iPr)Cl_3$ was also able to mediate the rearrangement of *O*-glycosides under milder reaction conditions, which did not result in the reduction of the keto function.[405] The analogous titanium(IV)-promoted pyranose-

Scheme 180. Sinaÿ's Synthesis of Methyl 5a-Carba-β-D-Idopyranoside (D-1119)[a]



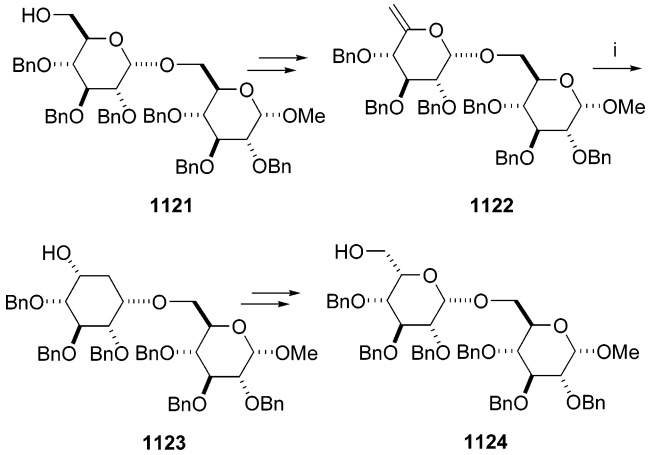
[a] Reagents: (i) furan, molecular sieves, TMSOTf, CH_3CN, −40 to 20 °C, 71%; (ii) MeONa, MeOH, 91%; (iii) I_2, PPh_3, imidazole, $PhCH_3$, 70 °C, 89%; (iv) NaH, DMF, 72%; (v) TIBAL, $PhCH_3$, 83%; (vi) NaH, MeI, DMF, 96%; (vii) O_3, CH_2Cl_2, MeOH, −78 °C, then $KHCO_3$, DMF, MeI, 62%; (viii) LAH, Et_2O, 76%; (ix) H_2, Pd/C, MeOH.

Scheme 181. Sinaÿ's Synthesis of Methyl 5a-Carba-β-D-Idopyranoside (L-1119)[a]



[a] Reagents: (i) Cl_3TiO/Pr, CH_2Cl_2, −78 °C, 95%.

Scheme 182. Synthesis of 5a′-Carbadisaccharide 1124[a]



[a] Reagents: (i) TIBAL, $PhCH_3$, 40 °C, 12%.

to-cyclohexane transformation of vinylic anomeric spiro-orthoesters has also been described.[406] This rearrangement has been extended to *O*-, *S*-, and *Se*-glycosides.

The rearrangement of *C*-glycosides, which would directly lead to carbasugars, would only succeed if the aglycon is sufficiently electron donating in nature.[407] The attempted rearrangement on *C*-alkyl glycosides, that fail to stabilize the proposed carbocation intermediate, results in preferential reductive cleavage of the endocyclic C_5-O bond by a hydroalumination−elimination reaction. On the basis of these observations, Sinaÿ and co-workers devised a synthetic strategy in which a *C*-furyl glycoside, derived from D-glucose, was converted to a partially protected carba-β-D-idopyranoside (Scheme 180).[408] The furyl aglycon was thus used as a masked form of the hydroxymethyl moiety at C_5. The preparation of *C*-furyl glycoside **1116** from 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (**1115**) was carried out by routine transformations including TMSOTf-mediated glycosylation with furan, deacylation, iodination, and elimination. Alcohol **1117**, which was obtained by treatment of alkene **1116** with TIBAL, was methylated and submitted to oxidative cleavage of the furan with ozone to reveal the masked carboxylic, which was immediately methylated to give methyl carba-β-D-iduronate **1118**. Reduction with lithium aluminum hydride then gave methyl carba-β-D-idopyranoside (D-**1119**) (Scheme 180).

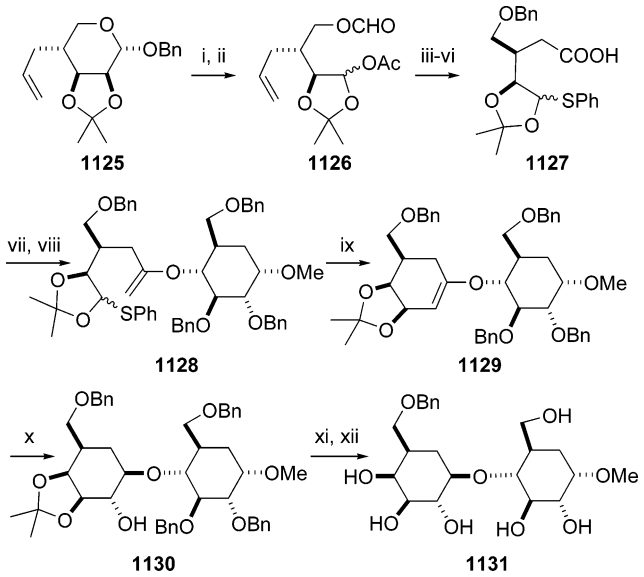
An alternative route was devised, by the same authors, for the synthesis of methyl carba-β-L-idopyranoside (L-**1119**) (Scheme 181).[408] Ketone **1120** was obtained in 95% yield by the Ti(IV)-promoted nonreductive rearrangement of hex-5-enopyranoside **1024**. Methylenation of **1120** with the Tebbe reagent, hydroboration with BH_3·THF, oxidative workup, and debenzylation yielded methyl 5a-carba-β-L-idopyranoside (L-**1119**).

The TIBAL-promoted rearrangement has also been applied to 5-hexenopyranosides containing more complex aglycon moieties (Scheme 182).[409] When applied to hex-5-enopyranoside **1122**, which is α-linked to a sugar aglycon, this led to transformation of the pyranose ring at the nonreducing end of the disaccharide into a carbocycle, affording (1−6) ether-linked pseudo-disaccharide **1123**, which was subsequently transformed into a 5′a-carbadisaccharide **1124** following previously described methodology.[408]

6.2.2.2.2. Oxocarbenium Ion−Enol Ether Cyclization. In a somewhat related work, Mootoo and co-workers disclosed a convenient procedure for preparing 5′a-carbadisaccharides based on the intramolecular capture of an oxocarbenium ion by an enol ether residue (Scheme 183).[410] The key intermediates, 1-thio-1,2-*O*-isopropylidene acetals (TIA), are easily activated to generate intermediate oxocarbonium ions and provided a convergent entry to *C*-glycosides,[411,412] or carbasugars. Thus, for the synthesis of 5′a-carba-β-galactodisaccharides, the branched pyranoside **1125** was prepared from D-lyxose and subjected to a sequence of reactions including Suárez's fragmentation of an anomeric alkoxy radical,[173] leading to **1126**. Acetal exchange, basic hydrolysis, and ozonolysis gave a mixture of TIA acids **1127**. To introduce the aglycon moiety, a DCC-mediated esterification was implemented and the key enol ether **1128** was obtained after Tebbe reaction. Activation with methyl triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine led to the cyclic enol ether **1129**. Finally, stereoselective hydroboration and deprotection afforded carbadisaccharide **1131** in a convergent manner.

6.2.2.2.3. Mukaiyama-Type Aldol Cyclization. Tatsuta and co-workers described a different approach for the conversion of carbohydrates to carbasugar derivatives based on a $SnCl_4$-promoted aldol-like cyclization of silylenol ethers (Scheme 184).[413] Their strategy involved a one-pot opening of furanose rings followed by acid-promoted cyclization. The use of this approach was illustrated in the total synthesis of carbasugar derivatives of biological interest such as pyralomycin (**33**),[414] the aminocarbasugars validamine (**12**) and valienamine

Scheme 183. Mootoo's Approach to 5a′-Carbadisaccharides[a]

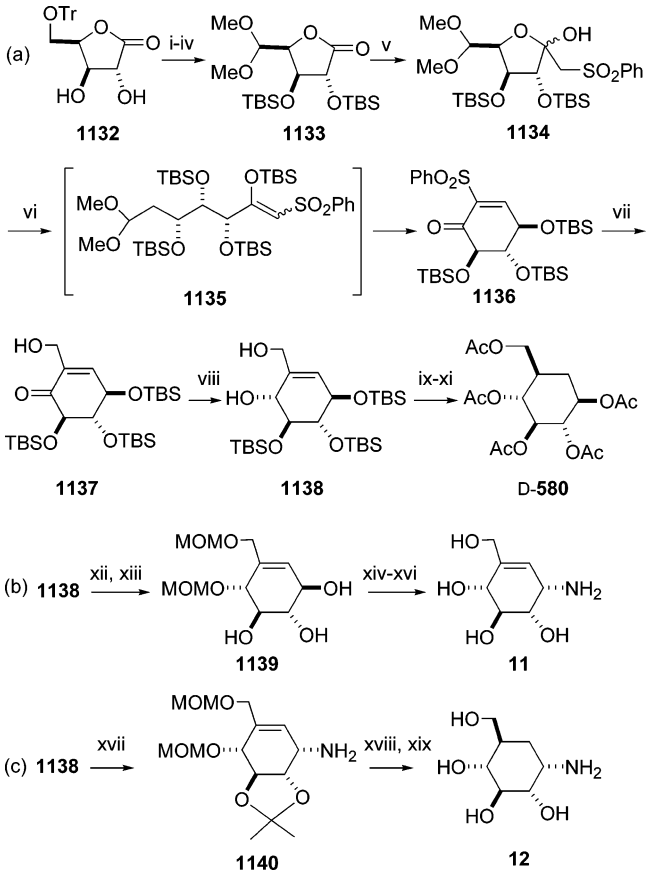


[a] Reagents: (i) Na, NH_3, THF, 92%; (ii) DIB, I_2, cyclohexane, 95%; (iii) PhSH, BF_3·OEt_2, −78 °C, then NaOMe, MeOH; (iv) NaH, BnBr, TBAI, DMF, 70% (two steps); (v) O_3, MeOH−CH_2Cl_2, −78 °C, then Ph_3P; (vi) $NaClO_2$, CH_3CN, 2-methyl-2-butene, 59% two steps; (vii) DCC, DMAP, methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside, 80%; (viii) Tebbe reagent, 80%; (ix) MeOTf, DTBMP, CH_2Cl_2, 64%; (x) BH_3SMe_2, then H_2O_2, NaOH, 72%; (xi) HCl, MeOH; (xii) Pd/C, EtOH, HCO_2H, 72% (two steps).

(**11**),[415] or the glyoxalase I inhibitor COTC.[416] Thus, D-xylose derivative **1132** was converted into the acetal **1133** and then reacted with lithiated methyl phenyl sulfone to give furanose **1134**. The latter was converted to cyclohexenone **1136** by ring opening with TBSOTf and then ring closing of the resulting labile enol silyl ether **1135**. To introduce the remaining hydroxymethyl group, a sequence of Michael reaction with tributylstannyl lithium followed by trapping of the produced anion with formaldehyde and subsequent desulfonylation was developed, and the desired α-hydroxymethylcyclohexenone **1137** was thus obtained. Stereoselective reduction of the carbonyl group in **1137** led to the key intermediate **1138**. Stereoselective hydrogenation of **1138** and deprotection led to 5a-carba-β-D-glucopyranose pentaacetate (D-**580**) (Scheme 184a). Valienamine (**11**) was produced from **1138** by Mitsunobu inversion of the allyl alcohol **1139** and deprotection (Scheme 184b). Validamine (**12**) was also prepared from **1138** via isopropylidene derivative **1140**, by catalytic hydrogenation over Raney-Ni and acidic deprotection (Scheme 184c).[415]

In a related report, Ikegami and co-workers described an efficient preparation of 5a-carba-D-gluco-, -galacto-, and -manno-type carbasugar derivatives from the corresponding sugar lactone orthoesters (Scheme 185).[417] The key step of this procedure is the acid-promoted intramolecular aldol cyclization of alkyl enol ethers, which in turn were prepared directly from spiro sugar orthoesters by a methyl anion insertion and a subsequent ring-opening reaction. Thus, the gluconolactone orthoester **1142** was converted into the enol ether **1143** by reaction with an excess amount of $AlMe_3$. Oxidation with DMSO/Ac_2O gave ketone **1144**, which was cyclized with $ZnCl_2$ in THF/H_2O to afford the carbasugar derivative **1145** with very high selectivity (Scheme 185a).[418] In an analogous manner, galactonolactone **1146** and mannonolactone **1148** were converted to carbasugar derivatives **1147** and **1149** with overall yields of 64% and 54%, respectively.

Scheme 184. Tatsuta's Approach to Carbasugars[a]

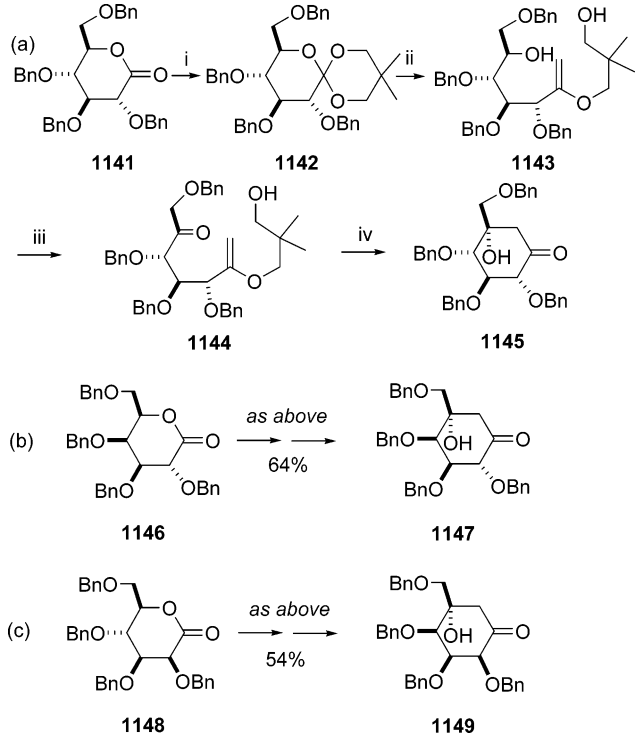


[a] Reagents: (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 90%; (ii) H_2, Pd/C, $CHCl_3$, 87%; (iii) DCC, py·TFA, DMSO/Et_2O; (iv) CSA, $HC(OMe)_3$, MeOH, 50 °C, 73% (two steps); (v) $MeSO_2Ph$, n-BuLi, THF, −78 °C, 94%; (vi) TBSOTf, 2,6-lutidine, CH_2Cl_2, 40 °C, 92%, then $SnCl_4$, CH_2Cl_2, −78 °C, 70%; (vii) n-Bu_3SnLi, HCHO, THF, −78 to 40 °C, 92%; (viii) $Zn(BH_4)_2$, Et_2O, 0 °C, 80%; (ix) H_2, Raney-Ni, EtOH, 77%; (x) 3% HCl, MeOH, 99%; (xi) Ac_2O, NaOAc, 70 °C, 82%; (xii) MOMCl, DIPEA, $ClCH_2CH_2Cl$, 50 °C, 85%; (xiii) TBAF, THF, 97%; (xiv) HN_3, Ph_3P, DEAD, THF, 81%; (xv) H_2, Raney-Ni, H_2O, 1,4-dioxane, quant; (xvi) 3% HCl, MeOH, 99%; (xvii) $Me_2C(OMe)_2$, CSA, DMF, 90 °C, 90%; (xviii) H_2, Raney-Ni, H_2O, 1,4-dioxane, quant; (xix) 3% HCl, MeOH, 99%.

6.2.2.3. Radical Cyclization. The radical cyclization of suitable carbohydrate derivatives was introduced for the synthesis of 4a-carbafuranoses rather than for the synthesis of 5a-carbapyranoses. The reason for this is that the formation of five-membered rings by 5-*exo*- (*digonal* or *trigonal*) radical ring closure was a better established synthetic process than the formation of six-membered rings. The intermediate radicals employed in the preparation of carbapyranoses have been generated mostly by the use of tributyltin hydride, and they differ mainly in the mode of radical cyclization employed.

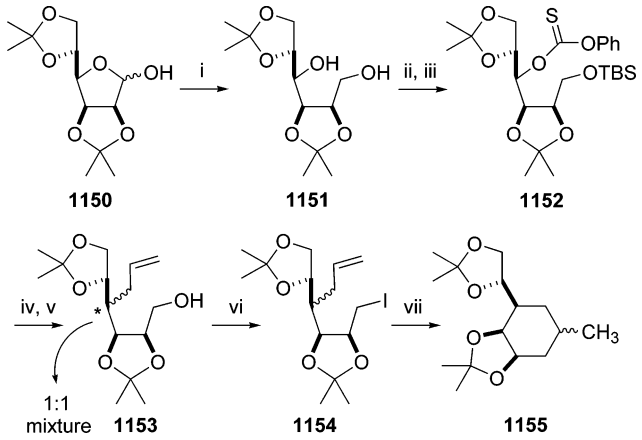
6.2.2.3.1. 6-exo-trig Radical Cyclization. 6.2.2.3.1.1. Tin Method. The first example of the preparation of a 5a-carbapyranose by 6-*exo-trig* radical cyclization was reported by Samuelsson and co-workers (Scheme 186).[359] Reduction of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**1150**) with sodium borohydride, according to Sinclair,[419] furnished diol **1151**. The latter, after protection of the primary hydroxyl group, was activated at O_4 by treatment with phenylchlorothionoformate (**1152**), allylated by treatment with allyltributylstannane,[420] and desilylated to give a 1:1 diastereomeric mixture of **1153**. The mixture was subsequently iodinated with triphenylphosphine, iodine, and imidazole[421]

Scheme 185. Ikegami's Approach to Carbasugar Derivatives[a]



[a] Reagents: (i) 2,2-dimethylpropanediol, TMSOMe, TMSOTf, $PhCH_3$, 94%; (ii) $AlMe_3$, CH_2Cl_2, 93%; (iii) Ac_2O, DMSO; (iv) $ZnCl_2$, THF, H_2O, 72% (two steps).

Scheme 186. Synthesis of 5a-Carbapyranose Derivative 1155 by 6-*exo-trig* Radical Cyclization[a]



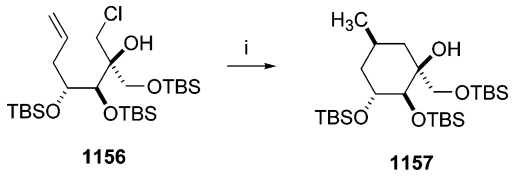
[a] Reagents: (i) $NaBH_4$, 79%; (ii) TBSCl, py; (iii) PhO(Cl)C=S, py, 91%, two steps; (iv) allyltributylstannane, *hν*; (v) TBAF, THF, 78%; (vi) imidazole, PPh_3, I_2, 89%; (vii) separation of isomers, $(n\text{-}Bu_3Sn)_2$, *hν*.

to give **1154**. The radical-induced cyclization of **1154** with bis(tributyltin) gave the 5a-carbapyranose derivative **1155**.

The second example was published, almost simultaneously, by Schmid and Whitesides (Scheme 187).[422] Radical ring closure of allyl derivative **1156** yielded carbasugar derivative **1157** in 75% yield. The homochiral derivative **1156** had been obtained by rabbit muscle aldolase-catalyzed aldol condensation of dihydroxyacetone phosphate and chloroacetaldehyde followed by silylation and allylation.

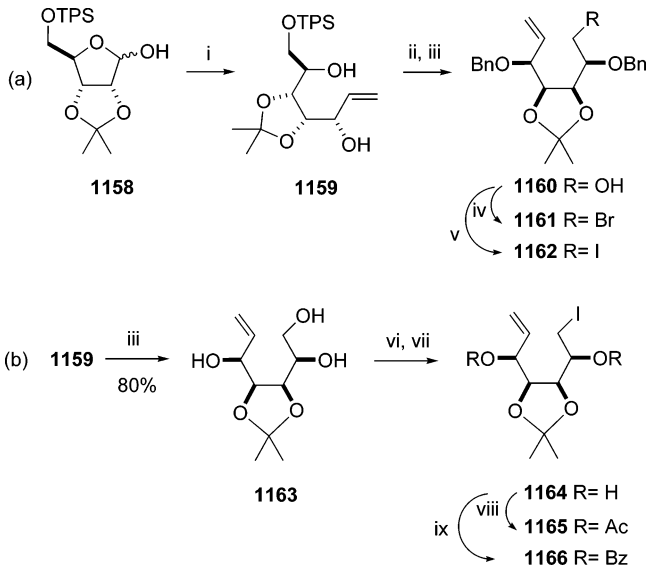
Redlich and co-workers published in 1992 a comprehensive study on the scope of the radical cyclization of hept-1-enitols for the preparation of 5a-carbasugars.[423] They reported the preparation and radical ring closure of 12,

Scheme 187. Synthesis of Carbasugar Derivative 1157 by Schmid and Whitesides[a]



[a] Reagents: (i) n-Bu_3SnH, AIBN, 75%.

Scheme 188. Synthesis of Precursors for Radical Cyclization[a]

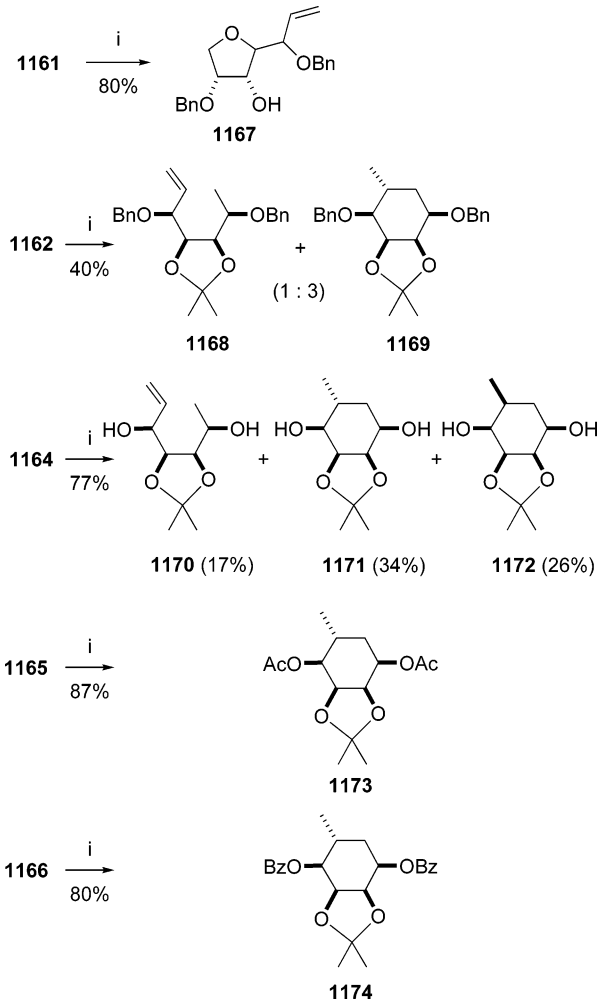


[a] Reagents: (i) vinylmagnesium bromide, THF, 79%; (ii) BnBr, NaH, DMF, 62%; (iii) TBAF, THF, 81% for **1160**; (iv) tetrabromoethane, PPh_3, THF, 92%; (v) imidazole, PPh_3, I_2, 79%; (vi) TsCl, py/CH_2Cl_2, 75%; (vii) NaI, TBAI, THF, 72%; (viii) Ac_2O, py, 92%; (ix) BzCl, py, 90%.

differently substituted hept-1-enitols, leading to several 6-deoxy-5a-carbapyranoses. As starting materials they employed four different carbohydrate derivatives (Scheme 188). Starting from D-ribose derivative **1158**, they prepared five different substrates for radical cyclization which differed either on the homolizable halogen (**1161**, **1162**) or on the protecting groups (**1162**, **1164**, **1165**, **1166**) (Scheme 188). A different behavior was found in the reaction of bromo and iodo derivatives **1161** and **1162** under typical radical cyclization conditions (Bu_3SnH, AIBN, C_6H_6) (Scheme 189). Accordingly, whereas **1162** reacted to give a mixture of 5a-carba-α-L-allo derivative **1169** and reduced **1168**, the reaction of **1161** resulted in the formation of substituted tetrahydrofuran **1167**, presumably via an ionic rather than a radical mechanism. The comparison between the radical cyclizations of iodides **1162** and **1164**−**1166** showed a striking effect of the protecting groups on the outcome of the radical cyclization. Thus, radical cyclization of acyl derivatives **1165** and **1166** was completely stereoselective, whereas reaction of diol **1164** yielded a mixture of reduced **1170** and α-L-allo and *β*-D-talo derivatives **1171** and **1172**, respectively (Scheme 189).

Reaction of 2-lithio-1,3-dithiane with 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1175**) followed by isopropylidenation yielded a mixture of stereoisomeric dithianes **1176** and **1177**,[424] which were transformed into hept-1-enitols, **1179**, **1180**, and **1181**, according to Scheme 190. Radical cyclization of **1179** (Scheme 191) was completely regio- and stereoselective to yield 5a-carba-*β*-L-

Scheme 189. 6-*exo-trig* Radical Cyclization of Carbohydrate Derivatives[a]



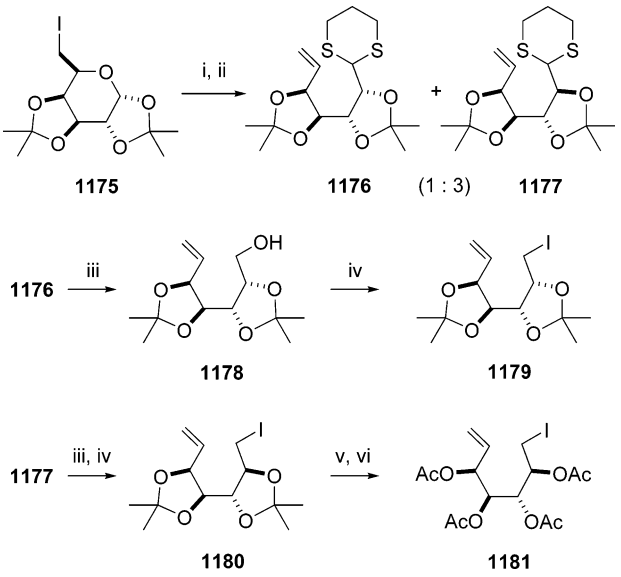
[a] Reagents: (i) n-Bu_3SnH, AIBN, PhH.

altropyranose derivative **1182**, whereas its epimer **1180** yielded 6a-carbaheptanose derivative **1183**. The latter result was ascribed to the *trans* orientation of one of the isopropylidene rings and was supported by the result of the radical cyclization of the more flexible **1181** (obtained by de-*O*-isopropylidenation of **1180** followed by acetylation, Scheme 190), in which a mixture of six-membered α-L-altro (**1184**) and *β*-D-fuco (**1185**) derivatives was obtained (Scheme 191).

Hept-1-enitols **1188**−**1190** were prepared from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**1150**), according to the reaction sequence shown in Scheme 192, and the results from their radical cyclization are displayed in Scheme 193. Finally, benzyl-*β*-D-galactopyranoside (**1196**) was converted to hept-1-enitol **1198**, and its radical cyclization yielded a 2:1 mixture of α-L-rhamno and *β*-D-gulo derivatives **1199** and **1200**, respectively (Scheme 194).

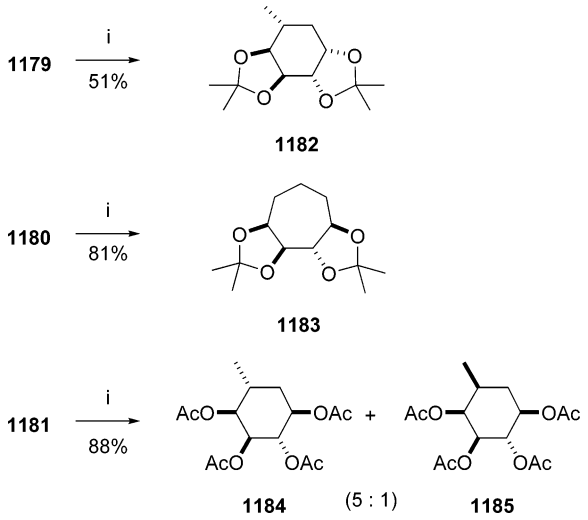
Unlike earlier contributions, the 6-*exo-trig* radical cyclization onto enol ether double bonds provided carbasugars oxygenated at C_6. Two examples of this approach are outlined in Schemes 195[425] and 196.[426] Bromo-aldehyde **1202** was synthesized from alcohol **1201**[427] by bromination and deprotection of the ethyldithioacetal. Compound **1203** (1:1 *Z*/*E* mixture) resulted from the Wittig reaction of the ylide obtained from (methoxymethyl)triphenylphosphonium chloride with **1202**. Radical cyclization of **1203** yielded a mixture of L- and D-carbasugar derivatives **1204** and **1205**. In related

Scheme 190. Synthesis of Precursors for Radical Cyclization[a]



[a] Reagents: (i) 1,3-dithiane, n-BuLi, THF/hexane, 89% 1:3 mixture; (ii) 2,2-dimethoxypropane, TsOH, dry acetone, 70% for **1176**, 75% for **1177**; (iii) MeI, 2,4,6-collidine, acetone/H_2O, reflux, then $NaBH_4$, EtOH/H_2O, 70% for **1178** and **1180**; (iv) I_2, imidazole, PPh_3, 84% for **1179,** 83% for **1180**; (v) 80% aq AcOH; (vi) Ac_2O, py, 57% (two steps).

Scheme 191. Radical Cyclization of Iodo Derivatives 1179−**1181**[a]

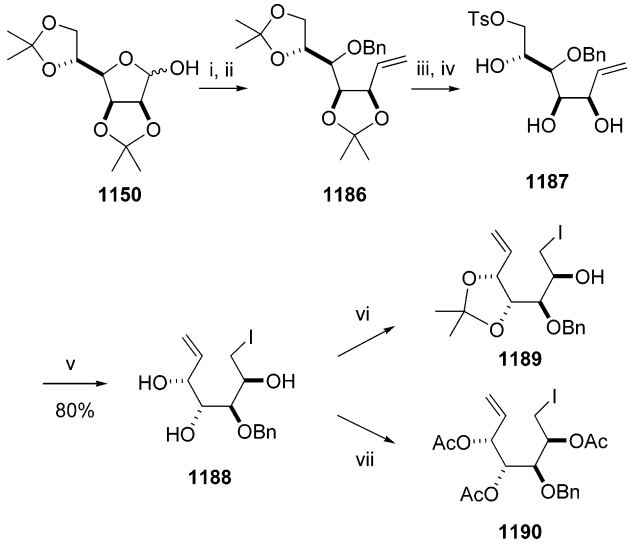


[a] Reagents: (i) Bu_3SnH, AIBN, PhH.

work, enol ether **1206** underwent radical cyclization upon treatment with Bu_3SnH to yield a (2:1) mixture of 6-methoxy-4-deoxy-L- and -D-carbasugar derivatives **1207** and **1208**, albeit in low yield (25%).

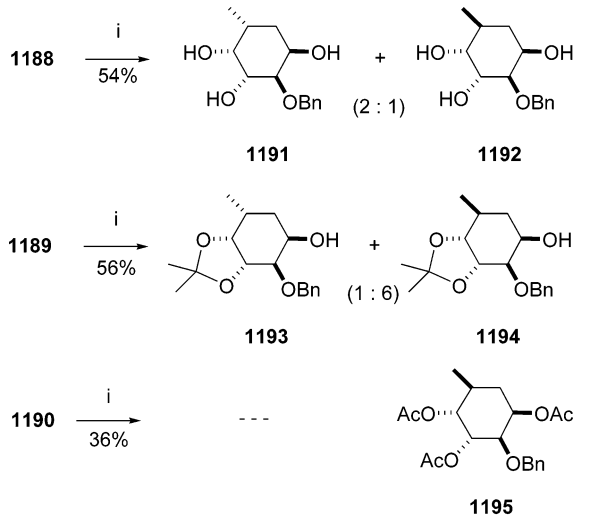
More recently, Wagner and Lundt[428] have used a 6-*exo-trigonal* radical cyclization approach for the synthesis of three different 5a-carbaheptopyranoses. This approach presents some different features from the preceding works. The use of 8-bromo-8-deoxy-2,3-unsaturated octono-1,4-lactones, where the olefinic radical trap is confined into a ring, renders the radical cyclizations completely regio- and stereoselective. Accordingly, octono-1,4-lactone **1211**, prepared from aldehyde **1210** by condensation with 2-(trimethylsiloxy)furan,[429] was converted to bromo derivative **1211**, which underwent radical cyclization in the presence of Bu_3SnH to yield bicyclic compound **1213** (Scheme 197). The latter was

Scheme 192. Preparation of Hept-1-enitols 1188−1190[a]



[a] Reagents: (i) $(Ph)_3PCH_3I$, n-BuLi, THF, 67%; (ii) BnBr, NaH, DMF, 84%; (iii) AcOH, 98%; (iv) TsCl, py/CH_2Cl_2, 52%; (v) imidazole, PPh_3, I_2, 78%; (vi) isopropenyl methyl ether, p-TsOH, DMF, 36%; (vii) Ac_2O, py.

Scheme 193. 6-*exo-trig* Radical Cyclization of Hept-1-enitols 1188−1190[a]

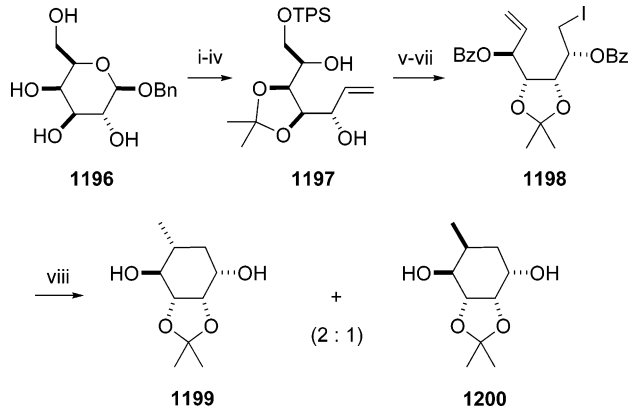


[a] Reagents: (i) Bu_3SnH, AIBN, PhH.

transformed, by reduction with $Ca(BH_4)_2$, into 5a-carba-6-deoxy-β-L-guloheptopyranose **1214**.

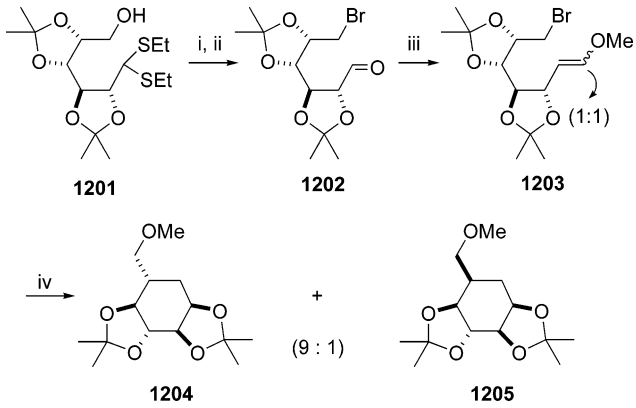
The second and third 5a-carbaheptopyranoses were obtained by radical cyclization of epimeric lactones **1219** and **1220**, which were prepared from commercially available D-glycero-D-guloheptonolactone **1215**, following the transformations outlined in Scheme 198. Compound **1215** was reduced to the corresponding heptose, subjected to a Kiliani homologation, and converted to the tri- and diacetonides **1216** and **1217** following literature methods.[430] The synthetic sequence continued with diacetonide **1217**, which was transformed into **1218** through a synthetic sequence which involved, among others, de-*O*-isopropylidenation and monobromination (Scheme 198). Treatment of **1218** with Et_3N led to a mixture of unsaturated lactones **1219** and **1220** by β-elimination and epimerization of the allylic C_4 position. Radical cyclization of lactones **1219** and **1220** (Scheme 199) was again completely stereoselective, yielding adducts **1221** and **1223**, reduction of which with $Ca(BH_4)_2$ yielded 5a-

Scheme 194. Synthesis and Radical Cyclization of Hept-1-enitol (1198)[a]



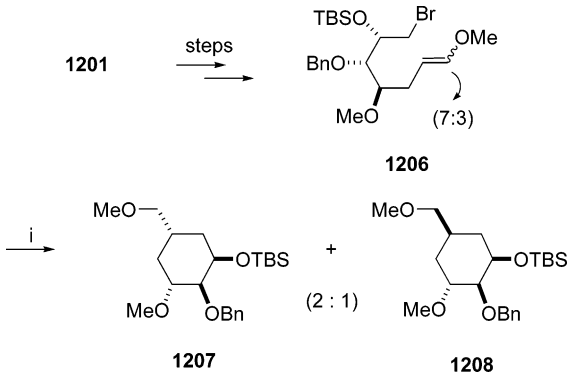
[a] Reagents: (i) TBSCl, imidazole, DMF, 85%; (ii) dry acetone, TsOH, $CaSO_4$, 78%; (iii) H_2, 10% Pd/C, $NaHCO_3$, MeOH, 93%; (iv) methyltriphenylphosphonium iodide, n-BuLi, THF, 60%; (v) TBAF, THF, 91%; (vi) TsCl, py/CH_2Cl_2, 20 h, then BzCl, 70%; (vii) NaI, TBAI, THF, 81%; (viii) n-Bu_3SnH, AIBN, PhH, then Ac_2O, py, 69% (two steps).

Scheme 195. Synthesis and 6-*exo-trig* Radical Cyclization of Enol Ether 1198[a]



[a] Reagents: (i) CBr_4, PPh_3, 70%; (ii) HgO, $HgCl_2$, acetone−H_2O, 80%; (iii) $Ph_3P{=}CHOCH_3$, THF, 50%; (iv) n-Bu_3SnH, AIBN, PhH, 60%.

Scheme 196. Synthesis and 6-*exo-trig* Radical Cyclization of Enol Ether 1206[a]

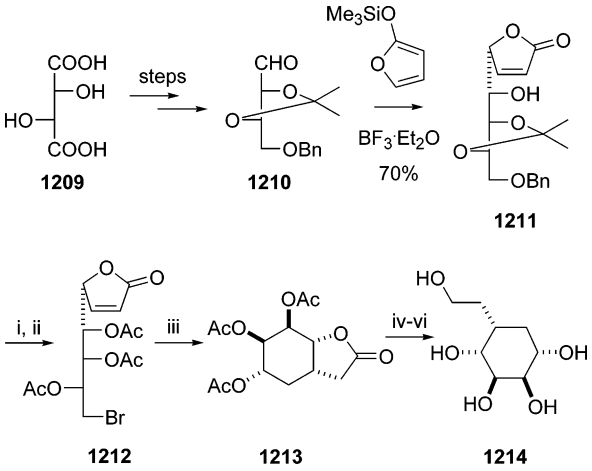


[a] Reagents: (i) n-Bu_3SnH, AIBN, PhH, 25%.

carba-L-glycero-α-L-galactoheptopyranose (**1222**) and 5a-carba-D-glycero-β-D-idoheptopyranose (**1224**), respectively. It is noteworthy that the hydrogen transfer at C_2 was also stereoselective and controlled by steric effects from the newly formed *cis*-fused bicyclic molecule.

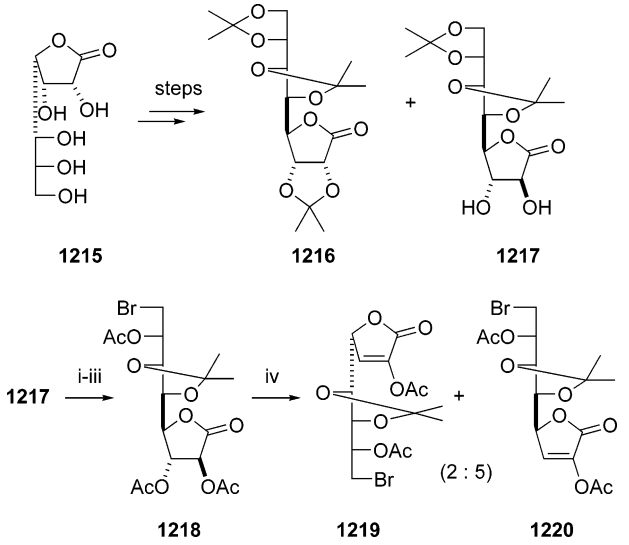
6.2.2.3.1.2. Radical Cyclizations Using Samarium(II) Iodide. Fernández-Mayoralas and co-workers[431] made use of an approach based on a SmI_2-promoted pinacol coupling[432]

Scheme 197. Synthesis of Carbasugar Derivative 1214[a]



[a] Reagents: (i) HBr in AcOH, then MeOH; (ii) Ac_2O, H^+, 51% from **1211**; (iii) n-Bu_3SnH, AIBN, EtOAc, 82%; (iv) HCl, MeOH (89%); (v) $Ca(BH_4)_2$, EtOH; (vi) Ac_2O, H^+, 51% from **1213**.

Scheme 198. Synthesis of Bromolactones 1219 and 1220[a]

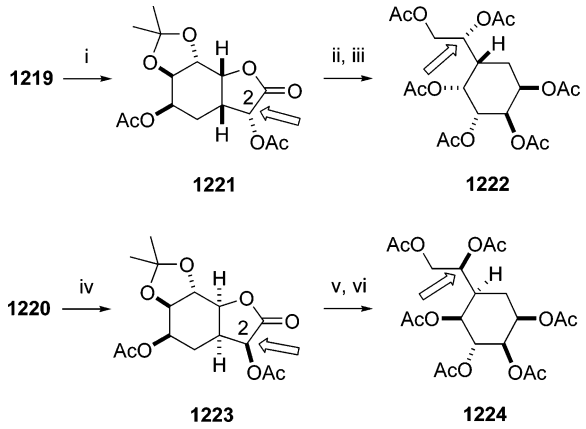


[a] Reagents: (i) TFA, H_2O, 84%; (ii) HBr in AcOH, then MeOH, 50% from **1217**; (iii) Ac_2O, py, 87%; (iv) Et_3N, CH_2Cl_2, 76%.

of a D-mannitol derivative in their stereodivergent syntheses of 5a-carba-α-L-galacto- (**1236**), 5a-carba-*β*-D-altro- (**1237**), 5a-carba-α-L-fuco- (**1238**), and 6-deoxy-5a-carba-*β*-D-altropyranose (**1239**) derivatives. Accordingly, diol **1225** (Scheme 200), prepared from 3,4-*O*-isopropylidene-1,6-di-*O*-trityl-D-mannitol, was subjected to a one-pot oxidation−pinacol coupling sequence[433] to yield a (1:9) mixture of cyclitols **1226** and **1227**. The key intermediates, *exo*-methylene cyclohexanes **1231**, **1232**, and **1233**, were obtained from *cis*-diol **1227** through a synthetic sequence outlined in Scheme 200. Interestingly, the authors discovered that the stereoselectivity on the hydroboration and hydrogenation of the exocyclic double bond in compounds **1231**−**1233**, leading to carbasugar derivatives, could be fine-tuned by changes in (a) the substitution at 2-OH and 3-OH and/or (b) the hydrogenation catalysts (Scheme 201).

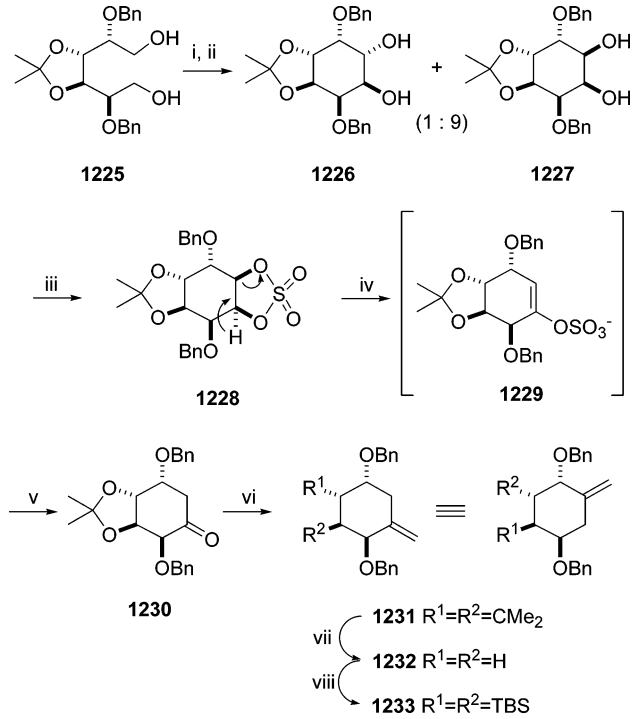
6.2.2.3.2. 6-exo-dig Radical Cyclization. Syntheses of carbasugars and derivatives involving 6-*exo-dig* radical cyclization have been reported by four different research groups. The first approach was disclosed by McDevitt and Fraser-Reid[434] in their synthesis of Tatsuta's penultimate intermediates for cyclophellitol (**9**) and (1*R*,6*S*)-**9**.[435] In their retrosyn-

Scheme 199. Radical Cyclization of Bromolactones 1219 and 1220[a]



[a] Reagents: (i) n-Bu_3SnH, AIBN, EtOAc, 73%; (ii) $Ca(BH_4)_2$, EtOH, 96%; (iii) Ac_2O, H^+, 83%; (iv) n-Bu_3SnH, AIBN, EtOAc, 73% + 9% of debrominated **1220**; (v) $Ca(BH_4)_2$, EtOH, 80%; (vi) Ac_2O, H^+, 77%.

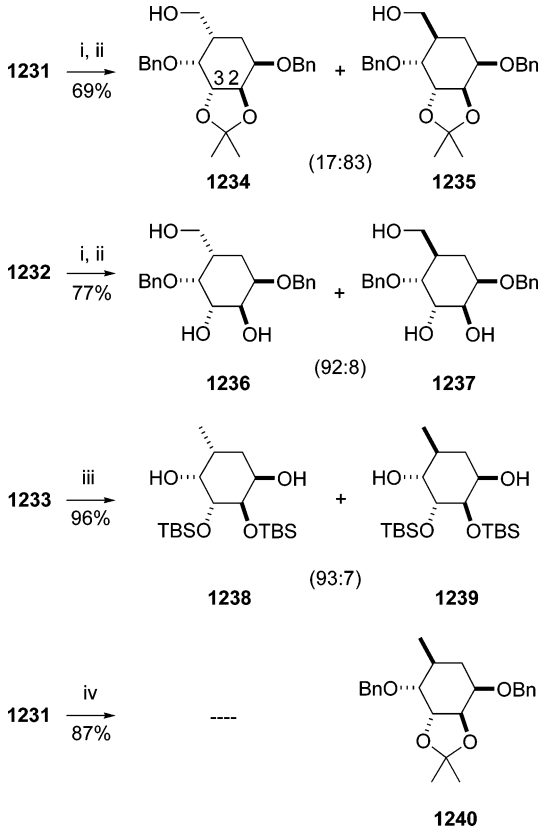
Scheme 200. Fernández-Mayoralas et al. SmI_2-Promoted Pinacol Coupling Strategy to Carbasugars[a]



[a] Reagents: (i) Swern oxidation; (ii) SmI_2, t-BuOH, THF, 82%; (iii) (a) $SOCl_2$, Et_3N, CH_2Cl_2; (b) $NaIO_4$, $RuCl_3$, CH_3CN, CCl_4, H_2O, 86% (2 steps); (iv) KOt-Bu, THF; (v) H_2SO_4, H_2O, THF, 86% (2 steps); (vi) $Ph_3P{=}CH_2Br$, $[Me_3Si]_2NK$, THF, 85%; (vii) TFA, MeOH, 98%; (viii) TBSOTf, $(i\text{-}Pr)_2EtN$, CH_2Cl_2, 89%.

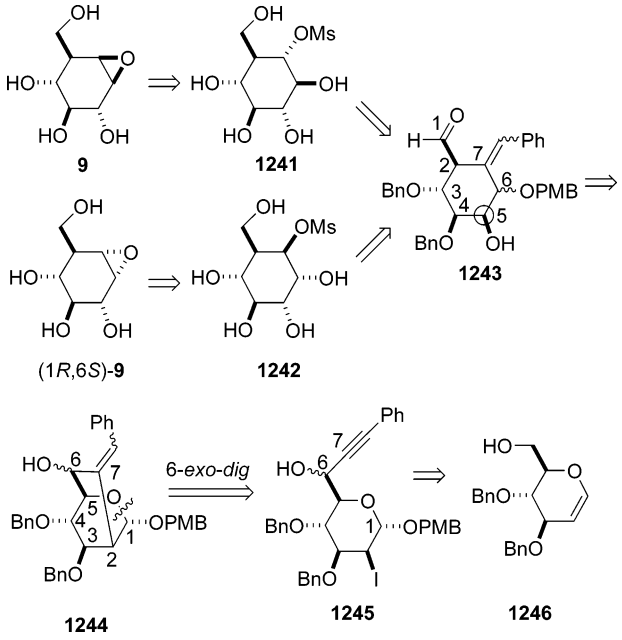
thesis, outlined in Scheme 202, iodo-alkynes **1245**, readily obtained from D-glucal derivative **1246**, underwent 6-*exo-dig* radical cyclization to generate a [2.2.2]oxabicyclic *p*-methoxybenzyl glycoside, **1244**, which upon unveiling of the anomeric position yielded *exo*-methylene cyclohexane **1243**. Finally, after inversion of the configuration at C_5 in the latter, the exocyclic double bond was retrosynthetically correlated with the mesylate functionality in Tatsuta's intermediates **1241** and **1242**. The synthetic sequence to common intermediate **1249** (Scheme 203) followed the guidelines outlined in the retrosynthesis: (a) addition of lithium phenylacetylide to a 6-formyl glucal derivative, (b) N-iodosuccinimide (NIS)-promoted glycosylation according to Thiem's

Scheme 201. Fernández-Mayoralas et al. Synthesis of Carbasugars[a]



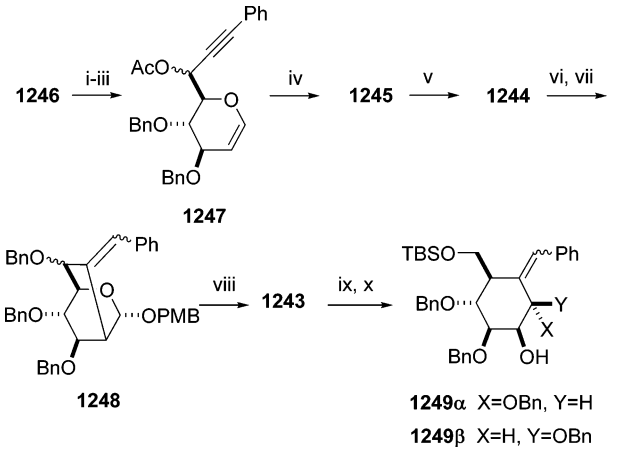
[a] Reagents: (i) borane·THF, THF; (ii) H_2O_2 (30%), NaOH (3 N); (iii) H_2, Pd/C (10%), EtOAc; (iv) H_2, Ni−Ra, MeOH.

Scheme 202. McDevitt and Fraser−Reid's Retrosynthesis of Cyclophellitol (9)



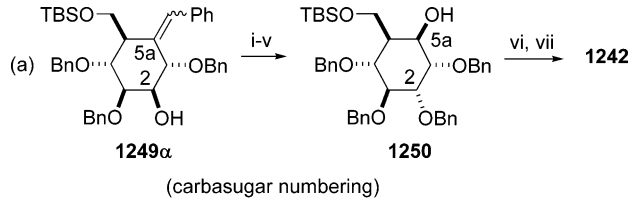
procedure,[436] (c) 6-*exo-dig* radical cyclization of the ensuing 2-deoxy-2-iodo derivative, and (d) deprotection of the anomeric *p*-methoxybenzyl group to unveil the carbasugar ring. Finally, **1249**α and **1249***β* were correlated with Tatsuta's intermediates **1242** and **1241**, respectively (Scheme 204a and b). These transformations involved inversion of the configuration at C_2, ozonolysis of the exocyclic double

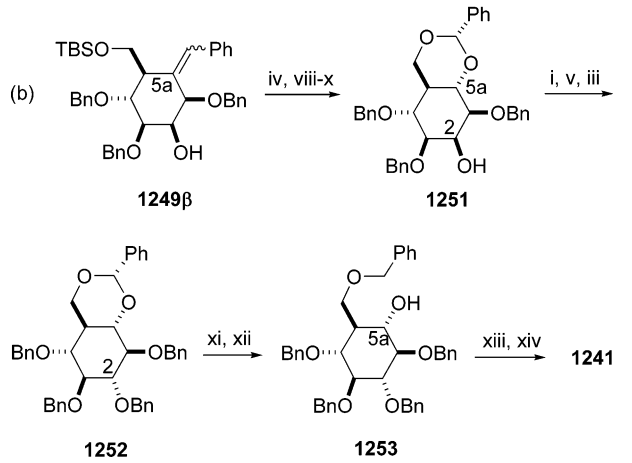
Scheme 203. McDevitt and Fraser−Reid's Synthesis of Key Intermediate 1249[a]



[a] Reagents: (i) Swern oxidation, THF; (ii) n-BuLi, lithium phenylacetylide, THF; (iii) Ac_2O, 82%, 3 steps; (iv) NIS, p-$OMePhCH_2OH$, CH_3CN, 92%; (v) n-Bu_3SnH, AIBN, PhH, 100%; (vi) NaOMe, MeOH; (vii) NaH, BnBr; (viii) DDQ, CH_2Cl_2/H_2O, 95%; (ix) H^-; (x) TBSCl.

Scheme 204. McDevitt and Fraser−Reid's Synthesis of Tatsuta's Key Intermediates 1241 and 1242[a]





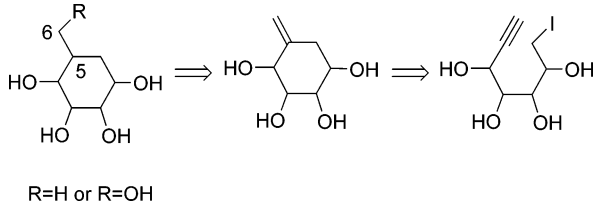
[a] Reagents: (i) Dess−Martin; (ii) $NaBH_4$; (iii) BnBr; (iv) O_3, PPh_3; (v) BH_3·Me_2S; (vi) MsCl; (vii) H_2, Pd−C/$Pd(OH)_2$, 82%; (viii) $NaB(OAc)_3H$; (ix) 1 N HCl; (x) $PhCH(OMe)_2$; (xi) $NaCNBH_3$; (xii) HCl; (xiii) MsCl; (xiv) H_2, Pd−C, 63%.

bond, stereodivergent reduction of the ensuing carbonyl group, and mesylation of the resulting 5a-OH (carbasugar numbering).

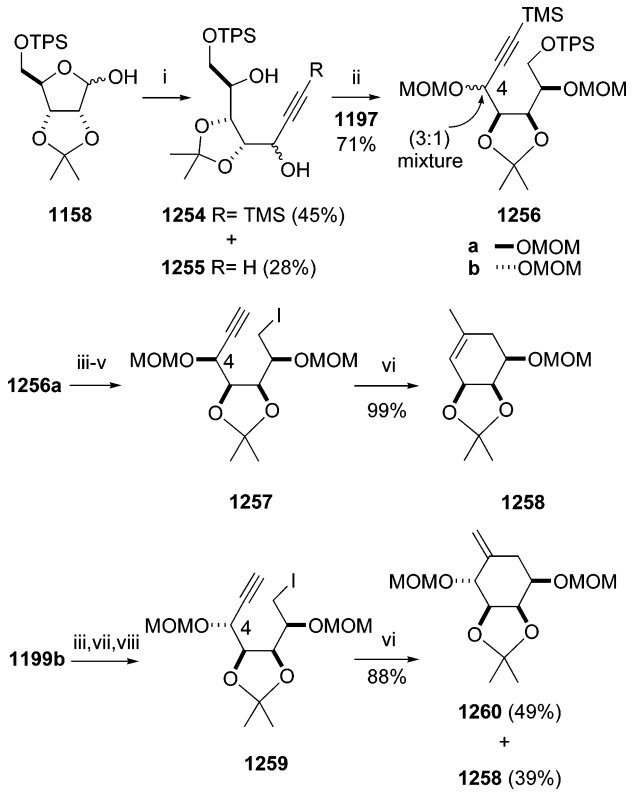
An approach which retrosynthetically correlated positions C_5 and C_6 of the carbasugar with the exocyclic double bond of an *exo*-methylenecyclohexane ensuing from a 6-*exo-dig* radical cyclization of a carbohydrate-derived iodo-alkyne (Scheme 205) was independently reported by two research groups.[437,438]

Maudru, Singh, and Wightman reported the conversion of D-ribose to carba-*β*-D-rhamno- and carba-α-L-gulopyranose pentaacetates, **1262** and **797**.[437] Thus, the ribose derivative **1158** was transformed into a diastereomeric

Scheme 205. Retrosynthesis of Carbasugars Based on 6-*exo-dig* Radical Cyclization



Scheme 206. Synthesis of Key Intermediates 1258 and 1260[a]

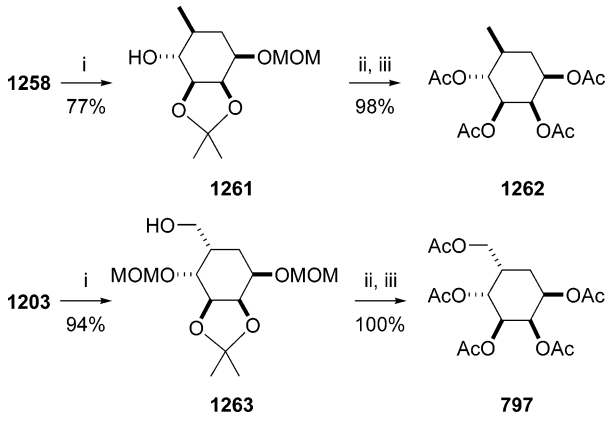


[a] Reagents: (i) lithium trimethylsilylacetylide, THF, 79%; (ii) MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 71%; (iii) chromatographic separation; (iv) major C_4 isomer, TBAF, THF, 91%; (v) imidazole, PPh_3, I_2, 71%; (vi) n-Bu_3SnH, PhH, AIBN, (99%); (vii) minor C_4 isomer, TBAF, THF, 96%; (viii) imidazole, PPh_3, I_2, 78%.

mixture of protected alkynes **1256** (Scheme 206); both of these diastereomers were processed separately to the primary iodides **1257** and **1259**. Radical cyclization of **1257** yielded cyclohexene **1258**[439] as the only isomer. On the other hand, radical ring closure of **1259** furnished a mixture of **1258** and *exo*-methylenecyclohexane **1260**. Hydroboration of **1258** and **1260** was regio- and stereoselective and, followed by deprotection and aceylation, yielded 5a-carba-β-D-rhamno- and 5a-carba-α-L-gulopyranose pentaacetates, **1262** and **797**, respectively (Scheme 207).

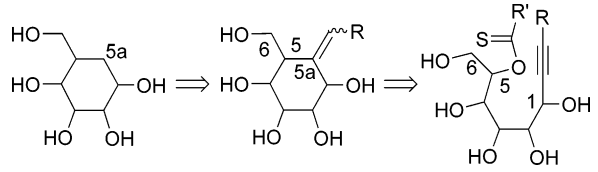
Gómez et al.[440] disclosed a different approach to carbasugars in which C_{5a} was retrosynthetically correlated with the exocyclic double bond of an *exo*-methylenecyclohexane produced by 6-*exo-dig* radical cyclization of an alkyne-thionocarbonate derived from D-mannose (Scheme 208). They reported the synthesis of 5a-carba-β-D-mannopyranose pentaacetate (**657**) from D-mannose. The synthetic scheme included homologation, by reaction with lithium phenylacetylide, of 2,3:4,6-di-*O*-isopropylidene-D-mannopyranose (**1264**) to yield diol **1265** (Scheme 209) as a very major isomer (65% isolated yield). This diol was converted, in two steps, to thionocarbonate **1266**, whose radical cyclization

Scheme 207. Synthesis of 5a-Carba-β-D-rhamno- and -α-L-gulopyranose Pentaacetates (1262 and 797)[a]

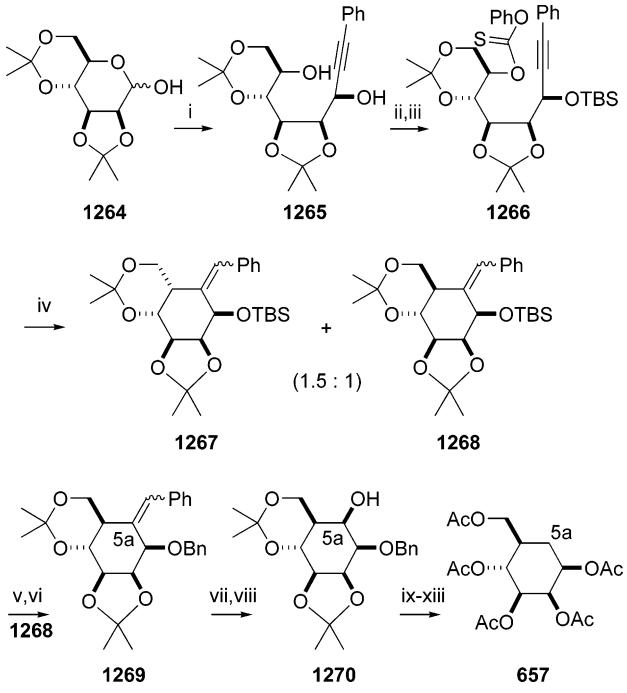


[a] Reagents: (i) $BH_3{\cdot}SMe_2$, THF, H_2O_2, NaOH; (ii) 6 M HCl, MeOH, 99%; (iii) Ac_2O, py, 99%.

Scheme 208. Gómez et al. Retrosynthesis of Carbasugars



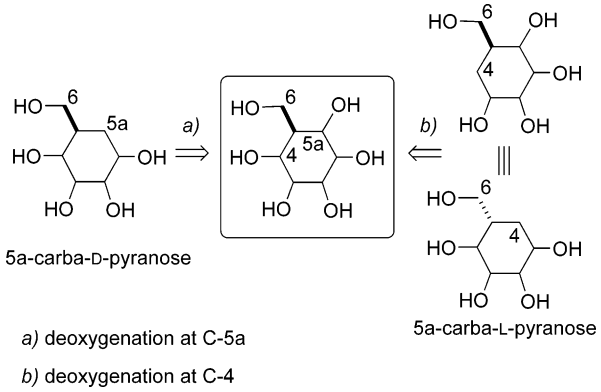
Scheme 209. Gómez et al. Synthesis of 5a-Carba-β-D-Mannopyranose Pentaacetate (657)[a]



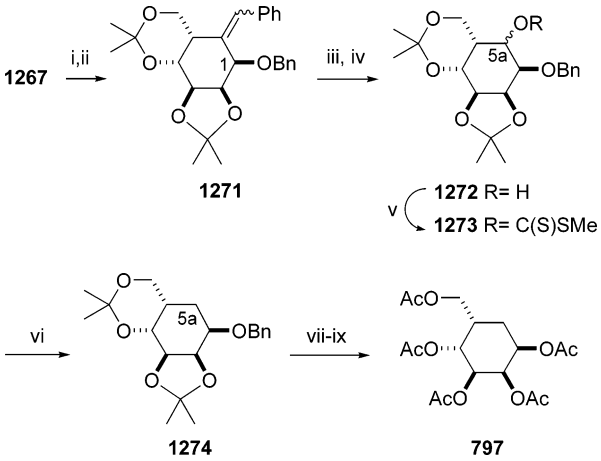
[a] Reagents: (i) lithium phenylacetylide, THF, chromatography, 65%; (ii) TBSCl, py, CH_2Cl_2, 65%; (iii) phenyl chlorothionoformate, py, MeCN, 80%; (iv) n-Bu_3SnH, AIBN, $PhCH_3$, 95%; (v) TBAF, THF, 91%; (vi) HNa, TBAI, BnBr; (vii) O_3, MeOH−CH_2Cl_2, then Me_2S; (viii) $BH_3{\cdot}SMe_2$, THF, 75% (three steps); (ix) HNa, CS_2, MeI; (x) n-Bu_3SnH, AIBN, $PhCH_3$, 85%, (two steps); (xi) H_2, Pd/C, MeOH; (xii) AcOH−THF−H_2O; (xiii) Ac_2O, py, 85% (three steps).

yielded a mixture of *exo*-methylenecyclohexanes **1267** and **1268**. Compound **1268** was transformed into 5a-carba-β-D-mannopyranose pentaacetate **657**, through a series of steps which included ozonolysis and reduction of the ensuing ketone to a hydroxyl group, followed by Barton−McCombie radical deoxygenation,[441] deprotection, and acetylation.

Scheme 210. Gómez et al. Stereodivergent Synthesis of Carbasugars from Polyoxygenated Intermediates



Scheme 211. Synthesis of 5a-Carba-α-L-gulopyranose Pentaacetate (797)[a]

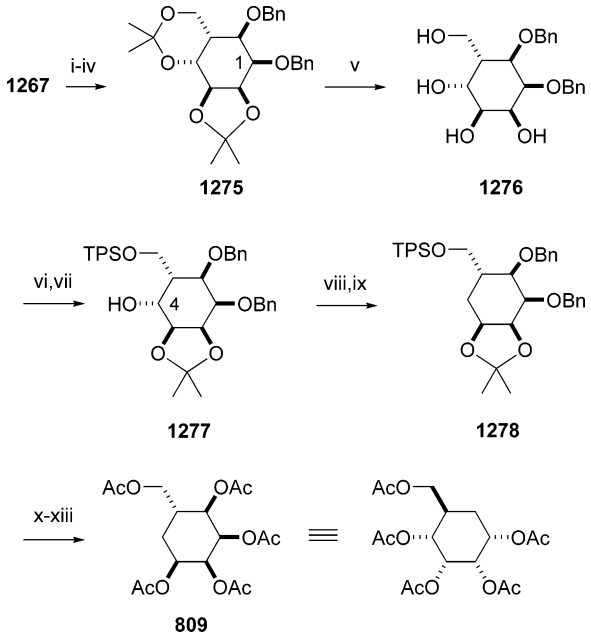


[a] Reagents: (i) TBAF, THF; (ii) HNa, TBAI, BnBr, 73%; (iii) O_3, Me_2S; (iv) $NaBH_4$, $CeCl_3$, 64%, two steps; (v) NaH, CS_2, MeI, 70%; (vi) n-Bu_3SnH, AIBN, $PhCH_3$, 75%; (vii) H_2, Pd/C; (viii) AcOH−THF−H_2O; (ix) Ac_2O, py, 75% (three steps).

The approach was extended, by the same authors,[442] to the stereodivergent preparation of D- and L-carbasugars from a single polyoxygenated intermediate by site-selective deoxygenation either at C_{5a} or at C_4 (Scheme 210). They illustrated this protocol with the preparation of 5a-carba-α-D-allo- (**809**) and 5a-carba-α-L-gulopyranose (**797**) pentaacetates from (L-) intermediate **1267**, and 5a-carba-β-L-talopyranose (L-**800**) from **1268** [the same intermediate previously used in the synthesis of 5a-carba-D-mannopyranose (**657**)]. Accordingly, deoxygenation at C_{5a} of intermediate **1267** led to 5a-carba-α-L-gulopyranose pentaacetate (**797**) (Scheme 211), whereas deoxygenation at C_4 allowed access to 5a-carba-α-D-allopyranose pentaacetate (**809**) (Scheme 212). The synthesis of the β-L-talo isomer L-**800** (Scheme 213), which required deoxygenation at C_4 on intermediate **1268**, was greatly facilitated by an unexpected 4,6- to 5a,6-isopropylidene ring rearrangement upon treatment of **1279** with phenylchlorothionoformate.

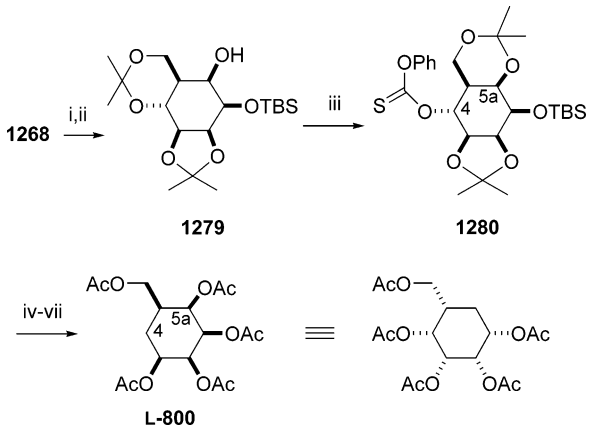
Along these lines, Gómez et al.[443] applied their methodology to the preparation of three carbasugars from a single polyoxygenated cyclohexanone (**A**, Scheme 214). They exploited the deoxygenation (either at C_{5a} or at C_4) of the two diastereoisomers (**B**, **C**, Scheme 214) originating from the stereoselective reduction of the C_{5a} ketone in compound **A**. Implementation of this approach led to the synthesis of 5a-carba-α-D-gluco-, -α-D-galacto-, and -β-L-gulopyranose pentaacetates. Their synthetic route started with *exo*-methylenecyclohexane **1284** prepared in four steps from alkyne **1281** (Scheme 215). Deoxygenation at C_{5a} of benzyl derivative **1285**, followed by ozonolysis, reduction, and deoxygenation furnished protected L-gulo derivative **1288**, which was subsequently deprotected and acetylated to yield 5a-carba-β-L-gulopyranose pentaacetate (**795**) (Scheme 216). Reduction of the C_{5a} keto group on hydroxy-ketone **1284** (Scheme 217) was completely stereoselective, generating a β-OH at C_{5a}, and deoxygenation at C_4 ultimately led to 5a-carba-α-D-galactopyranose pentaacetate (D-**570**). Synthesis of carba-α-D-glucopyranose pentaacetate (**922**) (Scheme 218), according to these guidelines, implied synthesis of an α-oriented 5a-OH (as in **1294**) and demanded deoxygenation at C_4 (**1292** → **1293**) prior to the reduction of the keto moiety at C_{5a}.

Scheme 212. Synthesis of 5a-Carba-α-D-allopyranose Pentaacetate (809)[a]



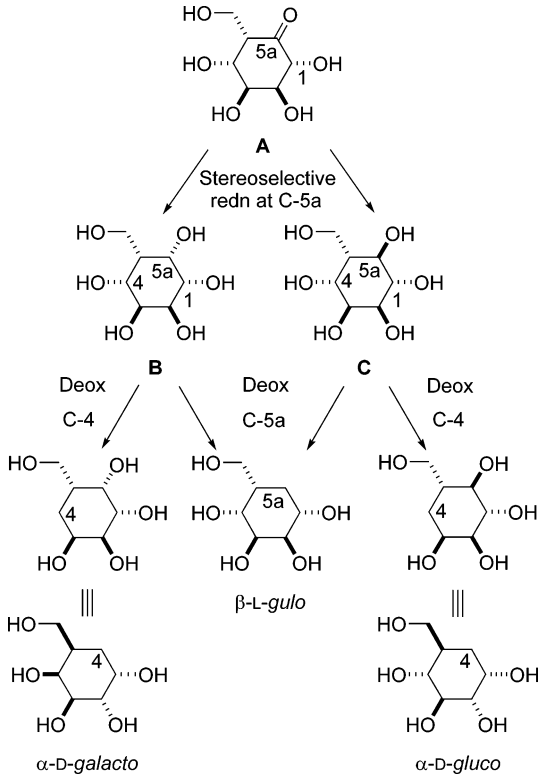
[a] Reagents: (i) TBAF, THF; (ii) O_3, Me_2S; (iii) $NaBH_4$, $CeCl_3$, 62% (two steps); (iv) HNa, TBAI, BnBr, 73%; (v) AcOH−THF−H_2O, 95%; (vi) TPSCl, imidazole, DMPA; (vii) 2-methoxypropene, TsOH, 45% (two steps); (viii) phenyl chlorothionoformate, py; (ix) n-Bu_3SnH, AIBN, $PhCH_3$, 59% (two steps); (x) TBAF, THF; (xi) H_2, Pd/C; (xii) AcOH−THF−H_2O; (xiii) Ac_2O, py, 86% (four steps).

Scheme 213. Synthesis of 5a-Carba-β-L-talopyranose Pentaacetate (L-800)[a]

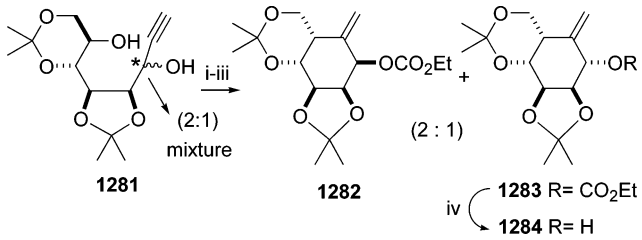


[a] Reagents: (i) O_3, Me_2S; (ii) $NaBH_4$, $CeCl_3$, 50%, (two steps); (iii) phenyl chlorothionoformate, py, 70%; (iv) n-Bu_3SnH, AIBN, $PhCH_3$, 90%; (v) TBAF, THF; (vi) AcOH−THF−H_2O; (vii) Ac_2O, py, 80% (three steps).

Scheme 214. Stereodivergent Route to Three Carbasugars from a Single Intermediate, A



Scheme 215. Synthesis of Key Intermediate 1284[a]

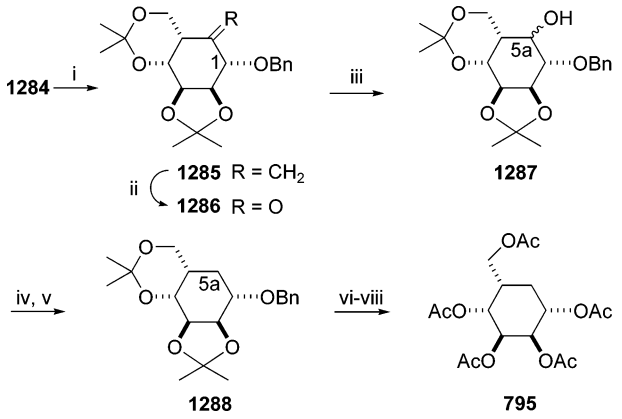


[a] Reagents: (i) $ClCO_2Et$, py, CH_2Cl_2, 57%; (ii) phenyl chlorothionoformate, py, CH_3CN, 76%; (iii) n-Bu_3SnH, AIBN, $PhCH_3$, 95%; (iv) K_2CO_3, MeOH, 70%.

6.2.2.3.3. 6-endo-trig Radical Cyclization. 6.2.2.3.3.1. Samarium(II) Iodide-Promoted Reactions. Vorwerk and Vasella reported the synthesis of two carbocyclic analogues of *N*-acetyl-2,3-didehydro-2-deoxy-D-neuraminic acid (**1295a** and **1295b**) by a ketyl-olefin radical cyclization induced by SmI_2.[444] Their retrosynthesis (Scheme 219) started with *N*-acetyl mannosamine (**1298**), which upon chain elongation with *tert*-butyl bromomethacrylate and oxidation at C_6 would lead to the key intermediate **1297**. SmI_2-induced 6-*endo*-*trigonal* ketyl cyclization of the latter paved the way to highly functionalized cyclohexane **1296**, the ultimate precursor for the 6a-carba-*N*-acetyl-D-neuraminic acid analogues. Their synthetic route (Scheme 220) demanded selective protection of O_3 in compound **1299**, as a *p*-methoxy benzyl ether, prior to chain homologation and formation of fully protected ketone **1297**. Treatment of **1297** with samarium(II) iodide led to a mixture of carbocyclic esters **1296a**−**b**, which were separated and submitted to dehydration with Martin's sulfurane[445] to yield β,γ-unsaturated ester **1300**. The desired carbasugars, **1295a**−**b**, were then prepared via phenylselenide **1302** by oxidation−elimination and deprotection.

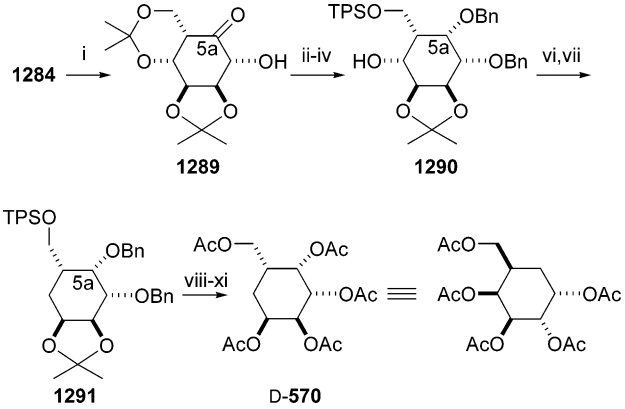
6.2.2.3.3.2. Tin Method. Gómez et al.[446] reported the preparation of the carbocyclic analogues of D-gluco- and

Scheme 216. Synthesis of 5a-Carba-β-L-gulopyranose Pentaacetate (795)[a]



[a] Reagents: (i) NaH, BnBr, THF, 80%; (ii) O_3, MeOH, then Me_2S; (iii) $NaBH_4$, $CeCl_3$, 90% two steps; (iv) NaH, CS_2, MeI, 80%; (v) n-Bu_3SnH, AIBN, $PhCH_3$, 70%; (vi) H_2, Pd/C; (vii) AcOH, THF, H_2O; (viii) Ac_2O, py, 70% (three steps).

Scheme 217. Synthesis of 5a-Carba-α-D-galactopyranose Pentaacetate (D-570)[a]

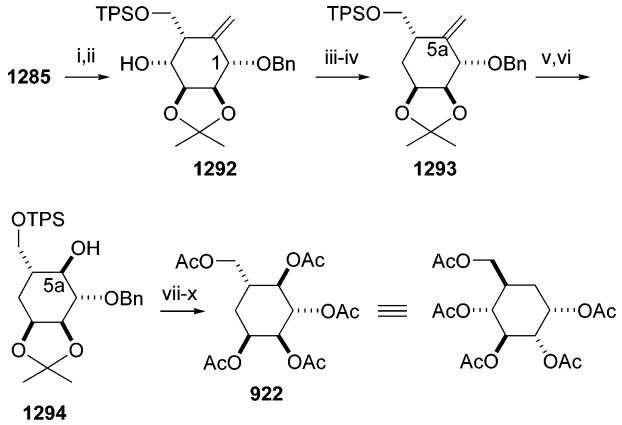


[a] Reagents: (i) O_3, MeOH, then Me_2S; (ii) $NaBH_4$, $CeCl_3$, 75% two steps; (iii) NaH, BnBr, THF, 72%; (iv) PPTS, MeOH, 85%; (v) TPSCl, NEt_3, DMF, 90%; (vi) NaH, CS_2, MeI, 90%; (vii) n-Bu_3SnH, AIBN, $PhCH_3$, 77%; (viii) TBAF, THF; (ix) H_2, Pd/C; (x) AcOH, THF, H_2O; (xi) Ac_2O, py, 70% (four steps).

D-galactopyranose **1303a**−**b**, by 6-(π-*exo*)-*endo-trig*[447] radical cyclization of D-gluco- and D-galacto-derived enynes **1305a,b** (Scheme 221). Their synthetic sequence started with diacetonides **1306**[448] (Scheme 222), which were homologated to alkynes **1307** according to the method of Toma and coworkers[449] and thence to enynes **1305**. Radical cyclization of compounds **1305** took place upon treatment with Bu_3SnH/AIBN and was completely regioselective, giving rise to alkenylstannanes **1304**. Finally, 5a-carba-β-D-gluco- and -galactopyranose pentaacetates (D-**580** and D-**760**, respectively) were prepared by deprotection, ozonolysis, and reduction of **1304**.

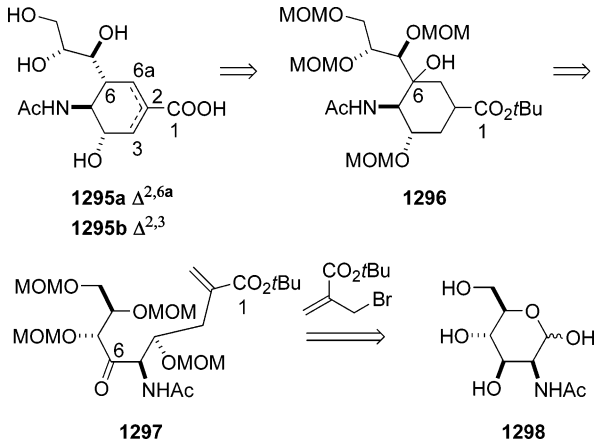
6.2.2.4. Ring-Closing Olefin Metathesis. A retrosynthetic analysis for carbapyranoses based on ring-closing metathesis (RCM), as previously mentioned for carbafuranoses, will imply the reaction[235] of a diene[236] precursor followed by appropriate manipulation of the resulting cyclohexene derivatives. Along these lines, four general approaches to carbapyranoses and derivatives have been described and are outlined in Scheme 223. Examples of these general approaches have been described in a recent review,[450] and only selected examples will be discussed here.

Scheme 218. Synthesis of 5a-Carba-α-D-glucopyranose Pentaacetate 922[a]



[a] Reagents: (i) PPTS, MeOH, 75%; (ii) TPSCl, imidazole, 90%; (iii) NaH, CS_2, MeI, 74%; (iv) n-Bu_3SnH, AIBN, $PhCH_3$, 72%; (v) O_3, MeOH, then Me_2S; (vi) $NaBH_4$, $CeCl_3$, chromatography, 60%, plus 5a-epi-**1294**, 24% (two steps); (vii) TBAF, THF; (viii) H_2, Pd/C; (ix) AcOH, THF, H_2O; (x) Ac_2O, py, 56% (four steps).

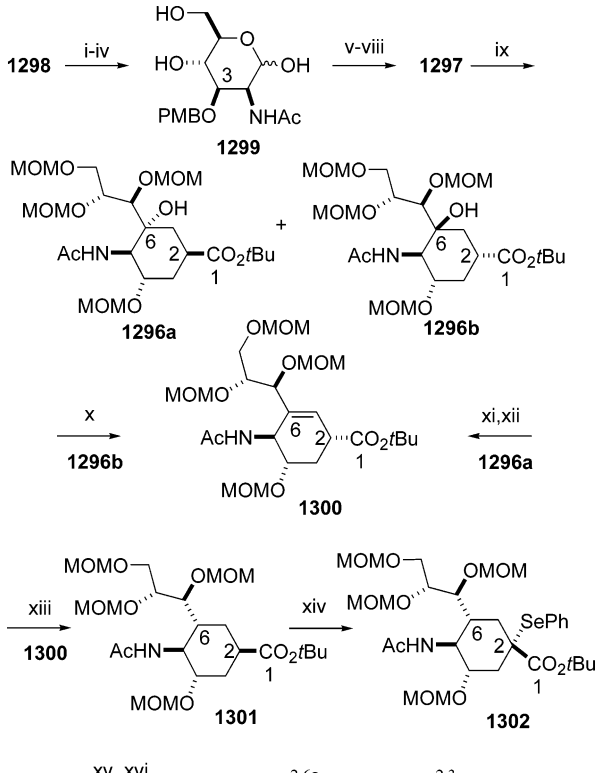
Scheme 219. Vorwerk and Vasella Retrosynthesis of Carbasugar Analogues of *N*-Acetyl-2,3-didehydro-2-deoxy-D-neuraminic Acid (1295a and 1295b)



Vasella and co-workers' approach (Scheme 223a) was used in the synthesis of (+)-valienamine (**11**) (Scheme 224) and carbasugar derivative (**1317**) (Scheme 225).[451] Addition of vinylmagnesium bromide to ketone **1308** (Scheme 224), readily obtained from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose,[452] yielded epimeric dienes **1309**. Ring-closing alkene metathesis, with Grubbs' catalyst **523**, of the major epimer gave cyclohexene **1310**. The transformation of **1310** into (+)-valienamine also included conversion of its tertiary allylic alcohol moiety to an allylic amine by a [3,3] sigmatropic rearrangement of an intermediate allylic cyanate **1312**. Finally, benzyl carbamate **1314**, readily obtained from isocyanate **1313** by treatment with benzyl alcohol, was deprotected under Birch conditions to give (+)-valienamine (**11**). An analogous reaction sequence was carried out with D-mannose-derived ketone **1315** and led to carbasugar derivative **1317** (Scheme 225).

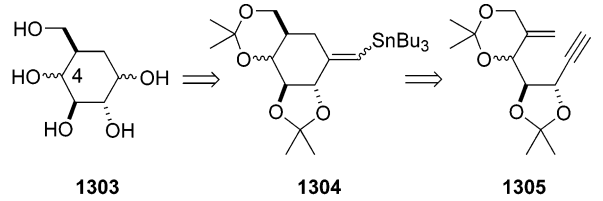
Two synthetic approaches to valienamine followed the retrosynthesis outlined in Scheme 223b. Jeon, Kim, and co-workers[453] used ketone **1318** as their starting material (Scheme 226). This compound, as in the case of ketone **1308**, was readily available from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose using a modification of the previously reported

Scheme 220. Synthesis of 1295a and 1295b[a]



[a] Reagents: (i) allylic alcohol, BF_3Et_2O, 80%; (ii) (4-methoxyphenyl)-acetaldehyde dimethyl acetal, TsOH, CH_3CN, 70%; (iii) 4-methoxybenzyl-2,2,2-trichloroacetimidate, TfOH, THF/Et_2O, 88%; (iv) (a) $Pd(PPh_3)_4{\cdot}HCO_2H$, Et_3N, dioxane; (b) AcOH, 92%; (v) In, MeCN/0.1 N HCl, TBAI, 70%; (vi) MOMCl, $(i\text{-}Pr)_2NEt$, TBAI, 91%; (vii) DDQ, 60% two steps; (viii) Dess−Martin periodinane, 98%; (ix) SmI_2, THF/HMPT, t-BuOH, 93% (**1296a**:**1296b** = 40:60); (x) Martin's sulfurane, CCl_4, 95%; (xi) Martin's sulfurane, CCl_4; (xii) 5% AcOH, 67%, two steps (also 2-epi-**1300**, 80:20 ratio); (xiii) H_2, Pd/C, 82%; (xiv) (a) LICA, THF; (b) Ph_2Se_2; (xv) (a) H_2O_2; (b) py, two steps (two isomers, 64:36), chromatography; (xvi) (a) HCl, MeOH; (b) CH_2N_2, (c) Ac_2O, MeOH, (d) Et_3N, H_2O, DOWEX H^-, **1295a** 62%, **1295b** 57%, two steps.

Scheme 221. Gómez et al. Retrosynthesis of Carbasugars Based on a 6-*exo-dig* Radical Cyclization

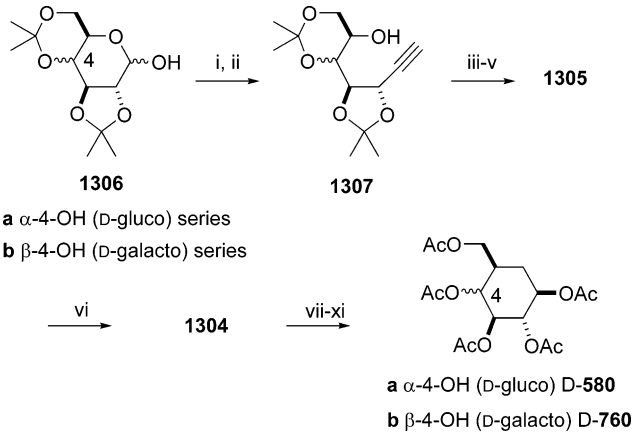


a α-4-OH (D-gluco) series

b β-4-OH (D-galacto) series

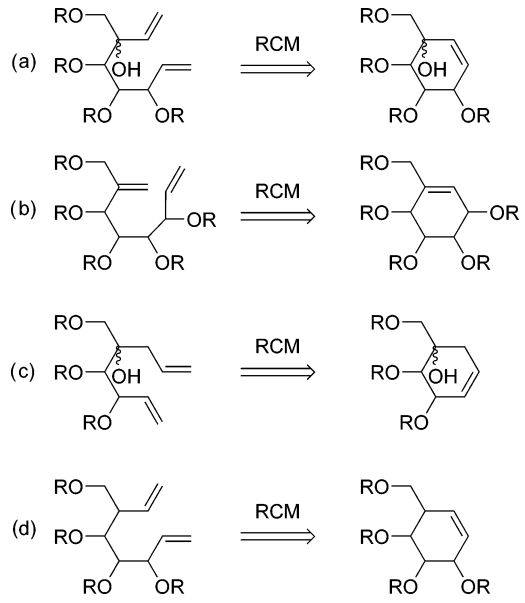
procedure.[454] After Wittig or Tebbe methylenation of **1318** followed by aldehyde deprotection and vinylmagnesium bromide addition to the carbonyl group, diene **1321** was obtained as an inseparable 70:30 epimeric mixture. The ring-closing metathesis reaction of **1321** in the presence of second-generation Grubbs' ruthenium catalyst **524b** gave cyclohexenol **929** (61% yield) along with its diastereomeric (1*S*) derivative (25% yield). Reaction of **929** with diphenylphosphoryl azide (DPPA) in the presence of DBU, followed by addition of 1 equiv of sodium azide, afforded **1322**, which was reduced to the related allylic amine by reaction with triphenylphosphine−ammonium hydroxide. Debenzylation using sodium in liquid ammonia provided valienamine, which was characterized as pentaacetate **1102**.

Scheme 222. Synthesis of 5a-Carba-*β*-D-gluco- and -galactopyranose Pentaacetates (D-580 and D-760)[a]



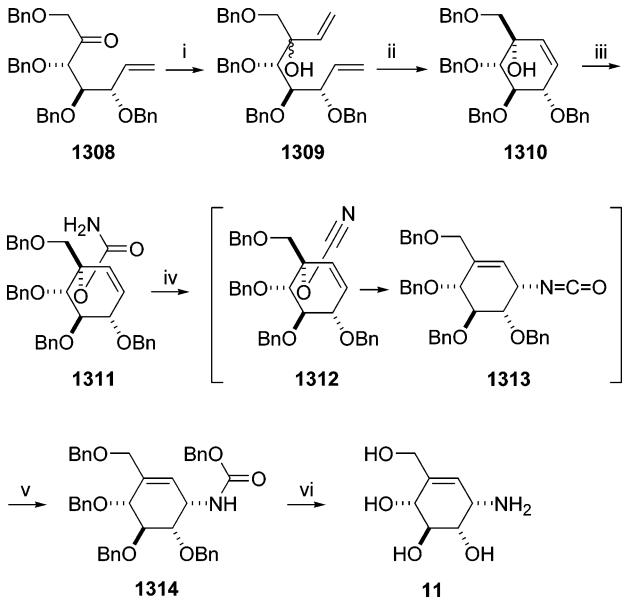
[a] Reagents: (i) (chloromethyl)triphenylphosphonium iodide, n-BuLi, DMPU (50% from **1306a**, 53% from **1306b**); (ii) n-BuLi, THF (73% from **1307a**, 75% from **1307b**); (iii) PDC, Ac_2O (**a** 82%, **b** 79%); (iv) $ClMgCH_2SiMe_3$, Et_2O (**a** and **b** 70%); (v) KH, THF (**a** 70%, **b** 68%); (vi) n-Bu_3SnH, AIBN, $PhCH_3$ (**a** 56%, **b** 75%); (vii) AcOH/THF/H_2O; (viii) Ac_2O, py (**a** 63%, **b** 72% two steps); (ix) O_3, SMe_2; (x) $BH_3{\cdot}SMe_2$; (xi) Ac_2O, py (**a** 58%, **b** 82% three steps).

Scheme 223. Retrosynthesis of Carbapyranoses from Carbohydrate Dienes Based on Ring-Closing Metathesis (RCM)



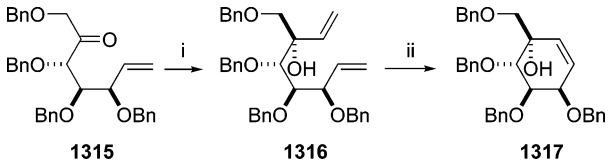
The second approach to valienamine, using RCM as in Scheme 223b, has been recently disclosed by Cumpstey (Scheme 227).[455] He described the conversion of diol **1323**, obtained as the major isomer of the vinyl magnesium addition to 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, to Fukase and Horii's intermediate for valienamine **929** (see Scheme 143). The regioselective protection of diol **1323** proved to be a difficult task, and the best result was obtained by treatment with 3,4-dimethoxybenzyl chloride (DMBCl) and NaH at 0 °C in DMF to give an inseparable 10:1 mixture of **1324** and **1325**. Pivaloylation of the mixture, removal of the DMB protecting groups, and oxidation furnished a separable mixture of ketones, from which **1326** was obtained in 81% yield. Wittig methylenation of the ketone gave diene **1327**, which smoothly underwent RCM mediated by Grubbs' second-generation catalyst, **525**, to give, after deacylation, Fukase−Horii's intermediate **929**.

Scheme 224. Synthesis of Valienamine (11) by RCM[a]



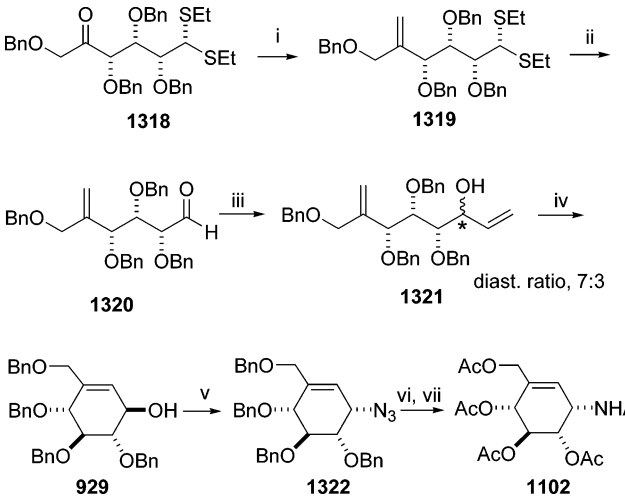
[a] Reagents: (i) vinylmagnesium bromide (86% major isomer, 1% minor isomer), separation of isomers; (ii) Grubbs' catalyst **523**, 58%; (iii) CCl_3CONCO, CH_2Cl_2, then K_2CO_3, MeOH, H_2O, 86%; (iv) PPh_3, Et_3N, CBr_4, CH_2Cl_2; (v) BnOH, 70% from **1311**; (vi) Na, NH_3/THF, 78%.

Scheme 225. Synthesis of Carbasugar Derivative 1317 by RCM[a]



[a] Reagents: (i) vinylmagnesium bromide, 95%; (ii) Grubbs' catalyst **523**, 89%.

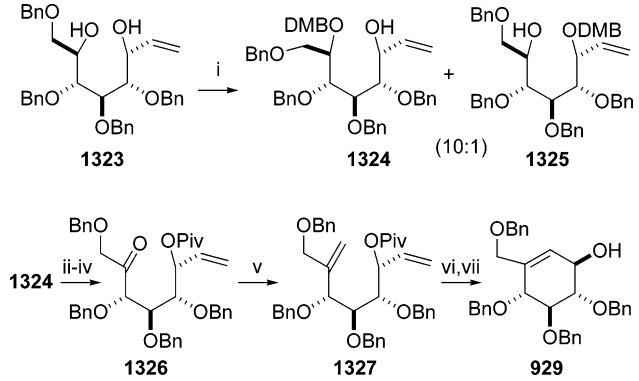
Scheme 226. Synthesis of Penta-*N,O*-acetyl Valienamine (1102) by RCM[a]



[a] Reagents: (i) Ph_3PCH_3Br, t-BuOK, PhH, 88% or Tebbe reagent (no other conditions were given), 78%; (ii) $HgCl_2$, HgO, aq CH_3CN, 80−90 °C; (iii) vinylmagnesium bromide, THF, −78 °C, 79% (two steps); (iv) Grubbs' catalyst **524**, 0.05 M, CH_2Cl_2, reflux; (v) (a) DPPA, DBU, $PhCH_3$, 0 °C; (b) NaN_3, 40 °C, 83%; (vi) Ph_3P, NH_4OH, py, 80%; (vii) (a) Na/NH_3, THF, −78 °C; (b) Ac_2O, py, 71%.

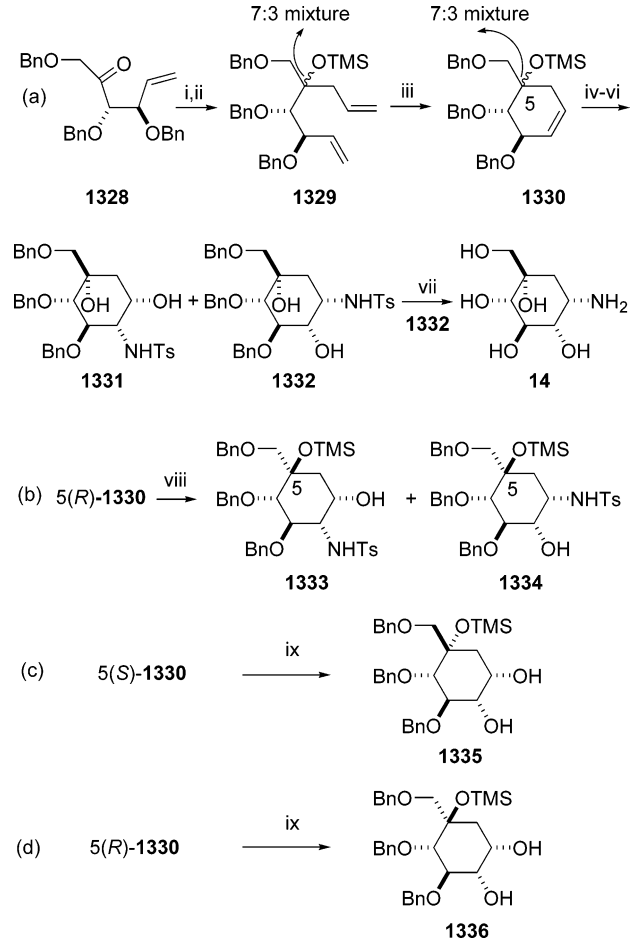
Eustache and co-workers followed the approach outlined in Scheme 223c in their synthesis of valiolamine (**14**) and carbasugar analogues from D-arabinose.[456] 2,3,5-Tri-*O*-benzyl-D-arabinose was converted to ketone **1328** (Scheme

Scheme 227. Total Formal Synthesis of Valienamine via Fukase−Horii's Intermediate 929[a]



[a] Reagents: (i) DMBCl, DMF, NaH, 0 °C, 57%, **1324/1325**, 10:1; (ii) PivCl, py, DMAP, 93%; (iii) CAN, CH_3CN, H_2O; (iv) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, chromatography, 81%; (v) Ph_3PCH_3Br, NaHDMS, THF, 63%; (vi) Grubbs' catalyst **525**, $PhCH_3$, 60 °C, 65%; (vii) NaOMe, MeOH, >99%.

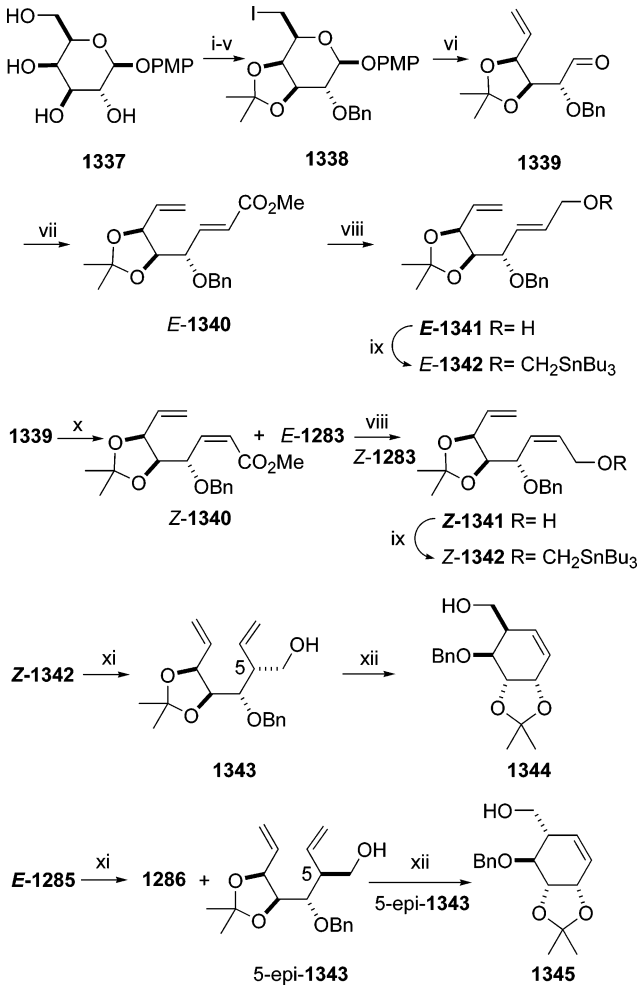
Scheme 228. Synthesis of Valiolamine (14) and Carbasugar Analogues by RCM[a]



[a] Reagents: (i) allylmagnesium bromide, 92% (7:3 epimeric mixture); (ii) TMSOTf, 2,6-lutidine, 82%; (iii) Schrock's catalyst, 92% (7:3 mixture of isomers); (iv) separation of isomers; (v) major isomer, TBAF, THF, 92%; (vi) OsO_4, chloramine T, $Et_3BnN^+Cl^-$, 5% (**1331**), 55% (**1332**); (vii) separation of regioisomers, then **1332**, Na/NH_3 liq, 50%; (viii) OsO_4, chloramine T, $Et_3BnN^+Cl^-$, 18% (**1333**), 36% (**1334**); (ix) OsO_4, NMMO, 85% (**1335**), 90% (**1336**).

228a), which, upon treatment with allylmagnesium bromide and silylation, led to epimeric dienes **1329**. The RCM reaction of the mixture of dienes **1329** was carried out with Schrock's catalyst (**526)** and furnished cyclohexenes **1330**.

Scheme 229. Synthesis of Carbasugar Analogues by RCM[a]



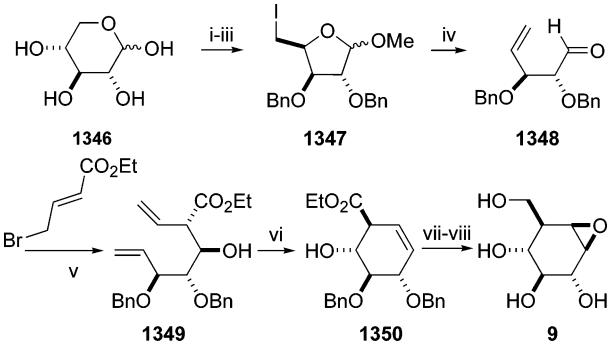
[a] Reagents: (i) TPSCl, py; (ii) dimethoxypropane, TsOH; (iii) NaH, BnBr, DMF; (iv) TBAF, THF, 88%, four steps; (v) imidazole, triiodoimidazole, PPh_3, 95%; (vi) Zn, EtOH, 99%; (vii) $PPh_3{=}CHCO_2Me$, CH_3CN, 95%; (viii) LAH, THF, 72% (*E*-**1341**), 85% (*Z*-**1341**); (ix) n-Bu_3SnCH_2I, KH, THF, 84% (*E*-**1342**), 81% (*Z*-**1342**); (x) $PPh_3{=}CHCO_2Me$, MeOH, 1:1 mixture *Z*−*E*-**1340**, 99%; (xi) n-BuLi, THF, 67% (**1343**), 62% (3:2 mixture, **1343** and 5-epi-**1343**); (xii) Grubbs' catalyst **523**, 68% (**1344**), 79% (**1345**).

cis-Aminohydroxylation of the desilylated major isomer 5(*S*)-**1330** furnished valiolamine (**14**). *cis*-Aminohydroxylation of 5(*R*)-**1330** led to a mixture of protected 5-epi-valiolamine (**1333**) and isomer **1334** (Scheme 228b). Finally, *cis*-dihydroxylation of cyclohexenes 5(*S*)-**1330** and 5(*R*)-**1330** (Scheme 228c,d) was completely stereoselective, leading to functionalized carbasugar derivatives **1335** and **1336**, respectively.

Van Boom and co-workers reported the approach outlined in Scheme 223d in their synthesis of carbasugar derivatives **1344** and **1345** (Scheme 229).[457] Their synthetic route (Scheme 229) started with primary iodide **1338** prepared from *p*-methoxyphenyl-*β*-D-galactopyranoside (**1337**). Wittig reaction of open-chain aldehyde **1339**, obtained by Vasella's rearrangement[458] of **1338**, led to dienes *Z*- and *E*-**1340**, which were finally transformed into 1,7-dienes **1343** and 5-epi-**1343** by a [2,3]-Wittig−Still rearrangement.[459] RCM of these dienes, with Grubbs' catalyst, led to carbasugar derivatives **1344** and **1345**.

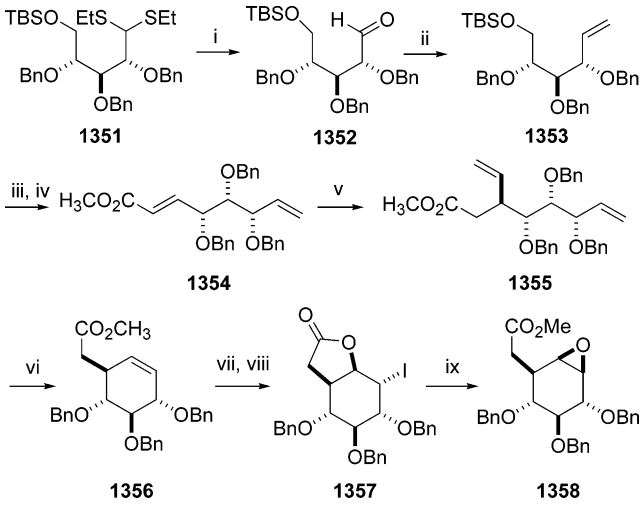
Madsen and co-workers have recently disclosed an additional example of the ring closure outlined in Scheme 223d in their approach to cyclophellitol (Scheme 230).[460] Their

Scheme 230. Madsen's Group Synthesis of Cyclophellitol (9) by RCM[a]



[a] Reagents: (i) MeOH, HCl; (ii) I_2, PPh_3, imidazole, THF, 74% (two steps); (iii) $BnOC(NH)CCl_3$, TfOH, dioxane, 90%; (iv) Zn, THF/H_2O, 78%; (v) Grubbs' catalyst **524**, CH_2Cl_2, 91%; (vi) DIBAL-H, THF, then $NaBH_4$, H_2O, 64%; (vii) MCPBA, CH_2Cl_2, 56%; (viii) H_2, $Pd(OH)_2/C$, MeOH, 100%.

Scheme 231. Synthesis of Cyclophellitol Derivative 1358 by RCM[a]



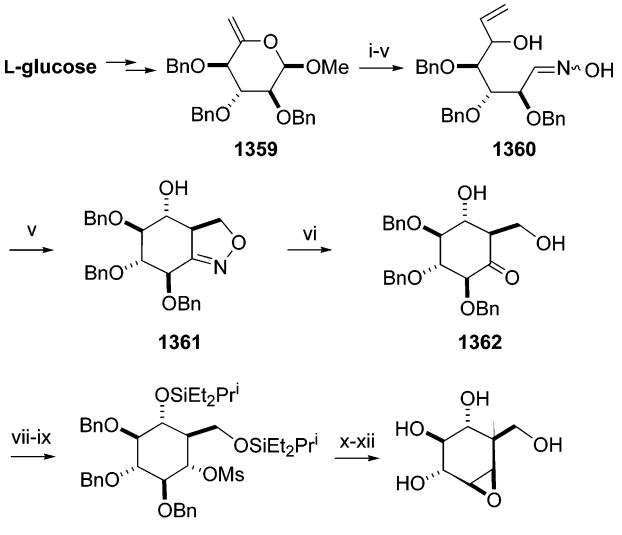
[a] Reagents: (i) HgO, $HgCl_2$, acetone−H_2O, reflux, 80%; (ii) $Cp_2TiClAlMe_3$, py, $PhCH_3$−THF, −78 °C, 80%; (iii) DMSO, $COCl_2$, Et_3N, CH_2Cl_2, −78 °C; (iv) Ph_3PCHCO_2Me, CH_2Cl_2, −30 to −25 °C, 89% (two steps); (v) $(CH_2{=}CH)_2CuMgBr$, TMSCl, THF, −78 °C, 90%; (vi) Grubbs' catalyst **523**, 0.02 M CH_2Cl_2, 60 h, 92%; (vii) LiOH, aq THF, 25 °C; (viii) KI, I_2, $KHCO_3$, aq THF, 92% (two steps); (ix) Na_2CO_3, MeOH, 98%.

synthesis takes place in eight steps and 14% overall yield and uses three consecutive organometallic reactions as the key steps. Thus, zinc-mediated fragmentation of iodide **1347**, readily obtained from D-xylose (**1346**), indium-mediated coupling between **1348** and ethyl 4-bromocrotonate, and ruthenium-catalyzed RCM of **1349** paved the way to cyclohexene **1350**. The latter was reduced and deprotected to furnish **9**.

An earlier synthesis of **9** by RCM had already been described by Ziegler and co-workers (Scheme 231).[461] Methylenation of **1352**, prepared from thioacetal **1351**, under Tebbe's conditions provided alkene **1353**, which was transformed into the α,β-unsaturated ester **1354**. Conjugate addition of magnesium-based vinyl cuprate, using conditions previously described by Hanessian,[462] afforded diene **1355** with both high yield and selectivity. Ring-closing metathesis reaction of **1355** followed by iodolactonization and basic treatment yielded cyclophellitol precursor **1358**.

6.2.2.5. Cycloaddition Reactions. The 1,3-dipolar intramolecular cycloaddition reaction of carbohydrate derivatives constitutes a powerful tool for the preparation of hydroxylated cyclohexane derivatives. In such processes, the key intermediates, nitrile oxides, nitrones, or silyl nitronates, are generated *in situ* and then intramolecularly trapped by the alkene to give an heterocycle, which at a later stage can be ring-opened to provide the desired carbocycle.

Scheme 232. Synthesis of Cyclophellitol (9) by Intramolecular 1,3-Dipolar Cycloaddition[a]



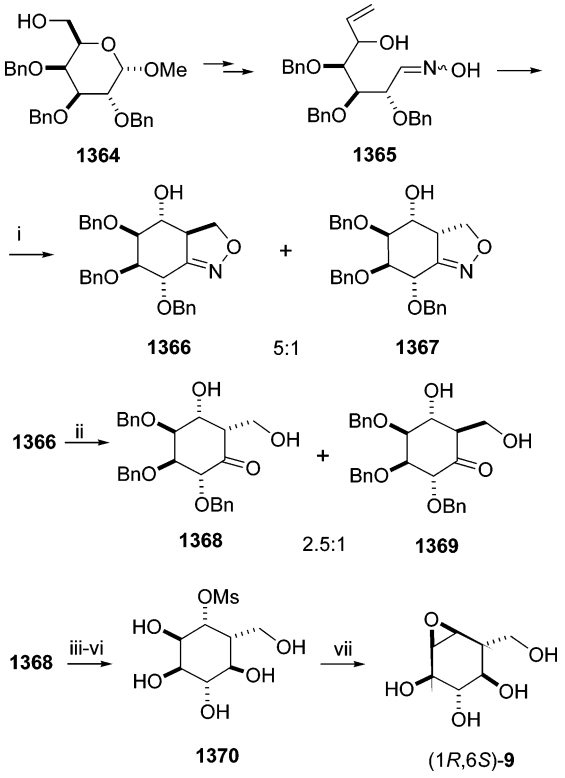
[a] Reagents: (i) dicyclohexylborane, THF, then H_2O_2, NaOH, 85%; (ii) oxalyl chloride, DMSO, Et_3N, then PH_3PCH_2, 75%; (iii) HCl, aq dioxane; (iv) H_2NOH, py, 80% (two steps); (v) NaOCl, CH_2Cl_2, 70%; (vi) H_2, Raney-Ni W-4, aq dioxane, AcOH, 80%, py, 89%; (vii) i-Pr(Et)$_2$SiOTf, 2,6-lutidine, 90%; (viii) BH_3[zmd]SMe_2, 60%; (ix) MsCl, py, 75%; (x) H_2, $Pd(OH)_2$; (xi) NaOMe, CH_2Cl_2, 0 °C; (xii) TBAF, THF, 40% (three steps).

In 1990, Tatsuta et al.[435a] described the first total synthesis of the carbasugar-related inhibitor (+)-cyclophellitol (**9**), with the key step of the strategy being an intramolecular [3 + 2] cycloaddition reaction of a nitrile oxide to an alkene (Scheme 232). Accordingly, L-xylo-hex-5-enopyranoside (**1359**), prepared in several steps from L-glucose, was transformed into oximes **1360** and then oxidized with NaOCl to obtain the isoxazoline **1361** as a single product. Opening of the heterocycle was then achieved by hydrogenolysis in acidic media to afford the corresponding keto-diol **1362**, which was finally converted to cyclophellitol (**9**).

The same strategy was used for the preparation of cyclophellitol analogues, needed for structure−activity relationship studies (Scheme 233). In order to gain access to (1*R*,6*S*)-cyclophellitol,[463] the main adduct (**1366**) resulting from the intramolecular 1,3-dipolar cycloaddition of galactose derivative **1364** was subjected to hydrogenolysis under acidic conditions in order to promote epimerization of the hydroxymethyl substituent α to the ketone. Further transformations of the correct keto-diol **1368** permitted access to (1*R*,6*S*)-**9** (Scheme 224). This protocol was also exploited for the synthesis of aziridine[464] and thiirane analogues of cyclophellitol.[465]

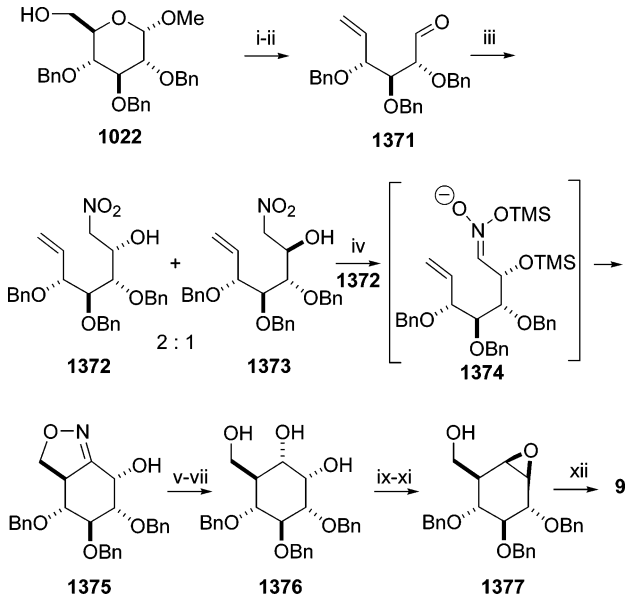
Ishikawa and collaborators[466] also exploited an intramolecular dipolar cycloaddition reaction in their approach to cyclophellitol (**9**) (Scheme 234). The Henry reaction of nitromethane with a D-glucose derivative provided the authors with the required additional carbon atom and the nitro group, which would serve as the reaction partners in a nitronate−olefin cycloaddition process. The bromination and zinc-mediated reductive cleavage of D-glucose derivative **1022** gave enal **1371**. The aldehyde was treated with

Scheme 233. Synthesis of (1*R*,6*S*)-Cyclophellitol, by Intramolecular 1,3-Dipolar Cycloaddition[a]



[a] Reagents: (i) NaOCl, CH_2Cl_2, 90%; (ii) H_2, Raney-Ni W-4, aq dioxane, AcOH, 70%; (iii) BH_3 Me_2S, 80%; (iv) i-Pr(Et)$_2$SiOTf, imidazole, 60%; (v) MsCl, py, 75%; (vi) H_2, $Pd(OH)_2$, 90% two steps; (viii) NaOMe, CH_2Cl_2, 0 °C, 80%.

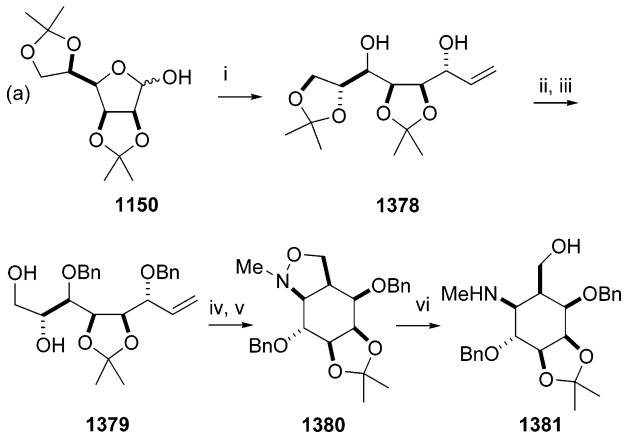
Scheme 234. Synthesis of Cyclophellitol by Intramolecular Silyl Nitronate Cycloaddition[a]



[a] Reagents: (i) CBr_4, Ph_3P, CH_2Cl_2; (ii) Zn, 80% MeOH, reflux; (iii) CH_3NO_2, 1,1,3,3-tetramethylguanidine, THF, 58% from **1022**; (iv) TMSCl, Et_3N, DMAP, THF; (v) TsOH, THF, 55% from **1372**; (vi) TBSOTf, Et_3N, CH_2Cl_2, 95%; (vii) $Mo(CO)_6$, CH_3CN, 90 °C; (viii) DIBAL-H, $PhCH_3$, −78 °C, 51% (two steps); (ix) trimethyl orthoformate, Ac_2O, 140 °C; (x) K_2CO_3, MeOH; (xi) MCPBA, 56%; (xii) H_2, Pd/C, 90%.

nitromethane, and one of the resulting nitroalcohols, **1372**, converted stereoselectively to oxazoline **1375** by intervention of the corresponding silyl nitronate, **1374**. The oxazoline was then transformed, by $Mo(CO)_6$-mediated reductive N−O bond cleavage and selective protective group manipulations, into the pivotal triol **1376**, which was uneventfully converted to cyclophellitol (**9**).

Scheme 235. Synthesis of Aminocarbasugar Analogue 1381[a]



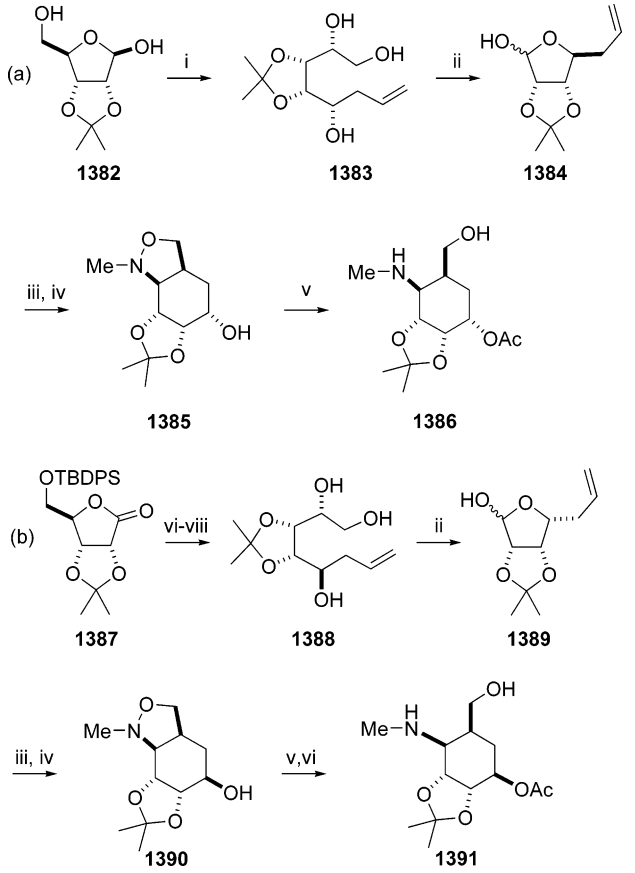
[a] Reagents: (i) $CH_2CHMgBr$, THF, 93%; (ii) $PhCH_2Br$, NaH, THF, 79%; (iii) aq AcOH, 64%; (iv) $NaIO_4$, aq MeOH; (v) MeHNOH·HCl, $NaHCO_3$, aq EtOH, reflux, 65% (2 steps); (vi) H_2, $Pd(OH)_2$, EtOH, AcOH, 60%.

Reactions involving nitrones as intermediates have also been developed for the synthesis of aminocarbasugars by several groups. Shing and co-workers[232] described a short method of preparing five- and six-membered carbasugars involving a stereoselective intramolecular nitrone cycloaddition as the key step. In their protocol, they converted 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**1150**) into diol **1378** by chellation-controlled addition of vinylmagnesium bromide (Scheme 235). Diol **1378** was then protected as the corresponding benzyl ether, which was selectively hydrolyzed to form the vicinal diol **1379**. Glycol cleavage, oxidation followed by immediate reaction with *N*-methylhydroxylamine, and *in situ* cyclization then gave isoxazolidine **1380** as the major adduct in *ca.* 6:1 stereoselectivity. Selective hydrogenolysis of the N−O bond in **1380** furnished the functionalized aminocarbasugar **1381**.

In a closely related work, Singh and collaborators[467,468] prepared aminocarbasugars using intramolecular nitrone cycloaddition reactions of D-ribose derivatives (Scheme 236). Diastereoselective addition of diallylzinc to 2,3-*O*-isopropylidene-D-ribose (**1382**) gave the D-allo-triol **1383** whereas treatment of 2,3-*O*-isopropylidene-D-ribonolactone (**1387**), with allylmagnesium chloride, followed by reduction with DIBAL and desilylation yielded the isomeric triol **1388**. Periodate cleavage of both triols, **1383** and **1388**, gave hemiacetals **1384** and **1389**, which, on treatment with *N*-methylhydroxylamine followed by heating of the crude nitrones in toluene, led to the cycloadducts **1385** and **1390**, respectively. Final hydrogenation of isoxazolidines **1385** and **1390** over Pearlman's catalyst gave acetyl 4-deoxy-4-methylaminocarba-α- and -β-D-talopyranosides (**1386** and **1391**, respectively) in quantitative yield. This strategy has been recently applied by the same group to the synthesis of carbasugar derivatives in which the hydrogens of the 5a-methylene group in the carbasugar have been replaced by fluorine atoms, on the assumption that these fluorinated compounds would have modified biological activities owing to the electronic and stereoelectronic effects associated with the fluorine atoms.[469]

During the synthesis of potential α-glucosidase inhibitors with an aminocarbasugar structure (i.e., **1398**), Farr et al.[470] examined the diastereoselectivity of the intramolecular nitrile

Scheme 236. Synthesis of Aminocarbasugars from D-Ribose[a]



[a] Reagents: (i) diallylzinc, Et_2O, 93%; (ii) $NaIO_4$, aq MeOH; (iii) MeHNOH·HCl, $NaHCO_3$, aq EtOH, reflux, 98% for **1384**, quant for **1389**; (iv) $PhCH_3$, reflux, 68% for **1385**, 95% for **1390**; (v) Ac_2O, py, 4-DMAP, quant; (vi) $Pd(OH)_2$/C, MeOH, quant; (vi) allylmagnesium chloride, THF, −78 °C, MeOH, quant; (v) DIBAL-H, $PhCH_3$, −78 °C; (vi) TBAF, THF, 63% (three steps).

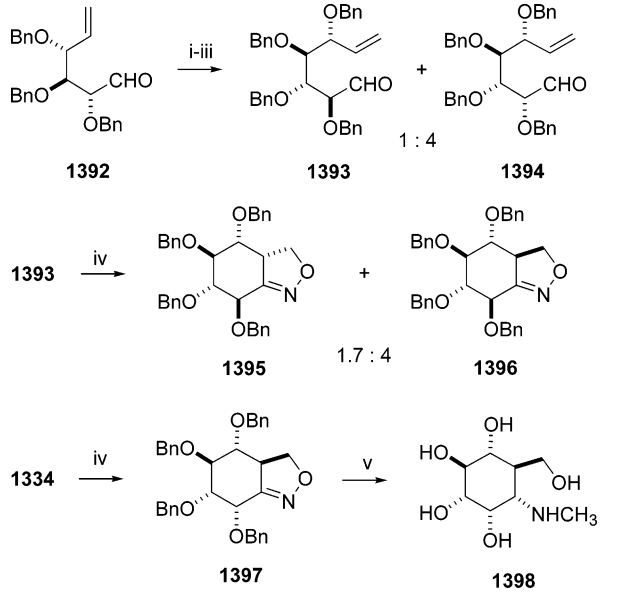
oxide, nitrone, and oxime cycloaddition reaction of olefinic aldehydes **1393** and **1394** (Scheme 237). In all cases, the configuration of the 2-OH in the aldose largely determines the stereoselectivity of the ring closure in the cycloaddition reactions.

6.2.2.6. Claisen Rearrangement. Nagarajan and Sudha reported the Claisen rearrangement of diene glycal **1401** as an efficient entry to carbasugars (Scheme 238).[471] They have developed the transformation of a glycal derivative into a cyclohexanic derivative, which after controlled hydroxylation led to three carbasugars: 5a-carba-α-D-glucopyranose (D-**81**), 5a-carba-α-D-mannopyranose (D-**587**), and 5a-carba-*β*-D-glucopyranose (D-**79**). Thus, diene **1401**, prepared by Wittig reaction of aldehyde **1400**, was heated in a sealed tube at 240 °C to afford the rearranged carbocycle **1402** in 84% yield. Reduction of the aldehyde led to **1403** (Scheme 238a), which upon catalytic OsO_4 dihydroxylation, from the less hindered *β*-face, gave after debenzylation 5a-carba-α-D-glucopyranose (D-**81**) (Scheme 238b). On the other hand, MCPBA treatment of benzyl ether **1405** and acid-catalyzed aqueous opening of the ensuing epoxide led to a mixture of diols that were processed separately by catalytic hydrogenolysis to 5a-carba-α-D-mannopyranose (D-**587**) and 5a-carba *β*-D-glucopyranose (D-**79**) (Scheme 238c).

6.2.3. From Other Natural Sources

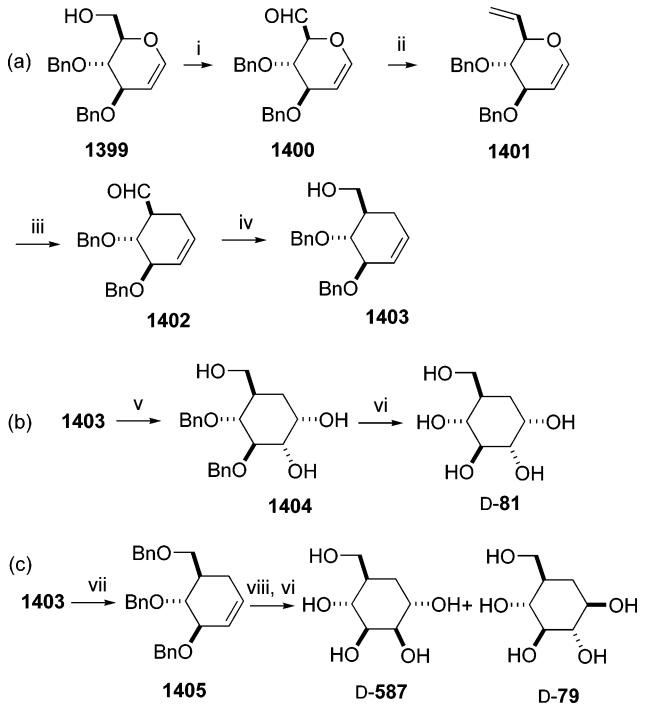
6.2.3.1. From Quinic Acid. The cyclohexane skeleton and the rich functionality present in (−)-quinic acid (**1406**), as well as its relatively low cost, have made it an attractive optically active precursor for the synthesis of carbasugars and derivatives.[472] Molin et al.[473] reported the first example of the synthesis of a carbasugar from **1406** (Scheme 239). Thus, acetalization of **1406** in acidic media proceeds with concomitant lactonization the give lactone **1407**. Opening of the lactone ring and careful oxidation of the released

Scheme 237. Synthesis of Aminocarbasugar Derivatives[a]



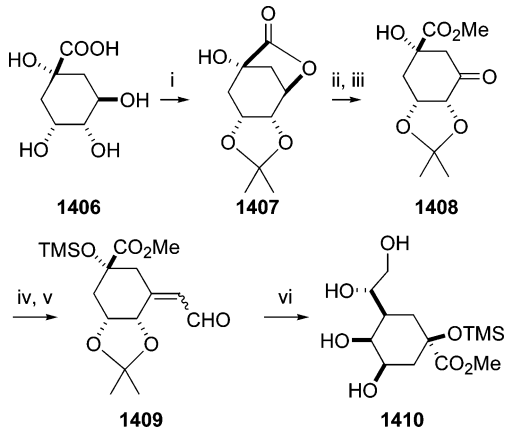
[a] Reagents: (i) n-BuLi, 1,3-dithiane, THF, −30 °C, then **1392**; (ii) $PhCH_2Br$, NaH, DMF, 67%, two steps; (iii) NCS, $AgNO_3$, aq CH_3CN, 51%; (iv) NH_2OH, MeOH, then NaOCl, 75% from **1393** and 82% from **1394**; (v) H_2, Pd/C, HOAc, 76%.

Scheme 238. Synthesis of 5a-Carba-α-D-glucopyranose (D-81), 5a-Carba-α-D-mannopyranose (D-587), and 5a-Carba-*β*-D-glucopyranose (D-79)[a]



[a] Reagents: (i) PDC, 4A molecular sieves, CH_2Cl_2, 65%; (ii) Ph_3MePl, $NaNH_2$, Et_2O, 62%; (iii) *o*-dichlorobenzene, 240 °C, 84%; (iv) $NaBH_4$, THF, 90%; (v) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, t-BuOH, H_2O, 95%; (vi) 20% $Pd(OH)_2$/C, H_2, 55 psi, 100% (all cases); (vii) NaH, DMF, BnBr, 85%; (viii) MCPBA, H_2O, 10% H_2SO_4, 48 h (34% D-**587**; 26% D-**79**).

Scheme 239. Synthesis of the Carbasugar Analogue of *β*-KDO (1410)



[a] Reagents: (i) acetone, H^+, 85%; (ii) MeOH, NaOMe; (iii) $CrO_3 \cdot 2Py$, CH_2Cl_2, 15 min, 65% (two steps); (iv) Me_3SiCl, Et_3N, DMAP, 80%; (v) LDA, diethyl chlorophosphate, −70 °C, THF, then HOOC−COOH, H_2O, 63%; (vi) 9-BBN, THF, 0 °C, then $BH_3 \cdot$THF, −30 °C, then H_2O_2, NaOAc, 20%; (vii) PPTS, EtOH, 55 °C, 6% (three steps).

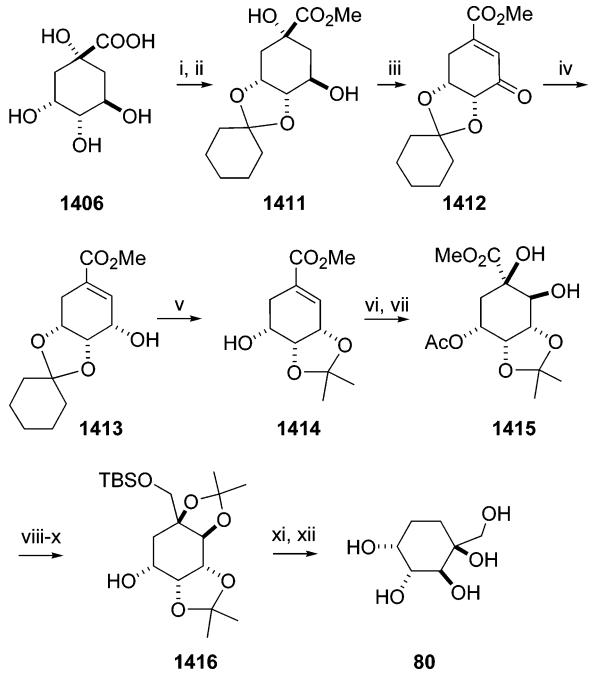
hydroxyl group gave ketone **1408**. After protection of the tertiary alcohol, the side chain was introduced via a modified Wittig reaction to give enals **1409**. Reduction of the aldehyde moieties in **1409** with 9-BBN followed by hydroboration of the double bond and alkaline peroxide oxidation yielded, after deprotection, the carbasugar analogue of 3-deoxy-*β*-D-manno-2-octulopyranosonic acid (*β*-KDO) **1410**.

In a series of papers, Shing and co-workers described their extensive efforts in the application of (−)-quinic acid (**1406**) as the chiral educt to the preparation of carbasugars and related compounds. They reported the first enantioselective preparation of carba-*β*-D-fructopyranose (**80**) (Scheme 240).[474] Thus, oxidation of the alcohol **1411**, obtained from **1406** in two steps, with PCC gave the unsaturated enone **1412**, which was then stereoselectively reduced with $NaBH_4$ to form alcohol **1413**. Thermodynamically controlled isopropylidenation of **1413** gave the more stable acetonide **1414**, which was esterified to the corresponding acetate. Stereocontrolled hydroxylation of the double bond was then successfully used to obtain diol **1415**. Protection of the diol **1415**, subsequent reduction with DIBAL-H, and silylation produced alcohol **1416**, which was further elaborated to carba-*β*-D-fructopyranose (**80**) by a two-step sequence involving radical deoxygenation and eventually deprotection.[475,476]

McComsey and Maryanoff streamlined this route by conducting the deoxygenation step at an earlier stage.[477] Thus, the α,*β*-unsaturated ketoester **1414** was readily deoxygenated by a radical-based methodology to give enoate **1417** in good yield. These findings paved the way to both carba-*β*-D-fructopyranose (D-**80**) and to carbasugar derivative **1420**, a carba-isostere of the clinically useful antiepileptic drug topiramate (**1421**) (Scheme 241a). Since enantiomeric (+)-quinic acid is not readily available, a different route was later developed by the same group for the preparation of the enantiomers L-**80** and L-**1420**.[478] The starting material in this case was (1*S*,2*R*)-1,2-dihydroxycyclohexa-3,5-diene-1-carboxylic acid (**1422**) prepared by microbial oxidation of benzoic acid with *Alcaligenes eutropyus* strain B9.4 (Scheme 241b).[479]

Following the sequence developed by McComsey and Maryanoff,[477] Shi and co-workers prepared several carbocyclic analogues of fructopyranose-derived ketones and used them as chiral reagents for asymmetric epoxidation of *trans*-olefins.[480]

Scheme 240. Synthesis of 5a-Carba-*β*-D-fructopyranose (80)[a]

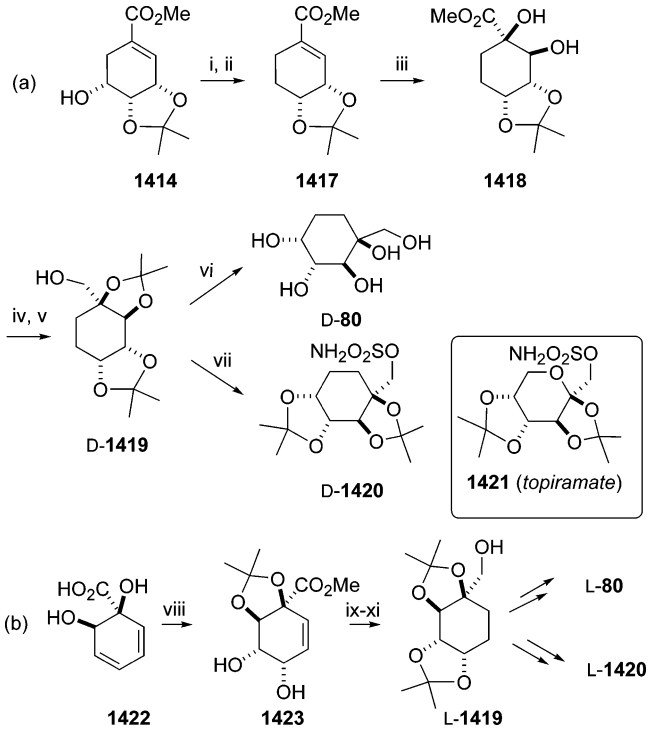


[a] Reagents: (i) cyclohexanone, PhH, DMF, Dowex 50WX8, 79%; (ii) NaOMe, MeOH; (iii) PCC, 3A molecular sieves, py, CH_2Cl_2, 90%; (iv) $NaBH_4$, MeOH, 0 °C, 82%; (v) acetone, TsOH, 88%; (vi) Ac_2O, py, 100%; (vii) OsO_4, trimethylamine-*N*-oxide, py, H_2O, t-BuOH, 90%; (viii) 2-methoxypropene, CSA, CH_2Cl_2, 70%; (ix) DIBAL-H, THF, 0 °C, 79%; (x) TBSCl, imidazole, DMAP, CH_2Cl_2, 91%; (xi) phenyl chlorothionoformate, py, DMAP, CH_2Cl_2, then n-Bu_3SnH, AIBN, toluene, 82%; (xii) 50% aq TFA, 65%.

As an extension of their initial studies in the synthesis of carba-*β*-D-fructopyranose, Shing and co-workers prepared many useful quinic acid-related precursors for carbasugar synthesis. For instance, DIBAL-H reduction of enone **1412** furnished diol **1424**, which was shown to be a useful intermediate for the synthesis of different carbasugars. Protection, as silyl ethers, of the hydroxyl groups in **1424** followed by hydroboration of the double bond and alkaline peroxide oxidation paved the way to cyclohexane derivative **1425**, which was converted to 5a-carba-*β*-D-mannopyranose (D-**590**) (Scheme 242a).[481,482] Protection, as benzyl ethers, of the hydroxyl groups in **1424**, followed by the stereocontrolled hydroboration−oxidation sequence and subsequent esterification, gave the acetyl derivative **1426**. Corey−Winter deoxygenation of the diol arising from **1426** yielded key olefin intermediate **1427** (Scheme 242b), which was a suitable substrate for either *cis*- or *trans*-dihydroxylation leading to diols **1428** or **1429**, which are precursors to 5a-carba-α-D-glucopyranose (D-**81**) and 5a-carba-α-D-mannopyranose (D-**587**), respectively (Scheme 242c,d).

Additionally, diol **1424** has been used by Shing and co-workers as the starting material for the synthesis of several related compounds, including an inhibitor of glyoxalase COTC,[474] cyclophellitol and its diastereomers,[483−485] (+)-crotoepoxide,[486] validamine and its C_2 epimer,[487] and valiolamine and its diastereomers (Scheme 243).[488,489] Thus, the cyclic sulfate **1430**, prepared from **1424** by standard functional group transformations, underwent regioselective ring opening with different nucleophiles (PhSeNa or Bu_4NI), with the degree of regioselectivity being strictly connected with the size of the nucleophile, to provide, after elimination, the

Scheme 241. Synthesis of Carbasugar Analogues of Fructopyranose (80) and Topimarate (1420)[a]



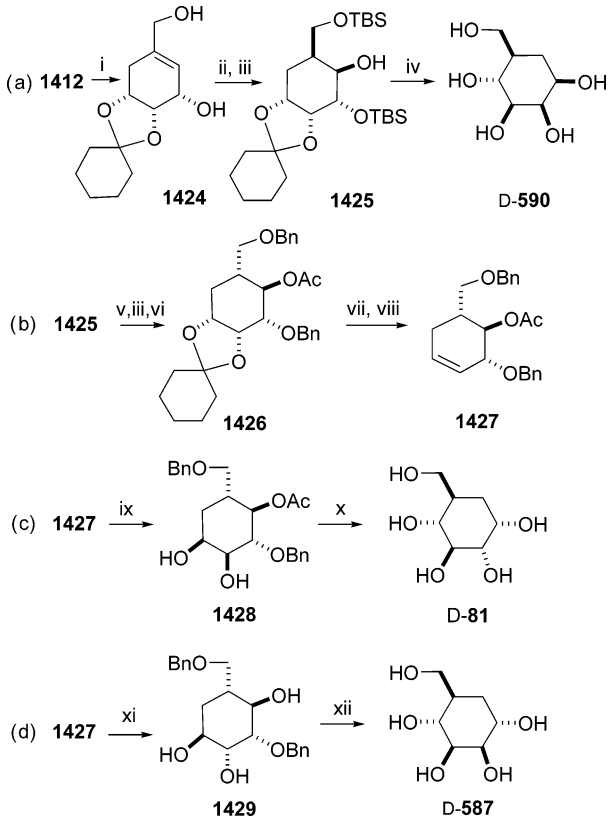
[a] Reagents: (i) phenyl chlorothionoformate, py, 67%; (ii) n-Bu_3SnH, (t-$BuO)_2$, $PhCH_3$, reflux, 76%; (iii) OsO_4, trimethylamine-*N*-oxide, py, H_2O, t-BuOH, 81%; (iv) 2-methoxypropene, CSA, CH_2Cl_2, 80%; (v) DIBAL-H, THF, 0 °C, 75%; (vi) 50% aq TFA, 91%; (vii) NH_2SO_2Cl, Et_3N, DMF, 0 °C, 64%; (viii) trimethylsilyldiazomethane, MeOH, PhH, 96%; then DMP, HCl, acetone, 98%; then OsO_4, NMMO, t-BuOH, H_2O, acetone, 73%; (ix) H_2, Pd−C, EtOAc, 95%; (x) DMP, HCl, acetone, 80%; (xi) DIBAL-H, THF, 85%.

key intermediate **1431**. The configuration of the hydroxyl group in **1431** was inverted, via Mitsunobu reaction, to **1432**, which was subsequently treated with *m*-chloroperbenzoic acid to give an inseparable mixture of oxiranes **1433**, which upon deprotection generated cyclophellitol (**9**) and its (1*R*,-6S)-diastereoisomer.[484]

Cyclic sulfates (i.e., **1430**, **1436**) have been key intermediates in the synthesis of validamine (**12**) and (1*R*-,2*R*)-valiolamine (or 1-epi-2-epi-valiolamine) (**1439**) (Scheme 244). The nitrogen functionality was introduced, in **1434** and **1435**, by employing a regioselective opening of the cyclic sulfate by azide anion. Inversion of the adjacent stereogenic center by trifluoromethanesulfonylation, and subsequent displacement with tetrabutylammonium acetate and hydrolysis gave alcohols **1435** and **1438**. Deacylation and hydrogenolysis then led to 5a-carbaaminopyranoses **12** and **1439**.[487,489]

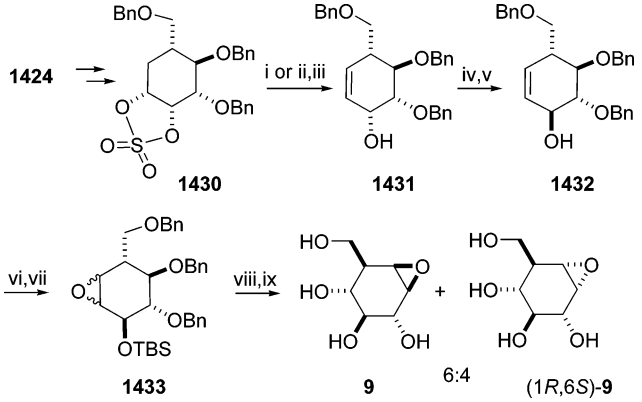
Additionally, the same group developed two different routes for the synthesis of valienamine (**11**), in which the elimination of the tertiary alcohol from quinic acid was used to install the double bond in the required position. The first approach (Scheme 245a) uses the regioselective opening of a cyclic sulfite, **1441**, by lithium azide, to generate a 2-epi-valienamine derivative, **1442**, that was processed by inversion of the configuration at C_2 to provide the target molecule **11**.[490] In the second route (Scheme 245b), valienamine (**11**) was produced directly from a cyclohexene precursor in which the configuration at C_2 was first established by a two-step sequence and, then, the nitrogen functionality was efficiently introduced in an allylic acetate, **1446**, using a palladium-

Scheme 242. Synthesis of Carbapyranoses by Shing et al.[a]



[a] Reagents: (i) DIBAL, $PhCH_3$, 0 °C, 90%; (ii) TBSCl, imidazole, DMAP, CH_2Cl_2, 100%; (iii) 9-BBN, THF, then 3 M NaOH, H_2O_2, 86% for **1425**, 94% for **1426**; (iv) 50% aq TFA, 100%; (v) NaH, BnBr, TBAI, THF, 72%; (vi) Ac_2O, py, DMAP, 97%; (vii) TFA, CH_2Cl_2, 97%; (viii) 1,1′-thiocarbonyldiimidazole, toluene, reflux, then $(MeO)_3P$, reflux, 85%; (ix) OsO_4, trimethylamine-*N*-oxide, py, H_2O, t-BuOH, 90%; (x) NaOMe, MeOH, then Rh−C, H_2, EtOH, 81%; (xi) HCOOH, H_2O_2, reflux, then NaOH, THF, reflux, 45%; (xii) $Pd(OH)_2$, H_2, EtOH, 100%.

Scheme 243. Synthesis of Cyclophellitol and (1*R*,6*S*)-Cyclophellitol by Shing et al.[a]

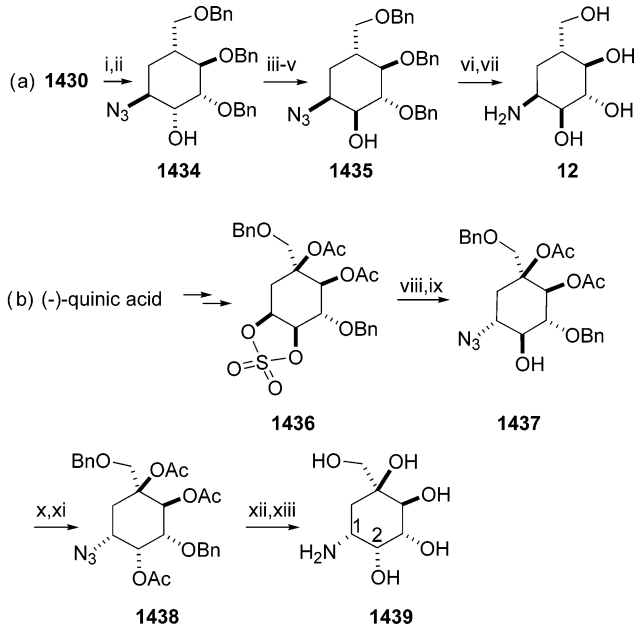


[a] Reagents: (i) TBAI, THF, reflux, then DBU, xylene, reflux, H_2SO_4, H_2O, THF, 61%; (ii) PhSeNa, EtOH, THF, 0 °C, H_2SO_4, H_2O, 80%; (iii) MCPBA, CH_2Cl_2, −40 °C, then $(i\text{-}Pr)_2NEt$, $PhCH_3$, 80 °C, 72%; (iv) PhCOOH, DIAD, PPh_3, $PhCH_3$, 0 °C, 93%; (v) K_2CO_3, MeOH, 94%; (vi) TBSCl, imidazole, DMAP, CH_2Cl_2, 91%; (vii) MCPBA, CH_2Cl_2, 72%; (viii) TBAF, THF, 94%; (ix) Pd−C, H_2, EtOH, 93%.

catalyzed reaction.[491] Application of this Pd-catalyzed coupling reaction allowed the preparation of *N*-alkylated 2-epi-valienamines.[492]

More recently, González and co-workers have recognized quinic acid-derived lactone **1448** as a good starting material to access a wide range of carbasugar derivatives (Scheme

Scheme 244. Synthesis of Validamine (12) and 1-Epi-2-epi-valiolamine (1439) by Shing et al.[a]



[a] Reagents: (i) LiN_3, DMF, 105 °C; (ii) H_2SO_4, H_2O, THF, 82%, two steps (5.7:1 diastereomeric mixture, **1434** major isomer); (iii) Tf_2O, py, CH_2Cl_2, 96%; (iv) n-Bu_4NOAc, THF, 80 °C, 81%; (v) NaOMe, MeOH, 98%; (vi) H_2, Ra−Ni, EtOAc; (vii) Na, liq NH_3, THF, −78 °C, 36%, two steps; (viii) LiN_3, DMF, then H_2SO_4, THF, 50%; (ix) K_2CO_3, MeOH, 88%; (x) Tf_2O, py, CH_2Cl_2, 78%; (xi) n-Bu_4NOAc, THF, 80 °C, 95%; (xii) K_2CO_3, MeOH, 80%; (xiii) H_2, $Pd(OH)_2$, EtOH, 73%.

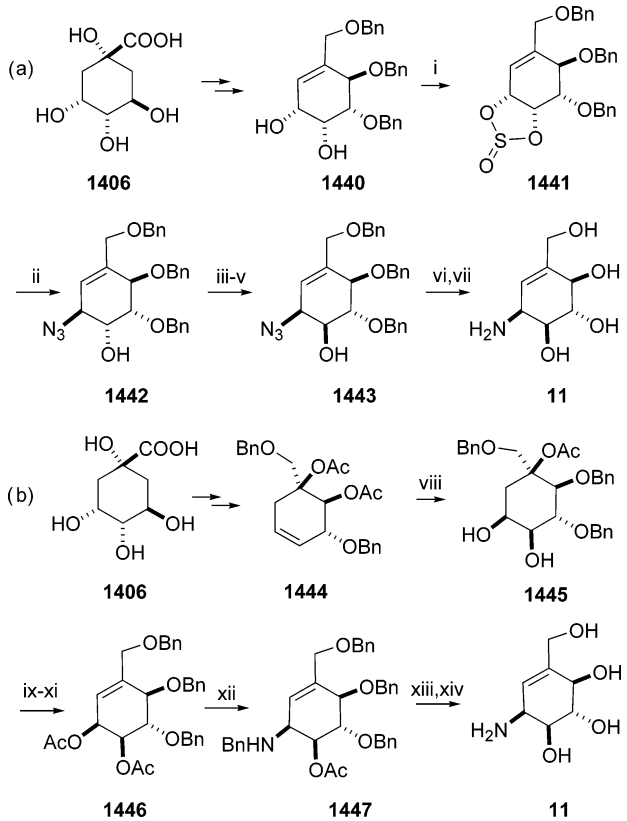
246).[493] This biased intermediate, that can be obtained in three steps from quinic acid, benefits from a diastereoselective oxidation at the 5,6-double bond with either OsO_4 or MCPBA to obtain *cis*-analogues **1449** and **1450** or *trans*-derivatives **1451** and **1452**, respectively.[494] They have extended this strategy to the synthesis of aminocarbasugars which are positional stereoisomers of valiolamine.[495]

Quinic acid (**1406**) has been utilized by Peseke et al. as a building block for the syntheses of pyrazolo- and pyrimido-anellated carbasugars with defined stereochemistry (Scheme 247).[496] Ketone **1453**, available in four steps from **1406**, was subjected to treatment with carbon disulfide and alkyl halide in the presence of bases to afford the corresponding ketene dithioketal **1454**. This push−pull activated methylenecyclohexanone **1454** underwent a ring closure reaction with methylhydrazine hydrate to give the pyrazoloanellated carbasugar **1455**.

In the context of the synthesis of sialyl Lewis^x mimetics in which the D-galactose residue is replaced with appropriate glycomimetics, Hanessian et al. described the synthesis of the 4-deoxy-5a-carba-D-mannopyranose derivative **1458**, from quinic acid (Scheme 248).[497] Thus, methyl ester **1456** was subjected to oxidation, followed by β-elimination to afford the α,β-unsaturated ester derivative **1457**. Catalytic hydrogenation followed by reduction of the ester function gave the desired alcohol **1458**. This unit was further used to prepare pseudodisaccharide **1459**, which was found to be inactive in binding to E-selectin.

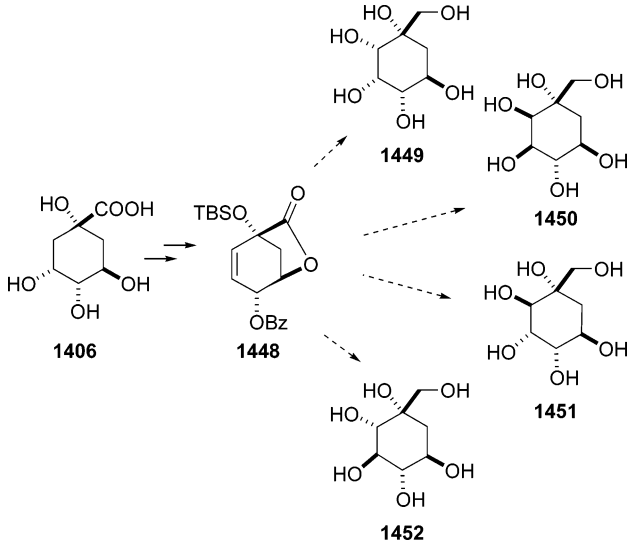
Quinic acid (**1406**) has also been used by several groups as a building block for the synthesis of carbasugar analogues of sialic acid with potent anti-influenza activity.[6l] Kim and co-workers reported that sialylmimetic **1462** exhibited good oral efficacy in the treatment and prophylaxis of influenza infection.[498,499] It was reasoned that the cyclohexane ring in

Scheme 245. Two Strategies for the Synthesis of Valienamine (11)[a]



[a] Reagents: (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 70%; (ii) LiN_3, DMF, 80 °C, 97%; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 98%; (iv) n-Bu_4NOAc, DMF, 80 °C, 61%; (v) MeOH, K_2CO_3, 100%; (vi) PPh_3, py, NH_4OH, 97%; (vii) Na/NH_3, THF, −78 °C, 68%; (viii) cat. $RuCl_3 \cdot 3H_2O$, EtOAc, CH_3CN, H_2O, $NaIO_4$, 0 °C, 81%, (ix) MeOH, K_2CO_3, 92%; (x) Ac_2O, py, DMAP, CH_2Cl_2, 96%; (xi) Martin sulfurane, PhH, reflux, 90%; (xii) $(Ph_3P)_4Pd$, Ph_3P, RNH_2, CH_3CN, reflux; (xiii) NaOMe, MeOH, 60% (two steps); (vii) Na, liq NH_3, THF, −78 °C, 68%.

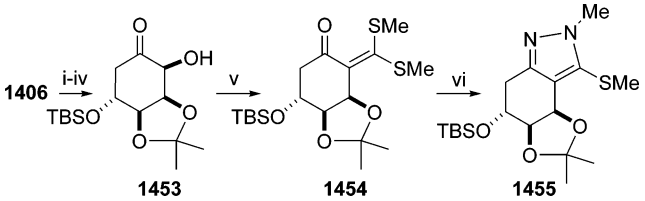
Scheme 246. Synthesis of Carbasugars by González et al.



1462 would adopt a similar conformation to that of the sialosyl-cation transition-state intermediate **1461** shown in Scheme 249. Indeed, compound **1462** is currently marketed, in the form of its orally active ethyl ester prodrug, as Tamiflu.[500]

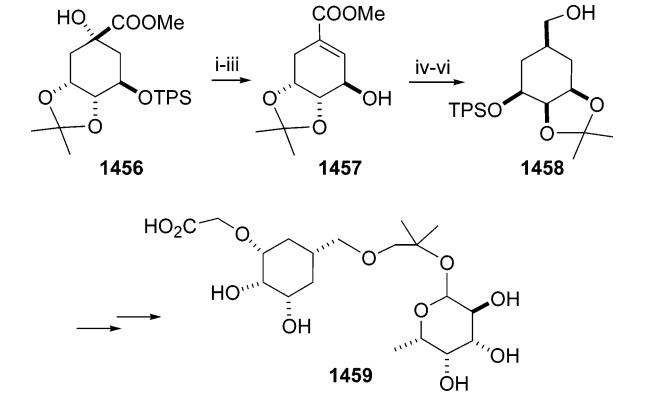
The synthesis developed by Kim and co-workers[498] was achieved from the quinic acid derivative **1463** (Scheme 250).

Scheme 247. Synthesis of Pyrazoloanellated Carbasugar 1455[a]



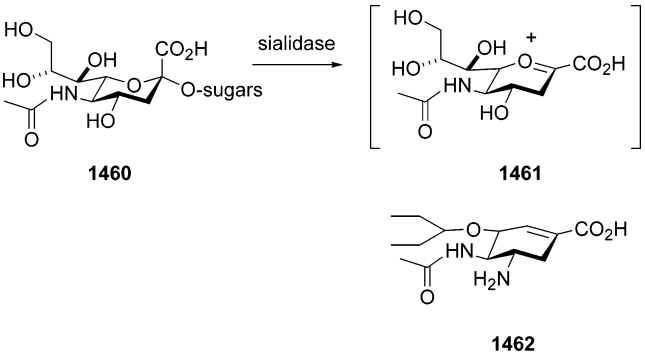
[a] Reagents: (i) acetone, dry HCl, 89%; (ii) Ac_2O, py, 92%; (iii) LAH, Et_2O, then $NaIO_4$, H_2O, 5 < pH < 6, 91% (two steps); (iv) TBSCl, DMF, imidazole, 80%; (v) NaH, CS_2, IMe, DMF, 79%; (vi) $MeNHNH_2$, MeOH, reflux, 52%.

Scheme 248. Synthesis of Sialyl Lewis^x Mimetics Based on Carbasugars[a]



[a] Reagents: (i) PDC, 16 h, 85%; (ii) $POCl_3$, 3 h, 84%; (iii) $NaBH_4$, EtOH, 92%; (iv) TPSCl, DMF, 16 h, 80 °C; (v) H_2, Pd/C, 1 h, 98%; (vi) LAH, 88%.

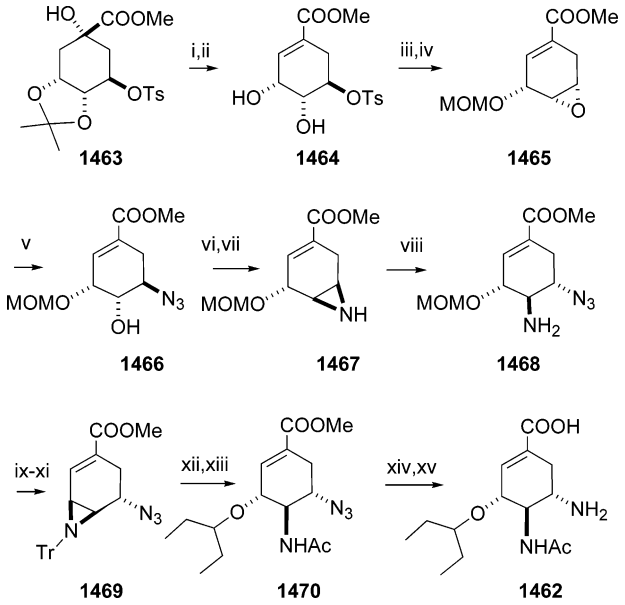
Scheme 249. Carbasugars as Transition-State Analogues



Selective dehydration of C_1-OH by treatment with sulfuryl chloride, followed by acetonide cleavage in refluxing methanol, afforded **1464**. Quantitative conversion of **1464** to the key epoxide **1465** was obtained by treatment with DBU and MOM-protection of the hydroxyl group. Epoxide ring opening by sodium azide furnished azido alcohol **1466**, which was further converted to aziridine **1467**, which underwent exclusive attack by azide ion at the C_5 position to give rise to intermediate **1468**. The final introduction of the 3-pentyl ether group at the C_3 allylic position was carried out by acid-catalyzed opening of the tritylaziridine **1469**.

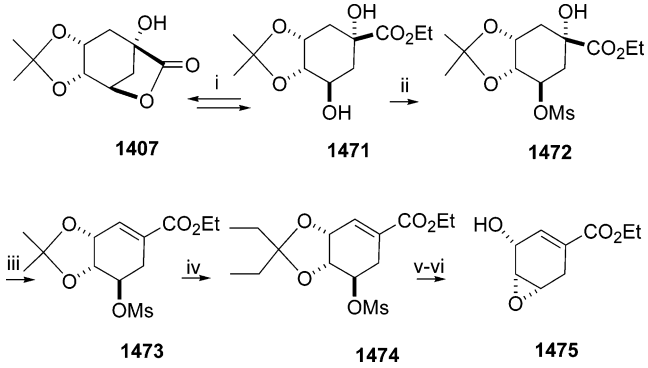
This sequence requires double inversion and repeated protection−deprotection of the (*R*)-hydroxyl group, so for large-scale preparation of **1462**, Rohloff et al.[501] designed a practical 12 step synthesis based on the access to the key epoxide **1475** (Scheme 251). Lactone acetonide **1407**, prepared in 90% yield by a modification of the Shing's method,[502] was converted to a 1:5 equilibrium mixture of

Scheme 250. Synthesis of Sialylmimetic (1462) According to Kim et al.[a]



[a] Reagents: (i) SO_2Cl_2, py; (ii) TsOH, MeOH, 54% (two steps); (iii) DBU, 100%; (iv) $MeOCH_2Cl$, $(i\text{-}Pr)_2EtN$, CH_2Cl_2, 97%; (v) NaN_3, NH_4Cl, MeOH, H_2O, 86%; (vi) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 99%; (vii) Ph_3P, THF, then Et_3N, H_2O, 78%; (viii) NaN_3, NH_4Cl, DMF, 85%; (ix) CH_3OH, HCl, 99%; (x) TrCl, Et_3N, CH_2Cl_2; (xi) CH_3SO_2Cl, Et_3N, 86% overall; (xii) BF_3Et_2O, 3-pentanol; (xiii) Ac_2O, py, DMAP, 69%; (xiv) Ph_3P, THF, then Et_3N, H_2O; (xv) KOH, THF, H_2O, 75%.

Scheme 251. Synthesis of Sialylmimetic (1462) According to Rohloff et al.[a]

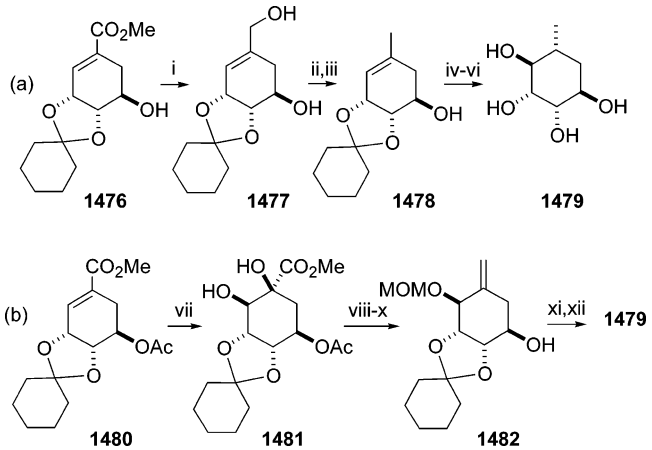


[a] Reagents: (i) NaOEt, EtOH, **1407**:**1471** 1:5; (ii) MsCl, Et_3N, CH_2Cl_2, 0−5 °C, 69% overall; (iii) SO_2Cl_2, py, CH_2Cl_2, −25 °C, then pyrrolidine, $(Ph_3P)_4Pd$, EtOAc, 35 °C, 42%; (iv) 3-pentanone, $HClO_4$, 95%; (v) $BH_3{\cdot}SMe_2$, CH_2Cl_2, TMSOTf, −20 °C, 95%; (vi) $KHCO_3$, aq EtOH, 96%.

lactone/hydroxy ester **1407**/**1471**, which was treated with methanesulfonyl chloride to afford the monomesylate **1472**. Dehydration in **1472** furnished unsaturated "shikimic" ring system **1473**, which after *trans*-ketalization to **1474** and reductive opening of the 3,4-pentylidene ketal gave rise to an intermediate alcohol, which in the presence of potassium bicarbonate was converted to the epoxide **1475**. Stereospecific conversion of **1475** to the desired **1462** was accomplished using azide chemistry by analogy to Kim's procedure.[499] The synthesis of **1475** has been further developed[503,504] in order to allow the manufacture of Tamiflu on a commercial scale.[505]

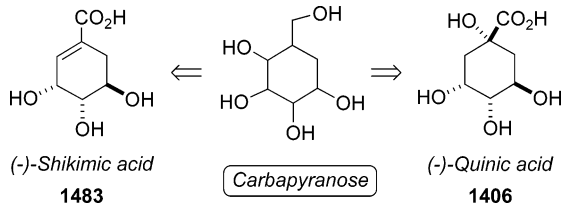
Panza and co-workers[506] and Murugan et al.[507] reported two alternative routes for the synthesis of the carbasugar analogue of L-rhamnose (Scheme 252). Both processes began with the conversion of quinic acid into (−)-shikimic ester derivatives according to literature procedures,[508,509] but they

Scheme 252. Synthesis of 5a-Carba-α-L-rhamnose (1479)[a]



[a] Reagents: (i) DIBAL-H, THF, 0 °C, 78%; (ii) Ph_3P, CBr_4, sym-collidine, 93%; (iii) SuperHydride, THF, 0 °C to rt, 92%; (iv) NapBr, KOH, 18-crown-6, THF, 85%; (v) 9-BBN, reflux, then NaOH, H_2O_2, 0 °C to rt, 90%; (vi) deprotection conditions not given; (vii) OsO_4, NMMO, t-BuOH, reflux, 3 h, 70%; (viii) MOMCl, Hünig's base, CH_2Cl_2, 87%; (ix) LAH, THF, 60 °C, 90%; (x) 1,1′-thiocarbonyldiimidazole, $PhCH_3$, reflux, then trimethyl phosphite, reflux, 9 h, 85%; (xi) Pd−C, H_2, MeOH, 40 psi, 8 h, 97%; (xii) HCl, MeOH, 10 h, 95%.

Scheme 253. Quinic and Shikimic Acids as Carbasugar Precursors

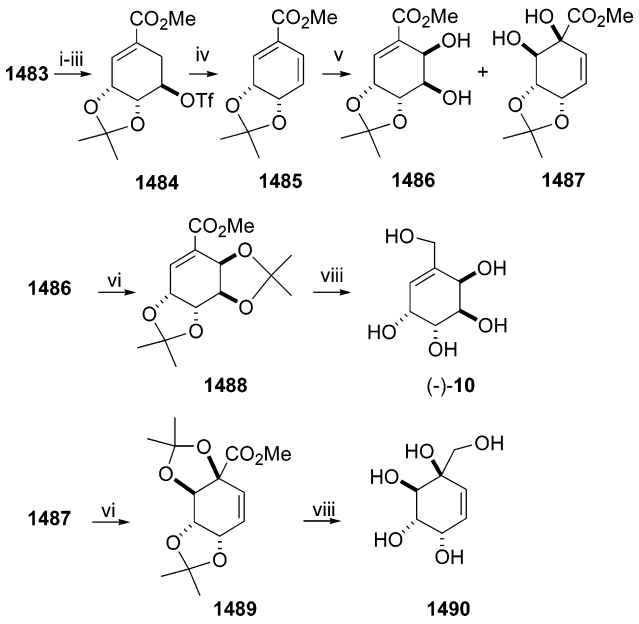


diverge in the way the missing hydroxyl and methyl groups were installed. In Panza's route, the carboxylic ester of the "shikimate" was first reduced to a methyl group (**1476** → **1478**) and then a hydroboration−oxidation sequence allowed the introduction of the missing hydroxyl group and at the same time established the required stereochemistry at the two newly formed stereocenters (Scheme 252a).[506] In the second route, dihydroxylation of the double bond in the shikimate derivative **1480** was carried out first (Scheme 252b). Conversion to the exo-olefin **1482**, stereoselective hydrogenation, and deprotection gave 5a-carba-α-L-rhamnose (**1479**).[507]

6.2.3.2. From Shikimic Acid. Although (−)-shikimic acid (**1483**) shares many structural features with carbasugars, its use as starting material has been restricted owing to its limited availability, normally from the fruit of *Illicium* plants,[510] and high price. Under these circumstances, quinic acid (**1406**) had become the starting material of choice in the synthesis of carbapyranose derivatives, albeit sometimes through a "shikimate" derivative, as has been shown in the previous section (Scheme 253).

More recently, however, an alternative source of shikimic acid has been reported from microbial fermentation of glucose using a recombinant shikimate-synthesizing *Escherichia coli*.[511] Such an improvement may lead to a pronounced expansion in the synthetic utilization of shikimic acid. In fact, the shikimic acid produced by fermentation has already been used as raw material for the manufacture of Tamiflu, shortening by four steps the original route described from quinic acid.[505] Singh and co-workers have reported the synthesis of the antipode of the naturally occurring herbicide

Scheme 254. Synthesis of Carbasugars from (−)-Shikimic Acid (1483)[a]



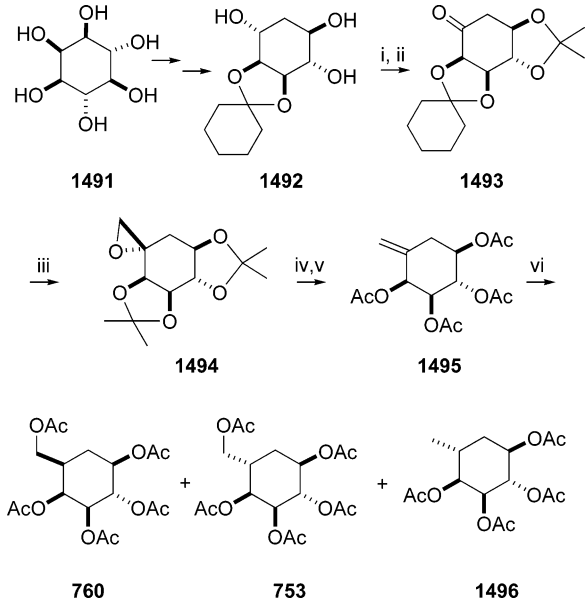
[a] Reagents: (i) CSA, MeOH, reflux, 10 h, 96%; (ii) $CMe_2(OMe)_2$, CSA, 2 h, 95%; (iii) Tf_2O, DMAP, py, CH_2Cl_2, −20 °C, 40 min, 98%; (iv) CsOAc, DMF, 2 h, 81%; (v) OsO_4, NMMO, t-BuOH−H_2O (10:1), 38% for **1486**, 35% for **1487**; (vi) $CMe_2(OMe)_2$, CSA, 2 h, 92% for **1488**, 82% for **1489**; (vii) DIBAL-H, THF, −10 °C, 1.5 h, 99%; (viii) TFA-H_2O (6:1), 2 h, 91% for (−)-**10**, 89% for **1490**.

MK7607 (**10**) and some other carbasugars using shikimic acid as the chiral template (Scheme 254).[28d] Shikimic acid (**1483**), obtained by isolation from Chinese star anise (*Illicium verum* Hook),[512] was converted into diene **1485** by transient elimination of triflate **1484**. Hydroxylation of **1485** gave diols **1486** and **1487** in a combined yield of 73%. These diols were protected as di-*O*-isopropylidene derivatives **1488** and **1489**, respectively, which were reduced with DIBAL to give after deprotection (−)-MK7607, (−)-**10**, and carbasugar **1490**.

6.2.3.3. From Cyclitols. *6.2.3.3.1. From Inositol.* myo-Inositol (**1491**) is the most abundant cyclitol occurring in Nature. Among nine inositol stereoisomers, seven are *meso* compounds, and therefore, when myo-inositol is chosen as the starting material, racemic carbasugars are obtained. In 1976, Suami, Ogawa, and co-workers reported the first synthesis of 5a-carba-β-DL-galactopyranose and 5a-carba-α-DL-altropyranose from myo-inositol (**1491**).[513] They developed a synthetic route which made use of 1,2-anhydro-5,6-*O*-cyclohexylidene-chiro-inositol (**1493**) (Scheme 255).[514] *O*-Isopropylidenation and Pfitzner−Moffat oxidation of **1492** afforded the inosose derivative **1493**, which was reacted with diazomethane to provide the spiro epoxide **1494**. Nucleophilic opening of the oxirane ring with hydriodic acid, followed by acetylation and elimination, gave exocyclic alkene **1495**. Hydroboration of **1495** followed by oxidation afforded 5a-carba-β-DL-galactopyranose pentaacetate (**760**), 5a-carba-α-DL-altropyranose pentaacetate (**753**), and 6-deoxy-5a-carba-α-DL-altropyranose tetraacetate (**1496**) in 13%, 17%, and 13% yield, respectively.[513]

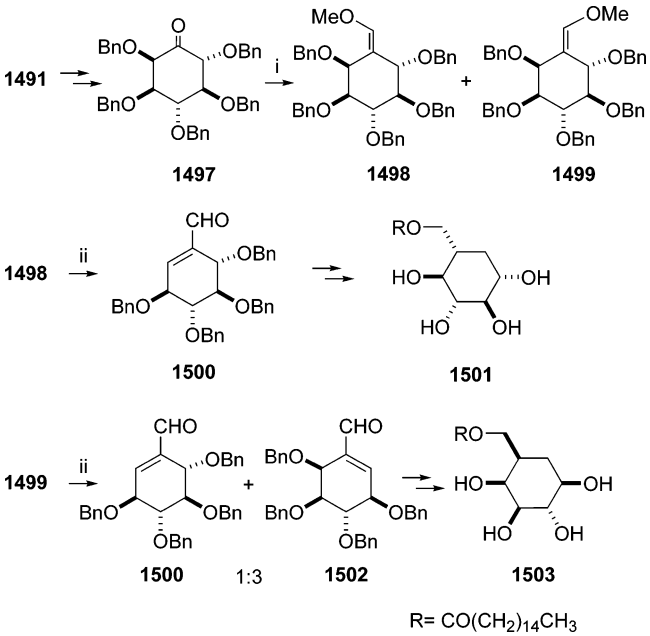
A different approach to carbasugar analogues from myo-inositol, that relies on a Wittig homologation, has been reported by Massy and Wyss (Scheme 256).[515] They disclosed the preparation of carbasugars related to β-gluco- and β-galactopyranose by reaction of ketone **1497** with

Scheme 255. Synthesis of 5a-Carba-β-DL-galactopyranose (760) and 5a-Carba-α-DL-altropyranose (753) from myo-Inositol (Only One Enantiomer Is Shown)[a]



[a] Reagents: (i) 2,2-dimethoxypropane, DMF, TsOH, 76%; (ii) Ac_2O, DMSO, 74%; (iii) CH_2N_2, 89%; (iv) NaI, HI, then Ac_2O, H_2SO_4, 40 °C, 47%; (v) Zn, AcOH, reflux, 75%; (vi) sodium tetrahydroborate, $BF_3{\cdot}Et_2O$, THF, then NaOH, H_2O_2, Ac_2O, H_2SO_4, 43%.

Scheme 256. Synthesis of 5a-Carba-gluco- and -galactopyranose Derivatives from myo-Inositol (Only One Enantiomer Is Shown)[a]

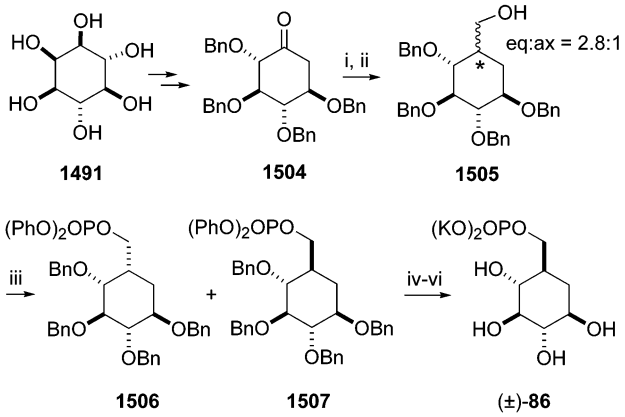


[a] Reagents: (i) $(CH_3OCH_2)Ph_3PCl$, n-BuLi, THF, 0 °C, 60%; (ii) Ac_2O, H_2SO_4, 40 °C, 41% for **1500**, 85% for **1502**.

methoxymethyltriphenylphosphonium chloride. Conversion of the resulting enol ethers **1498** and **1499** to aldehydes **1500** and **1502** took place with concomitant lose of a benzyloxy group. Unfortunately, conversion of these intermediates to the target compounds by hydrogenolysis of the benzyl groups and reduction of the double bonds was not straightforward and low yields of the desired products were obtained.

5a-Carbaglucopyranose-6-phosphate [(±)-**86**] was prepared by treatment of deoxy-scyllo-inososse (**1504**)[516] with methylenetriphenylphosphorane followed by hydroboration

Scheme 257. Synthesis of 5a-Carba-α-DL-glucopyranose-6-phosphate [(±)-86] from myo-Inositol (Only One Enantiomer Is Shown)[a]



[a] Reagents: (i) $CH_2{=}PPh_3$, THF, 86%; (ii) 9-BBN, THF, reflux, then NaOH, H_2O_2; (iii) $(PhO)_2POCl$, CH_2Cl_2, py, separation of isomers, 66% (two steps); (iv) H_2, 10% Pd/C, MeOH, 79%; (v) H_2, PtO_2, MeOH, 84%; (vi) KOMe, MeOH, 65%.

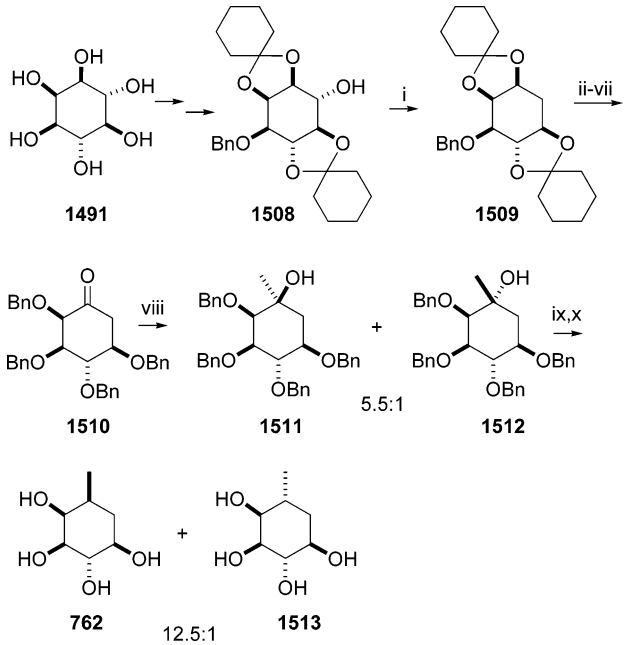
(Scheme 257). The overall procedure gave a 2.8:1 mixture of two epimeric alcohols **1505**, which were separated as diphenyl phosphates **1506** and **1507**. Deprotection of **1507**, by a two-step catalytic hydrogenation process first using Pd−C and then PtO_2, afforded the desired carbaglucopyranose-6-phosphate (±)-**86**.[85] This compound was shown to be an irreversible inhibitor of 2-deoxy-scyllo-inosose synthase, a key enzyme in the biosynthesis of 2-deoxystreptamine, which catalyzes the cyclization of D-glucose-6-phosphate into a six-membered carbocycle.[85]

van Boom and co-workers reported the transformation of partially protected myo-inositol derivative **1508** to 5a-carba-α-DL-fucopyranose and β-DL-galactopyranose derivatives (Scheme 258).[517] The route was based on the deoxygenation of the 6-OH and the replacement of the 1-OH by either a methyl or a hydroxymethyl group, respectively. The protocol for the synthesis of carbafucose **762** commences with radical deoxygenation of inositol derivative **1508**. Selective transketalization followed by benzylation and acid hydrolysis gave an intermediate diol which after protecting group manipulation was oxidized at 1-OH to give ketone **1510**. Treatment of **1510** with methyl magnesium bromide gave individual epimers **1511** and **1512** in 78% and 14% yield, respectively. Deoxygenation of the tertiary hydroxyl group in both epimers, followed by hydrogenolysis of the benzyl protective groups, furnished 5a-carba-α-DL-fucopyranose (**762**) along with a minor amount of its pseudoaxial epimer **1513**.

Alternatively, hydroxymethylation of ketone **1510** with benzyloxymethyllithium and subsequent deoxygenation of the epimerically pure addition product **1514** led to the exclusive formation of the fully benzylated carbagalactose derivative **1515**. Finally, removal of the benzyl groups by hydrogenolysis gave 5a-carba-β-DL-galactopyranose (**1516**) (Scheme 259).

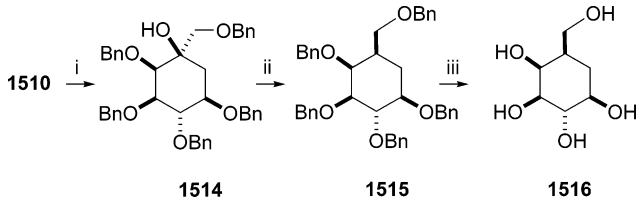
Very recently, Ogawa and co-workers succeeded in connecting myo-inositol with optically pure carbasugar derivatives (Scheme 260).[518,519] The optical resolution is carried out at an earlier stage of the processing by biodeoxygenation[520] of myo-inositol (**1491**) to produce mainly (−)-vibo-quercitol [(−)-**1517**], which is biochemically oxidized under the influence of the *Gluconobacter* sp. AB10277 to furnish (−)-2-deoxy-scyllo-inosose (**1518**) in high yield

Scheme 258. Synthesis of 5a-Carba-α-DL-fucose (762) from myo-Inositol (Only One Enantiomer Is Shown)[a]



[a] Reagents: (i) PhOC(═S)Cl, DMAP, CH_3CN, then n-Bu_3SnH, AIBN, toluene, 95%; (ii) TsOH, $HOCH_2CH_2OH$, CH_2Cl_2, 77%; (iii) BnBr, NaH, DMF; (iv) 80% HOAc, H_2O, reflux, two steps, 82%; (v) 4,4-dimethoxytritylchloride, py, 95%; (vi) NaH, BnBr, TBAI, DMF, then $PhSO_3H$, CH_2Cl_2, MeOH, 84%; (vii) Ac_2O, DMSO, 100%; (viii) MeMgBr, THF, −20 °C, 92%; (ix) MeOCOCl, DMAP, CH_3CN, then n-Bu_3SnH, AIBN, $PhCH_3$, reflux, 69%; (x) Pd/C, H_2, EtOH, quant.

Scheme 259. Synthesis of 5a-Carba-β-DL-galactopyranose (1516) from myo-Inositol (Only One Enantiomer Is Shown)[a]

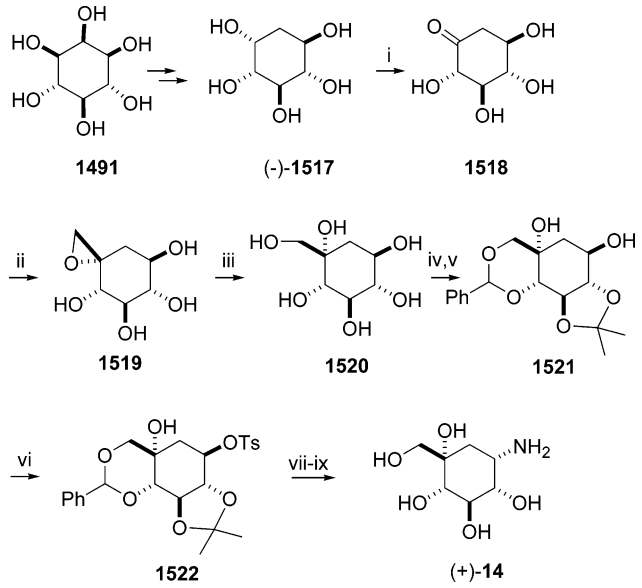


[a] Reagents: (i) $BnOCH_2Li$, THF, 74%; (ii) MeOC(O)COCl, DMAP, CH_3CN, then n-Bu_3SnH, AIBN, $PhCH_3$, reflux, 71%; (iii) Pd(C), H_2, EtOH, 97%

(Scheme 260). On treatment with diazomethane, the crude ketone could be converted into a crystalline spiro-epoxide **1519**, related to the key intermediate **1494** used in a previous route developed by the same authors. From compound **1519**, (+)-valiolamine (**14**) and (−)-β-valiol (**1520**), a versatile precursor for carbasugars, were readily synthesized. Thus, hydrolysis of **1519** gave (−)-β-valiol (**1520**). Additionally, **1519** was successfully transformed into the 5-hydroxyl derivative **1521**, which was tosylated and subjected to nucleophilic substitution with azide anion to afford, after hydrogenolysis and deprotection, (+)-valiolamine (**14**).

6.2.3.3.2. From L-Quebrachitol. L-Quebrachitol (**1523**) is a naturally occurring optically active inositol, obtained from the serum of rubber trees,[521] and is of interest as a chiral source for the syntheses of natural products.[522,523] In particular, L-quebrachitol was used by Ozaki et al. as a building block in an early synthesis of cyclophellitol.[524] Paulsen and his co-workers studied extensively the use of L-quebrachitol (**1523**) in the preparation of carbasugars and related carba-aminosugars. First, they described a lengthy approach for the synthesis of valienamine (Scheme 261).[525,526] In order to incorporate the side chain, inosose derivative **1524**,

Scheme 260. Synthesis of (+)-Valiolamine 14 from myo-Inositol[a]



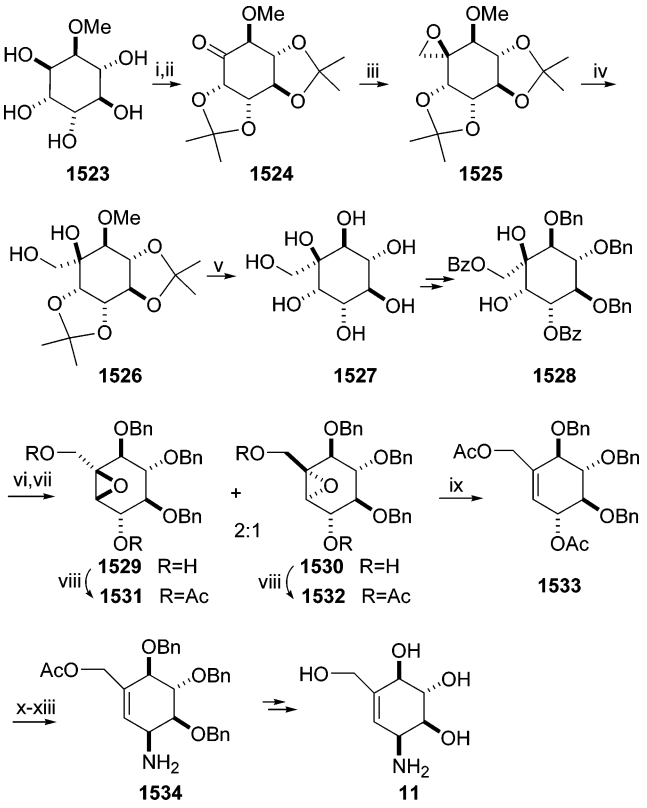
[a] Reagents: (i) *Gluconobacter* sp. AB10277, 80%; (ii) CH_2N_2, EtOH, MeOH, 44%; (iii) 3 M aqueous KOH, 100 °C, 32%; (iv) $PhCH(OMe)_2$, $TsOH·H_2O$, DMF, 50 °C; 59%; (v) 2-methoxypropene, $TsOH·H_2O$, DMF, 36%; (vi) TsCl, py, DMAP, quant; (vii) NaN_3, DMF, 120 °C, 88%; (viii) H_2, Raney-Ni, EtOH, Ac_2O, 76%; (ix) 2 M HCl, Dowex 50W × 2 (H^+), aq 1% NH_3, 90%.

prepared in two steps from L-quebrachitol, was converted to the spiroepoxide **1525**, which was hydrolyzed to the ring-opened product **1526**. Cleavage of the *O*-methyl group provided the completely deblocked heptaol **1527**, which was converted through a sequence of reactions involving protection and deprotection into diol **1528**. Mesylation of **1528** followed by base treatment afforded a mixture of epoxides **1529** and **1530**, which were isolated as the acetates **1531** and **1532**. Reaction of both isomers **1531** and **1532** with sodium iodide, followed by elimination, gave cyclohexene **1533**. The introduction of the amino group was finally achieved by selective protection of the primary alcohol, azide substitution at the allylic position, and reduction. Subsequent removal of the protecting groups in **1534** gave valienamine (**11**), which was isolated as the hydrochloride.

The same group devised a shorter route for the introduction of the hydroxymethyl chain in quebrachitol derivatives by a Wittig reaction followed by hydroboration (Scheme 262). The sequence started with the conversion of the quebrachitol (**1523**) into the protected 1-L-chiro-inositol (**1535**) by cleavage of the *O*-methyl group with BBr_3[527] and exhaustive *O*-isopropylidenation. Compound **1535** was next converted into the inosose **1536** by selective removal of the *trans*-isopropylidene moiety, monobenzylation, and oxidation. Wittig reaction with methyl(triphenylphosphonium) bromide and butyl lithium and subsequent hydroboration followed by oxidation led to the hydroxymethyl branched-chain derivative **1537**. A series of reactions (namely, protection of the primary hydroxyl group, *O*-debenzylation, and deoxygenation of the secondary alcohol) and removal of the protecting groups finally converted **1537** into in 5a-carba-α-D-galactopyranose (D-**3**).[528]

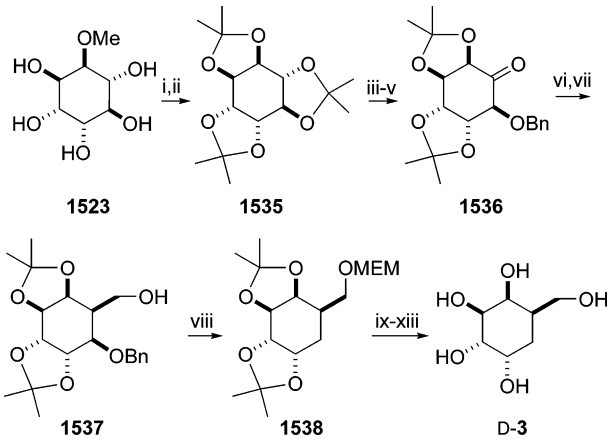
Paulsen and co-workers described yet another sequence to carbasugars based on a regio- and stereoselective 1,4-addition of ethyl 2-lithio-1,3-dithiane-2-carboxylate to enones **1539** (Scheme 263a) and **1543** (Scheme 263b), previously

Scheme 261. Synthesis of (+)-Valienamine 11 from Quebrachitrol 1523[a]



[a] Reagents: (i) 2,2-dimethoxypropane, TsOH, DMF, 80 °C, 85%; (ii) RuO_4, $NaIO_4$, K_2CO_3, CH_2Cl_2, H_2O, 81%; (iii) NaH, DMSO, Me_3SOI, THF, 50 °C, 57%; (iv) 1 N aqueous KOH, dioxane, 100 °C, 89%; (v) BBr_3, CH_2Cl_2, 0 °C, 79%; (vi) MsCl, py, 0 °C; (vii) NaOMe, MeOH, 50%; (viii) Ac_2O, py; (ix) NaI, NaOAc, acetone, 80 °C, then $POCl_3$, py, 72%; (x) NaOMe, MeOH, 93%; (xi) CH_3CN, BzCN, Et_3N, 54%; (xii) PPh_3, HN_3, DIAD, $PhCH_3$, 70%; (xiii) PPh_3, NH_3, MeOH, 61%.

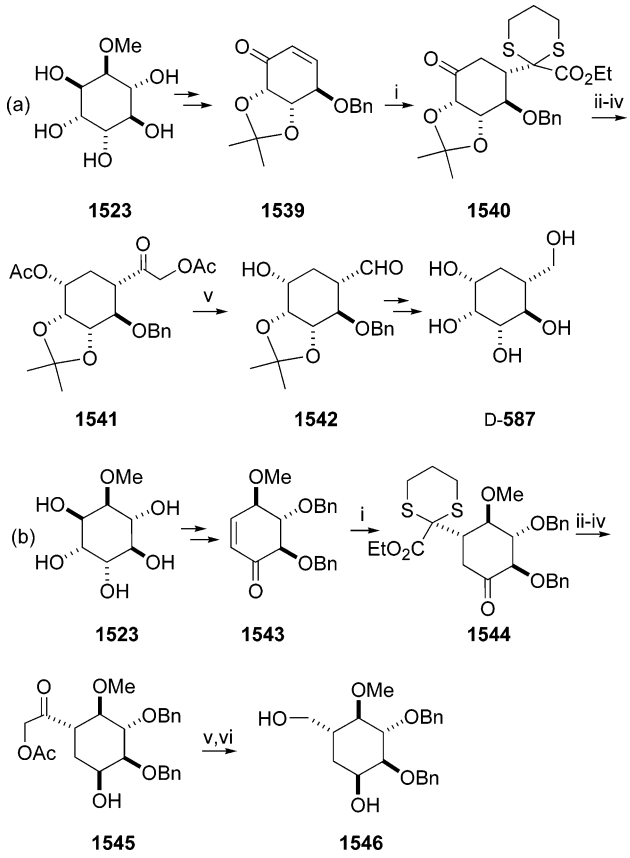
Scheme 262. Synthesis of 5a-Carba-α-D-galactopyranose (D-3) from L-Quebrachitol[a]



[a] Reagents: (i) 2,2-dimethoxypropane, TsOH, DMF, 80 °C, 85%; (ii) BBr_3, CH_2Cl_2, 0 °C, then 2,2-dimethoxypropane, DMF, 60 °C, 77%; (iii) AcOH, 70 °C, 88%; (iv) NaOH, BnBr, TBAI, CH_2Cl_2, 87%; (v) $Cl_2(CO)$, DMSO, Et_3N, CH_2Cl_2, 96%; (vi) $MePPh_3Br$, n-BuLi, THF, −30 °C, 85%; (vii) BH_3−THF, −50 °C, then H_2O_2, NaOH, 82%; (viii) MEMCl, $(i\text{-}Pr_2)NEt$, CH_2Cl_2, 85%; (ix) Pd−C, H_2, MeOH, 73%; (x) NaH, CS_2, MeI, THF, 91%; (xi) n-Bu_3SnH, AIBN, $PhCH_3$, 81%; (xii) 1 M HCl, MeOH, then Ac_2O, py, 60%; (xiii) NaOMe, MeOH, 78%.

prepared from L-quebrachitol. Subsequent reduction and shortening of the side chain in **1541** and **1545** allowed the preparation of 5a-carba-β-D-manno-pyranose (D-**587**) and a carba-α-D-glucopyranose derivative, **1546**.[528,529]

Scheme 263. Synthesis of 5a-Carba-α-D-mannopyranose (D-587) and 5a-Carba-α-D-glucopyranose Derivative 1546 from L-Quebrachitol[a]



[a] Reagents: (i) ethyl 2-lithio-1,3-dithiane-2-carboxylate, THF, 0 °C, 71% **1540**, 96% **1544**; (ii) LAH, THF, 69%; (iii) $HgCl_2$, Hg, 92%; (iv) Ac_2O, py, 63% **1541**, 74% **1545**; (v) $NaBH_4$, MeOH then $NaIO_4$, $NaBH_4$, 93% from **1545**.

Paulsen et al. also reported the reaction of cyclitol derivatives, bearing a free hydroxylic function, with saccharide triflates to yield carbadisaccharides containing an ether linkage between the carbasugar and the saccharide component. Accordingly, they prepared (1→6)- and (1→4)-linked carbadisaccharides, corresponding to isomaltose, and maltose or cellobiose, respectively. For example, the triflates **1547** (Scheme 264a) or **1550** (Scheme 264b) were displaced with protected α-D-carbaglucopyranose (**1548**) in the presence of sodium hydride to yield monocarbadisaccharides **1549** and **1551**.[530]

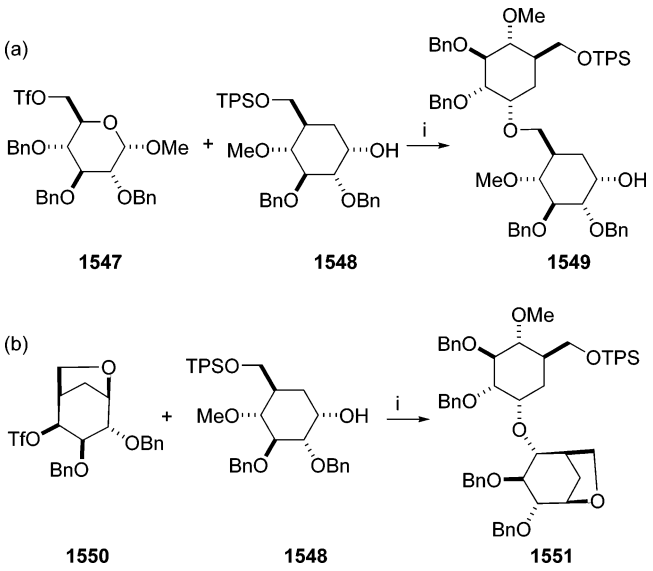
6.3. Synthesis of Seven- and Eight-Membered Carbasugar Analogues

In the last few years, there has been increasing interest in the preparation of carbasugars containing rings larger than the five- and six-membered rings already mentioned in this review. In this context, reports by several research groups have focused on the synthesis of seven- and eight-membered analogues which could be regarded as 6a-septanoses and 7a-octanoses (see Figure 49). Three different strategies have been employed for the ring-forming reaction, and carbohydrates have always been used as starting materials.

6.3.1. TIBAL-Induced Claisen Rearrangement

The thermal or triisobutylaluminum (TIBAL)-promoted Claisen rearrangement of 2-methylene-6-vinyltetrahydropyrans, which affords cyclooctanic derivatives by insertion of a C_2 unit, has been developed by Paquette's group.[531] Its

Scheme 264. Synthesis of Carbadisaccharides by Paulsen et al.[a]



[a] Reagents: (i) NaH, THF, 86% **1549**, 38% **1551**.

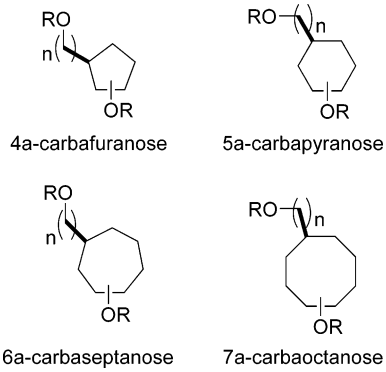
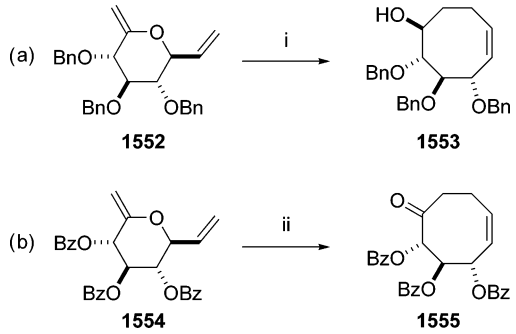


Figure 49. Seven- and eight-membered ring carbasugar analogues.

Scheme 265. Claisen Rearrangement of Sugar Dienes Leading to Eight-Membered Derivatives[a]



[a] Reagents: (i) TIBAL, $PhCH_3$, 50 °C, 98%; (ii) xylene, reflux, 12 h, 60%.

use in the carbohydrate field is more recent, and both the thermal[532] (**1554** → **1555**) and the TIBAL-catalyzed[407] (**1552** → **1553**) variations have been studied (see Scheme 265). Sinaÿ and co-workers made use of this transformation in the first reported synthesis of cyclooctanic carbasugars.[533] In their approach, the hydroxymethylene group was retrosynthetically correlated with a ketone by Tebbe reaction and hydroboration (Figure 50). They described the preparation of compounds **1563** and **1564** (Scheme 266) as well as their enantiomers **1571** and **1572**, respectively (Scheme 267), from isomeric D-glucose-derived alkenes **1556** and **1565** (see Schemes 266 and 267). The authors also studied the conformation of

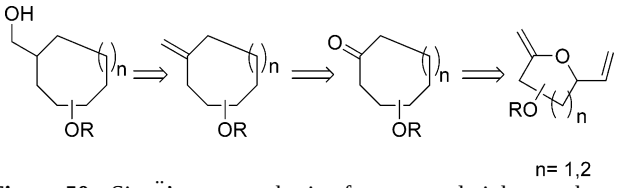
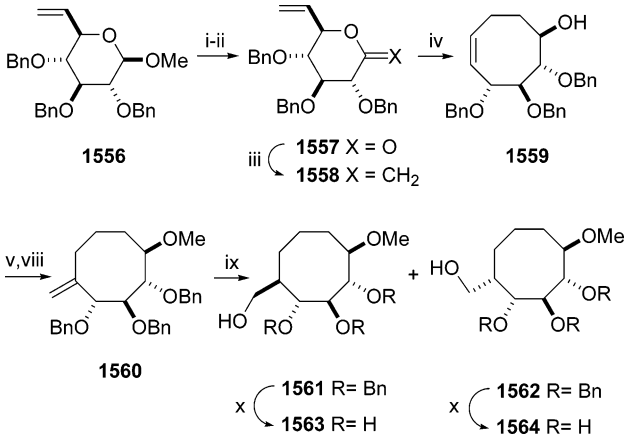


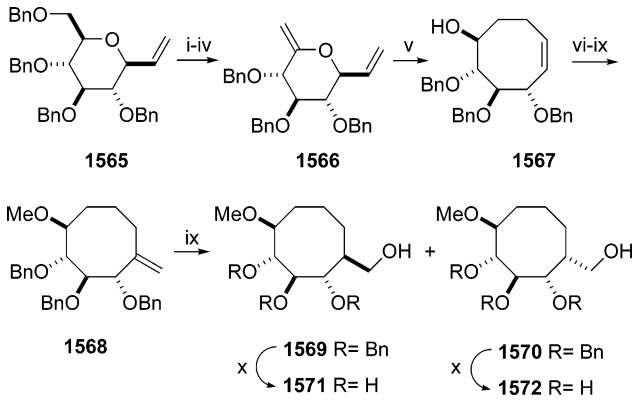
Figure 50. Sinaÿ's retrosynthesis of seven- and eight-membered carbasugars based on TIBAL-mediated Claisen rearrangement of sugar-dienes.

Scheme 266. Synthesis of Eight-Membered Ring Carbasugar Analogues[a]



[a] Reagents: (i) TfOH/AcOH/H_2O, 75%; (ii) PCC, 85%; (iii) Tebbe reagent, 84%; (iv) TIBAL, $PhCH_3$, 98%; (v) NaH, MeI, DMF, 60%; (vi) BH_3−THF, then NaOH, H_2O_2, 60%; (vii) PCC, 92%; (viii) Tebbe reagent, 82%; (ix) BH_3−THF, then NaOH, H_2O_2, 60%.

Scheme 267. Synthesis of Eight-Membered Ring Carbasugar Analogues[a]

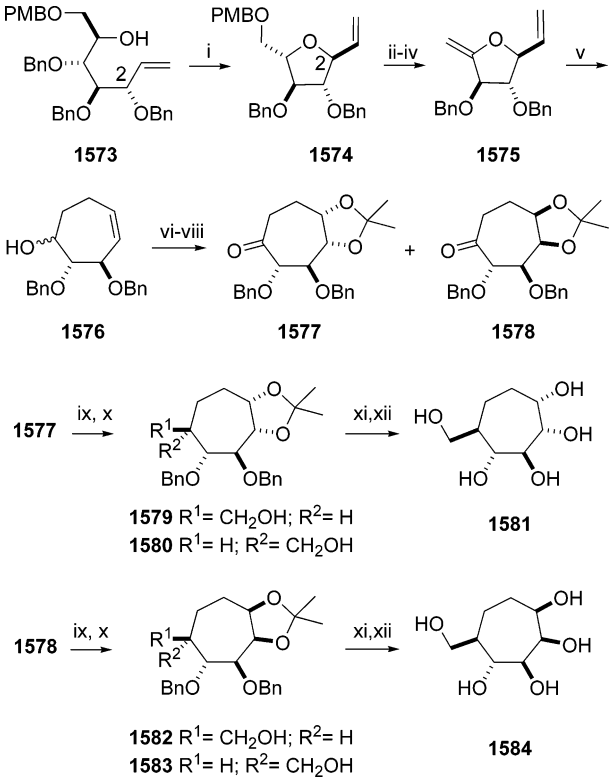


[a] Reagents: (i) TMSOTf, Ac_2O; (ii) NaOMe, MeOH; (iii) TsCl, py; (iv) NaI, TBAI, DMSO, then DBU; (v) TIBAL, $PhCH_3$, 98%; (vi) NaH, MeI, DMF; (vii) BH_3−THF, then NaOH, H_2O_2; (viii) PCC; (ix) Tebbe reagent; (x) BH_3−THF, then NaOH, H_2O_2 (no yields given).

compound **1561** in solution, on the basis of NMR data, and assigned it a boat chair conformation. On the other hand, the ^1H NMR spectrum of its hydrogenolysis product, **1563**, shows a close analogy with that of methyl β-D-glucopyranose, particularly in view of the coupling constants.

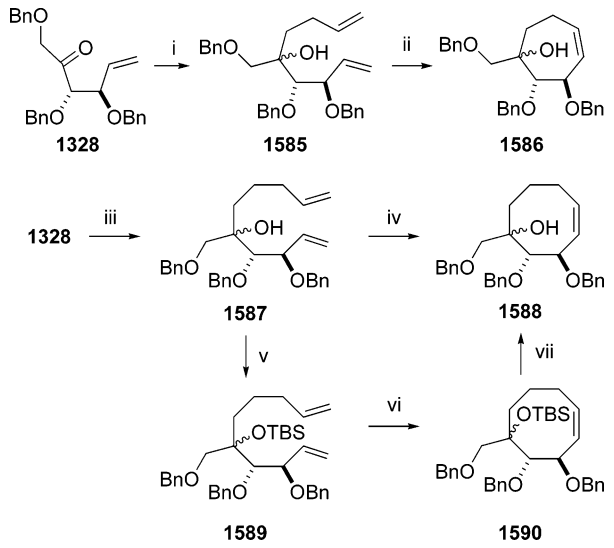
More recently, Sinaÿ and co-workers have reported the synthesis of cycloheptane carbasugars (Scheme 268).[534] The key step was a TIBAL-catalyzed Claisen rearrangement of a furanose diene leading to a functionalized cycloheptene. The final steps involved, as mentioned above, chain elongation from the ketone by Tebbe reaction and hydroboration. Accordingly, the synthetic protocol started with unsaturated alcohol **1573** by conversion into its corresponding triflate. On heating, this triflate was displaced by nucleophilic attack of O_2, and subsequent debenzylation afforded *C*-vinyl

Scheme 268. Synthesis of Seven-Membered Ring Carbasugar Analogues[a]



[a] Reagents: (i) Tf_2O, py, 68%; (ii) DDQ, 87%; (iii) TsCl, DMAP, py, 87%; (iv) NaI, TBAI, DMSO, then DBU, 93%; (v) TIBAL, $PhCH_3$, 83% (2:1 mixture); (vi) OsO_4, NMMO; (vii) $Me_2C(OMe)_2$, CSA; (viii) PCC, 56% (55:45 mixture), separation of isomers; (ix) Tebbe reagent, 63% (for **1577**), 71% (for **1578**); (x) BH_3-THF, then NaOH, H_2O_2, 69% (**1579**/**1580**, 75:25), 65% (**1582**/**1583**, 7:3); (xi) TFA; (xii) H_2, Pd/C, 75% (**1581**), 82% (**1584**).

Scheme 269. Synthesis and RCM Reaction of Dienes 1527, 1529, and 1531[a]



[a] Reagents: (i) butenylmagnesium bromide, 64% (1:1 epimeric mixture); (ii) Grubbs' catalyst **523**, 60%; catalyst **525**, 97%; (iii) pentenylmagnesium bromide, 70% (1:1 epimeric mixture); (iv) Grubbs' catalyst **523**, 29%; catalyst **525**, 0%; (v) TBSOTf, Et_3N, 89%; (vi) Grubbs' catalyst **523**, 86%; catalyst **525**, 0%; (vii) TBAF, THF, 85%.

furanoside **1574**, from which diene **1575** was prepared. TIBAL-induced rearrangement of the latter gave rise to cycloheptenes **1576**, which were further functionalized to keto-tetraols **1577** and **1578**. Finally, chain elongation of

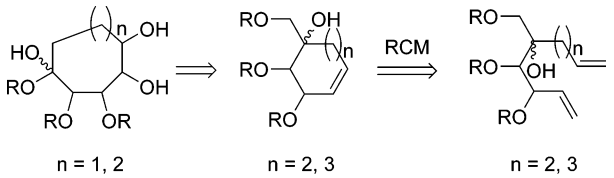
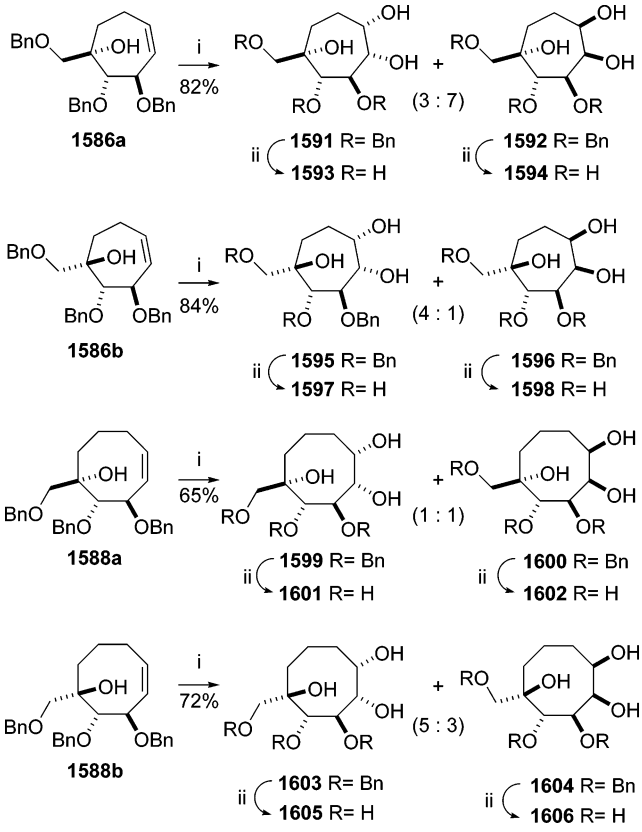


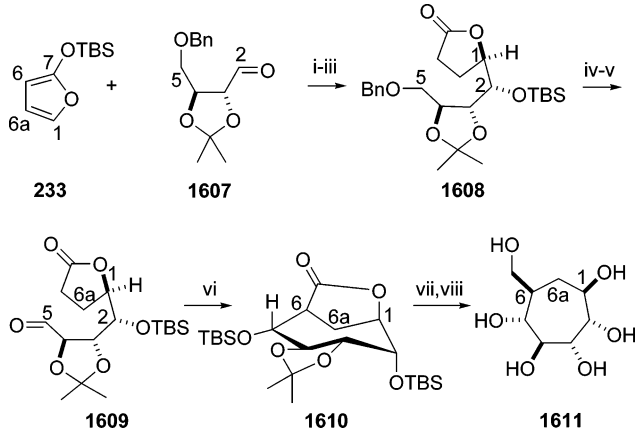
Figure 51. Sinay's retrosynthesis of seven- and eight-membered carbasugars based on RCM.

Scheme 270. Conversion of RCM Adducts to Seven- and Eight-Membered Carbasugars[a]



[a] Reagents: (i) OSO_4, NMMO, *t*-BuOH; (ii) H_2, Pd/C, MeOH, EtOAc.

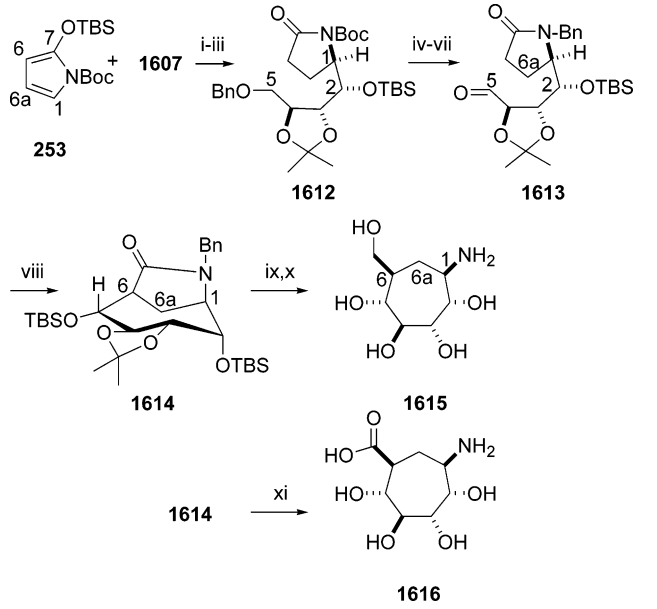
Scheme 271. Synthesis of Seven-Membered Carbasugar Analogues[a]



[a] Reagents: (i) $BF_3 \cdot OEt_2$, 80%; (ii) $NaBH_4$, $NiCl_2$; (iii) TBSOTf, 2,6-lutidine, 81%, 2 steps; (iv) H_2, $Pd(OH)_2$; (v) Swern oxidation, 76%, two steps; (vi) TBSOTf, $(i\text{-}Pr)_2NEt$, 76%; (vii) $LiBH_4$; (viii) 6 N aq HCl, 79%.

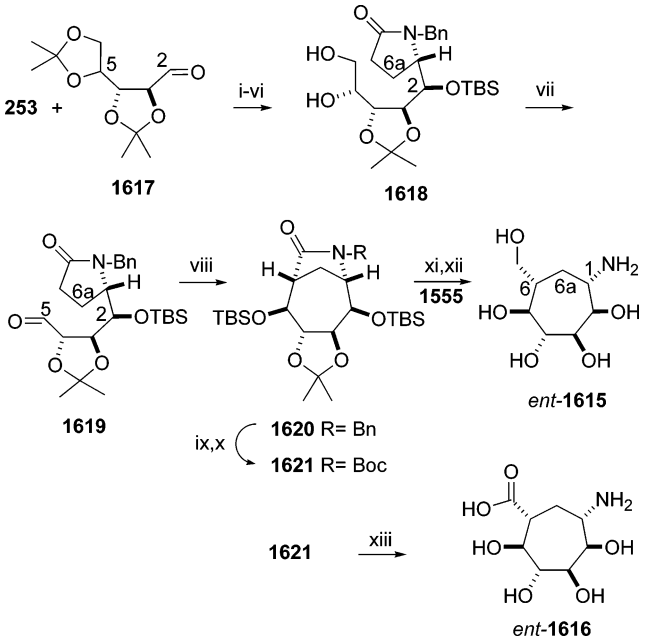
1577 and **1578** led to **1581** and **1584**. These cycloheptanic carbasugars, **1581** and **1584**, displayed a close analogy, in terms of coupling constants in ^1H NMR, with α-D-glucopyranose and β-D-mannopyranose, respectively.

Scheme 272. Synthesis of Seven-Membered Aminocarbasugar Analogues[a]



[a] Reagents: (i) $SnCl_4$, 80%; (ii) $NaBH_4$, $NiCl_2$; (iii) TBSOTf, 2,6-lutidine, 83%, two steps; (iv) CAN; (v) BnCl, 69%, two steps; (vi) H_2, $Pd(OH)_2$; (vii) Swern oxidation, 78%, two steps; (viii) TBSOTf, $(i\text{-}Pr)_2NEt$, 85%; (ix) $NaBH_4$; (x) 6 N aq HCl, 84%, two steps; (xi) 6 N aq HCl, 85%.

Scheme 273. Synthesis of Seven-Membered Aminocarbasugar Analogues[a]



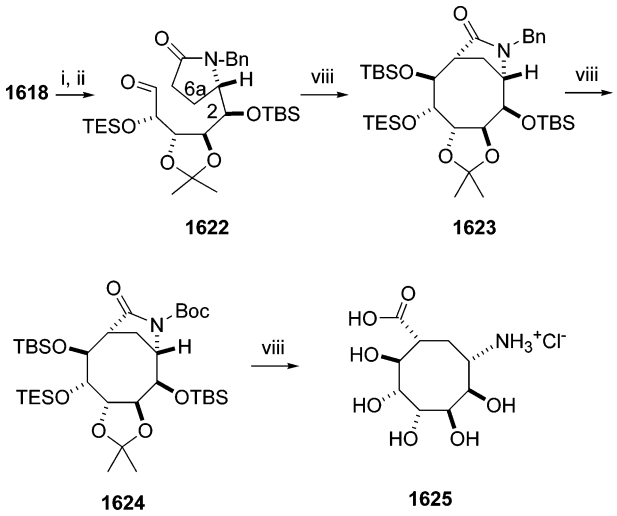
[a] Reagents: (i) $SnCl_4$, 81%; (ii) $NaBH_4$, $NiCl_2$; (iii) TBSOTf, 2,6-lutidine; (iv) CAN; (v) BnCl, 69%; (vi) aq AcOH, 48%, five steps; (vii) aq $NaIO_4$, 96%; (viii) TBSOTf, $(i\text{-}Pr)_2NEt$, 80%; (ix) Na, liq NH_3; (x) Boc_2O, DMAP, 90%, two steps; (xi) $NaBH_4$; (xii) 6 N aq HCl, 80%, two steps; (xiii) 6 N aq HCl, 85%.

6.3.2. Ring-Closing Metathesis

Sinaÿ and co-workers used a RCM strategy in their synthesis of seven- and eight-membered carbasugar analogues.[535] Their retrosynthetic analysis, shown in Figure 51, represents a nice extension of Eustache's approach for the synthesis of six-membered carbasugar analogues (see Scheme 223c).

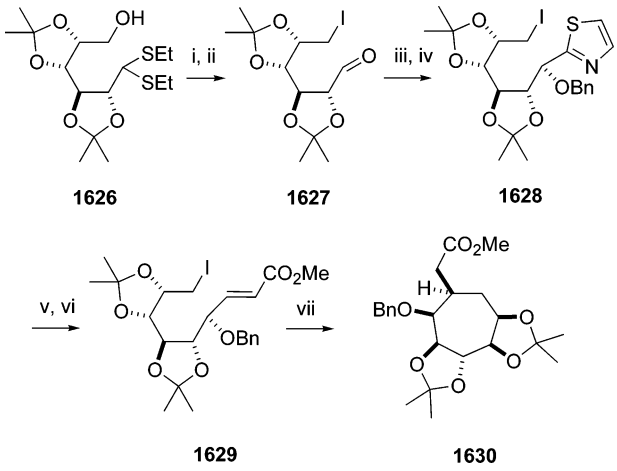
Accordingly, dienes **1585**, **1587**, and **1589** were prepared from alkenyl ketone **1328** (Scheme 269), and the key carbocyclization step was then examined using Grubbs' (**523**) and modified Grubbs' (**525**) catalysts, as the addends. The authors discovered a remarkable effect on the yields of the RCM depending on the catalyst and the (protected or not) substrate (see Scheme 269). The corresponding polyoxygenated cycloheptanes and cyclooctanes were obtained from cycloalkenes **1586** and **1588**, by *syn*-dihydroxylation followed by hydrogenolysis (Scheme 270).

Scheme 274. Synthesis of Eight-Membered Aminocarbasugar Analogues[a]



[a] Reagents: (i) TESOTf, py, DMAP; (ii) Swern oxidation, 81%, two steps; (iii) TBSOTf, $(i\text{-}Pr)_2NEt$, 85%; (iv) Na/NH_3; (v) Boc_2O, DMAP, 90%, two steps; (vi) 6 N aq HCl, 80%.

Scheme 275. Approach to Seven-Membered Carbasugars Based on 7-*exo-trig* Radical Cyclization[a]



[a] Reagents: (i) I_2, Ph_3P, $PhCH_3$, imidazole (70%); (ii) HgO, $HgCl_2$, acetone (75%); (iii) 2-(trimethylsilyl)thiazole (60%); (iv) NaH, BnBr (92%); (v) previous work; (vi) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2 (*E*, 73%; *Z*, 8%); (vii) AIBN, $HSnBu_3$, 80 °C, slow addition, 5 h, 50%.

6.3.3. Silylative Cycloaldolization

Recently, Casiraghi, Rassu, and co-workers have expanded their strategy (see Figures 45 and 48) to the synthesis of new nonracemic carbaheptanoses **1611**, **1615**, **1616**, *ent*-**1615**, and *ent*-**1616** and carbaoctanose derivative **1625** (Schemes 271−274).[536] Reaction of silyloxy furan **233** and L-threose derivative **1607**[537] furnished **1608**, which, after synthetic manipulations, led to 6a-carbaheptanose **1611** (Scheme 271) via tricyclic compound **1610**. Reaction of **1607** with silyloxy pyrrole **253**, following an analogous synthetic protocol (Scheme 272), led to aminocarbaheptanose deriva-

tives **1615** and **1616**. Finally, the use of 2,3:4,5-di-*O*-isopropylidene-D-arabinose (**1617**) as the aldehyde partner of silyloxy pyrrole **253** permitted the syntheses of *ent*-**1615**, *ent*-**1616** (Scheme 273), and carbaoctanose **1625** (Scheme 274). The key steps of these transformations were the intramolecular aldol reactions of compounds **1619** or **1622** and the hydrolytic or reductive opening of *N*-Boc lactams **1621** and **1624**.

6.3.4. 7-exo-trig Radical Cyclization

An approach to 6a-octanoses based on 7-*exo-trig* radical cyclization of a carbohydrate-derived α,β-unsaturated ester-iodide was reported by Marco-Contelles and de Opazo.[538] The synthetic route (Scheme 275) to the radical cyclization precursor was carried out in seven steps from compound **1626**.[427] Iodination of the latter, followed by desulfuration, afforded aldehyde **1627**, which, upon submission to Dondoni's one-carbon homologation process, generated thiazole derivative **1628** and thence α,β-unsaturated ester **1629**. Radical cyclization of **1629** was completely regio- and stereoselective to yield **1630** in 50% yield.

7. Compilation of Synthetic Methods of Carbafuranoses and Carbapyranoses

Suami and Ogawa already assembled the different carbasugars prepared prior to 1990.[16c] We have included, in Tables 5−9, a brief survey of the syntheses of carbafuranoses and carbapyranoses covered in this review. These tables are aimed to provide the reader with an idea of the efficiency of the synthetic methods employed in the preparation of the different carbasugars. Only free and fully acetylated carbasugars have been incorporated in the tables. In this context, Table 5 deals with the syntheses of carbafuranoses and Tables 6−9 comprise the syntheses of carbapyranoses.

8. Conclusion

Four decades have already elapsed since McCasland's group synthesized the first carbocyclic analogue of a carbohydrate: a *carbasugar*. At that time, they could only postulate—and perhaps imagine—that these *pseudo*sugars would enjoy enhanced chemical stability and could replace carbohydrates in their interaction with enzymes and, therefore, be endowed with interesting biological properties. A few years later, their prediction was supported by the discovery of biologically active natural products containing *carbasugars*. Since then, many new interesting biological activities associated with carbasugars, aminocarbasugars, carbaoligosaccharides, and different carbasugar analogues have been discovered. Today, carbasugars have become attractive targets for synthetic, biological, and conformational studies. It seems fair to predict that the future holds considerable promise for advances in all three of these areas, since many biological properties of carbasugars and derivatives might still be the subject of future studies.

Table 5. Synthesis of Carbafuranoses

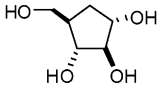
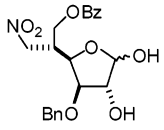
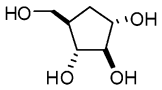
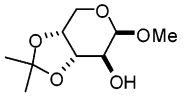
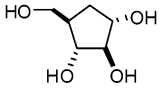
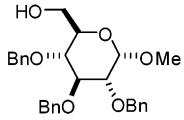
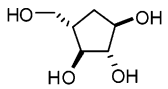
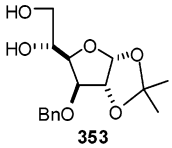
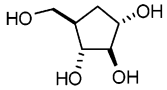
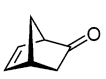
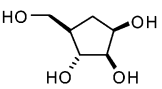
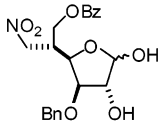
Carbafuranose	Starting material	Number of steps	Overall yield (%)	Reference
 α-D-*arabino*	 **366**	8	<5%	212
 α-D-*arabino*	 **374**	13	12	213
 α-D-*arabino*	 **454**	7	37	225
 α-L-*arabino*	 **353**	11	<5	210
 α-DL-*arabino*	 (±)-**153**	13	<5	160
 β-D-*arabino*	 **366**	8	<5	212

Table 5. Continued

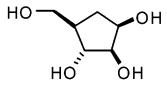
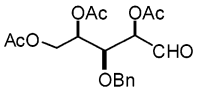
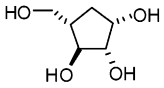
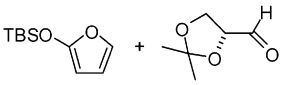
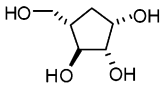
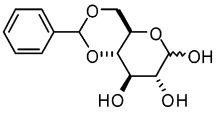
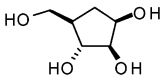
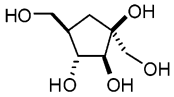
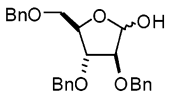
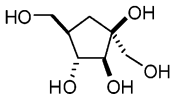
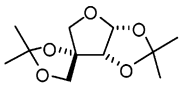
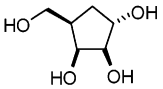
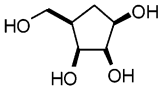
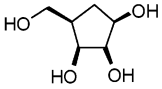
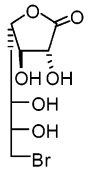
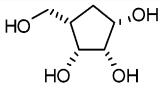
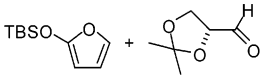
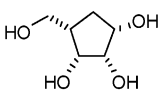
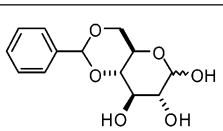
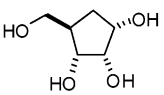
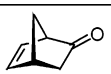
Carbafuranose	Starting material	Number of steps	Overall yield (%)	Reference
 β-D-*arabino*	 **348**	15	7	209
 β-L-*arabino*	 **233** **234**	9	11	177
 β-L-*arabino*	 **339**	10	8	207
 β-DL-*arabino*	 (±)-**153**	16	5	160
 D-*fructo*-	 **401**	10	17	219
 D-*fructo*-	 **539**	15	24	250
 α-D-*lyxo*	 (+)-**153**	12	8	160
 β-D-*lyxo*	 (+)-**153**	15	5	160
 β-D-*lyxo*	 **431**	8	28	223
 β-L-*lyxo*	 **233** **234**	9	17	177
 β-L-*lyxo*	 **339**	17	6	207
 α-D-*ribo*	 (+)-**153**	16	13	158

Table 5. Continued

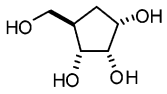
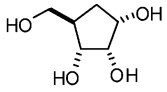
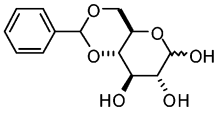
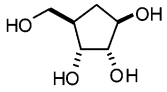
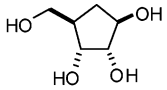
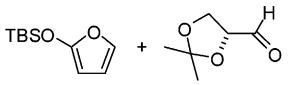
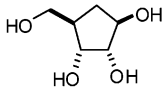
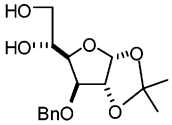
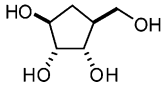
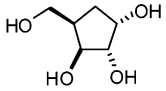
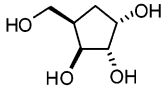
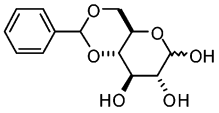
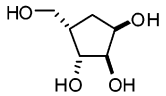
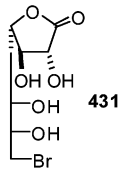
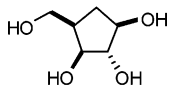
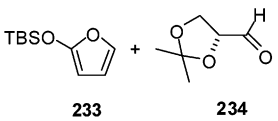
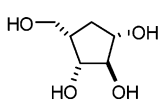
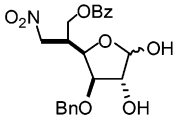
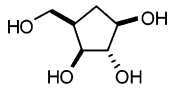
Carbafuranose	Starting material	Number of steps	Overall yield (%)	Reference
 **α-D-*ribo***	 **264**	8	<5	182
 **α-D-*ribo***	 **339**	18	<5	208
 **β-D-*ribo***	 **(+)-153**	13	27	158
 **β-D-*ribo***	 **233** **234**	8	22	177
 **β-D-*ribo***	 **353**	11	<5	210
 **β-L-*ribo***	 **264**	12	6	182
 **α-D-*xylo***	 **(+)-153**	9	9	160
 **α-D-*xylo***	 **339**	19	<5	208
 **α-L-*xylo***	 **431**	8	11	223
 **β-D-*xylo***	 **233** **234**	9	15	176
 **β-L-*xylo***	 **366**	8	<5	212
 **β-DL-*xylo***	 **(±)-153**	10	18	160

Table 6. Racemic Carbapyranoses

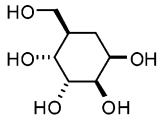
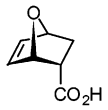
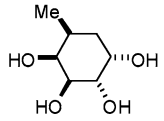
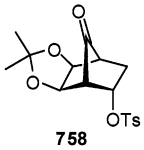
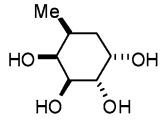
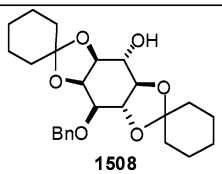
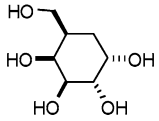
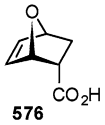
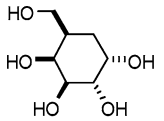
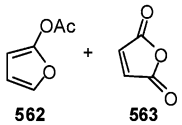
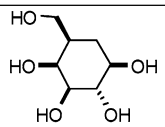
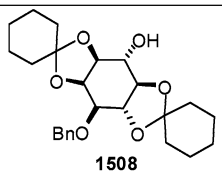
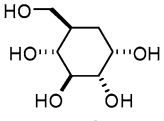
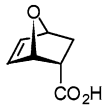
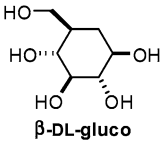
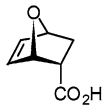
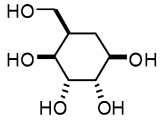
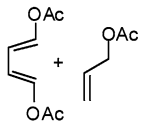
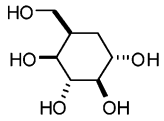
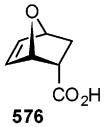
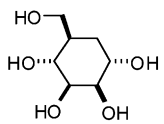
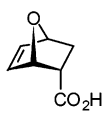
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 β–DL-*altro*	 **576**	6	<5	261
 α-DL-*fuco*	 **758**	7	24	324
 α-DL-*fuco*	 **1508**	10	29	517
 α-DL-*galacto*	 **576**	7	8	261
 α-DL-*galacto*	 **562** **563**	8	<5	11
 β-DL-*galacto*	 **1508**	10	23	517
 α-DL-gluco	 **576**	9	27	310
 β-DL-gluco	 **576**	7	14	261
 β-DL-*gulo*	 **571** **572**	4	23	12
 α-DL-*ido*	 **576**	4	9	261
 α-DL-*manno*	 **576**	6	<5	261

Table 6. Continued

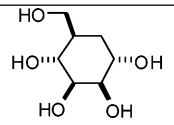
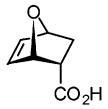
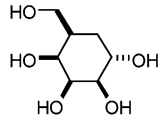
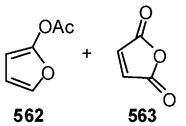
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 β-DL-*manno*	 **576**	6	6	261
	 **562** **563**	6	9	10

Table 7. Fully Acetylated, Racemic Carbapyranoses

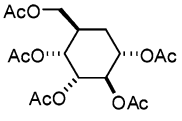
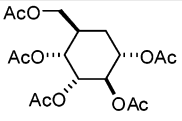
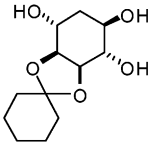
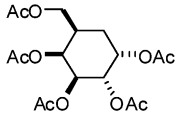
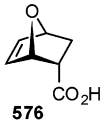
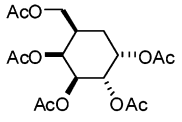
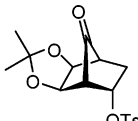
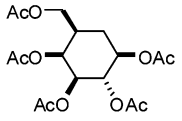
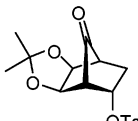
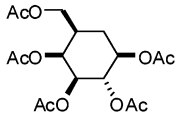
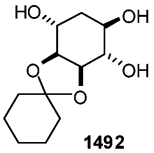
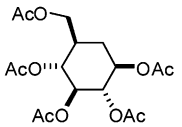
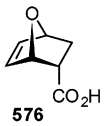
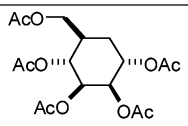
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 α-DL-*altro*	 **749**	4	17	322
 α-DL-*altro*	 **1492**	6	<5	513
 α-DL-*galacto*	 **576**	6	8	261
 α-DL-*galacto*	 **758**	5	43	324
 β-DL-*galacto*	 **758**	6	7	324
 β-DL-*galacto*	 **1492**	6	<5	513
 β-DL-*gluco*	 **576**	6	14	261
 α-DL-*manno*	 **749**	5	12	322

Table 7. Continued

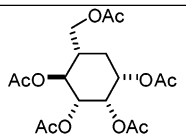
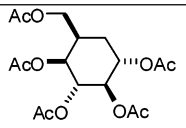
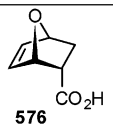
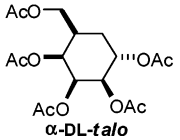
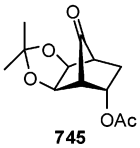
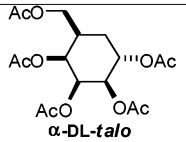
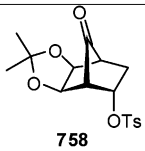
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 β-DL-*manno*	 **749**	5	12	322
 α-DL-*ido*	 **576**	6	<5	261
 α-DL-*talo*	 **745**	6	28	323
 α-DL-*talo*	 **758**	6	18	324

Table 8. Enantiomerically Pure Carbapyranoses

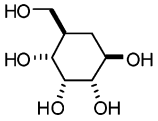
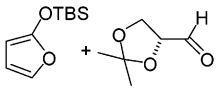
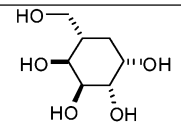
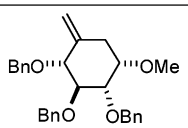
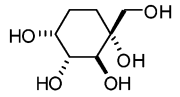
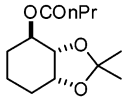
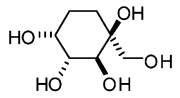
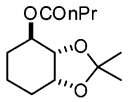
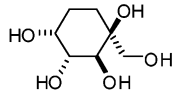
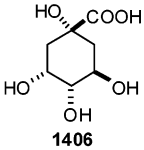
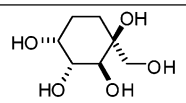
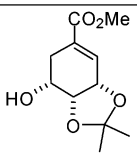
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 β–D-*allo*	 **233** **234**	8	5	176, 346
 β-L-*altro*	 **1024**	4	Not given	388
 α-D-*fructo*	 (±)-**874**	8	11	350
 β-D-*fructo*	 (±)-**874**	8	7	350
 β-D-*fructo*	 **1406**	12	12	475, 476
 β-D-*fructo*	 **1414**	6	22	477

Table 8. Continued

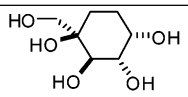
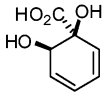
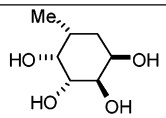
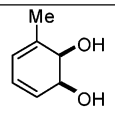
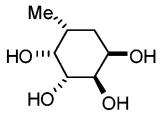
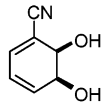
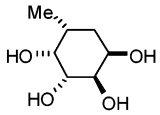
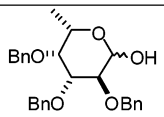
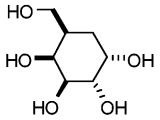
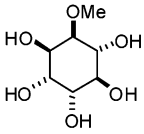
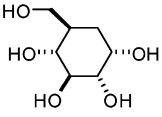
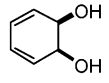
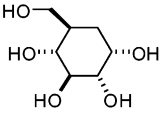
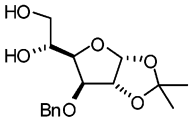
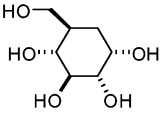
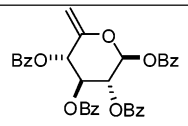
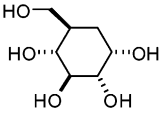
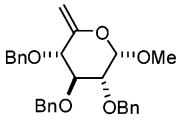
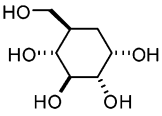
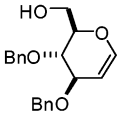
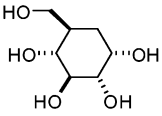
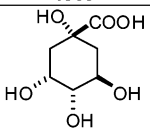
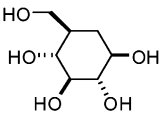
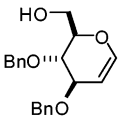
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 β-L-*fructo*	 **1422**	7	40	478
 α-L-*fuco*	 **815**	4	<5	335
 α-L-*fuco*	 **819**	7	13	336
 α-L-*fuco*	 **935**	9	33	87
 α-D-*galacto*	 **1523**	13	7	528
 α-D-gluco	 **787**	13	19	329
 α-D-gluco	 **985**	11	5	353
 α-D-gluco	 **1041**	8	20	383
 α-D-gluco	 **1024**	5	Not given	388
 α-D-gluco	 **1399**	6	29	471
 α-D-gluco	 **1406**	14	22	481, 482
 β-D-gluco	 **1399**	7	13	471

Table 8. Continued

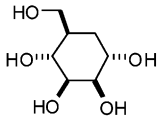
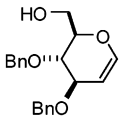
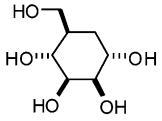
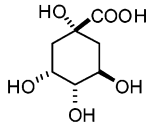
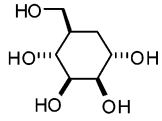
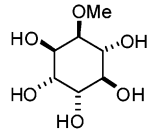
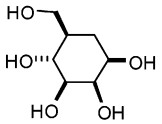
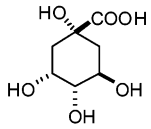
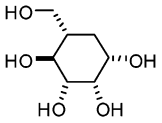
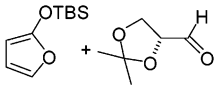
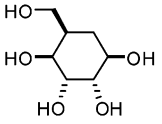
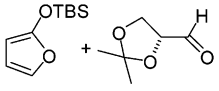
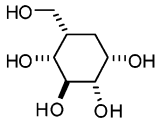
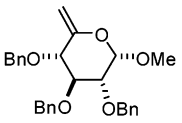
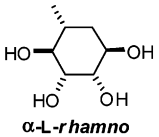
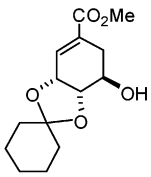
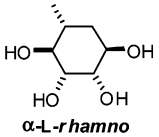
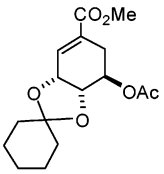
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 α-D-*manno*	 **1399**	7	9	471
 α-D-*manno*	 **1406**	11	<5	481, 482
 α-D-*manno*	 **1523**	16	7	528, 529
 β-D-*manno*	 **1406**	7	55	481, 482
 β-L-*manno*	 **233** **234**	11	10	346
 β-D-*gulo*	 **233** **234**	8	34	176, 346
 β-L-*ido*	 **1024**	5	Not given	388
 α-L-*rhamno*	 **1476**	6	45	506
 α-L-*rhamno*	 **1480**	6	35	507

Table 9. Enantiomerically Pure, Fully Acetylated, Carbapyranoses

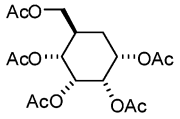
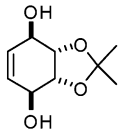
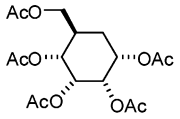
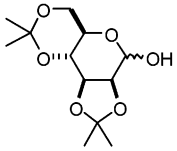
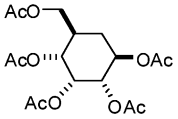
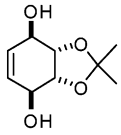
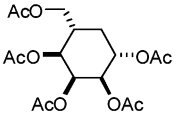
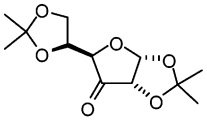
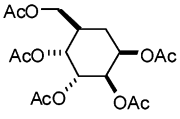
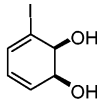
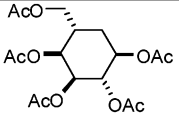
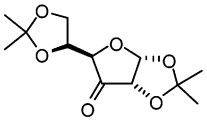
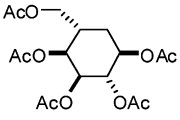
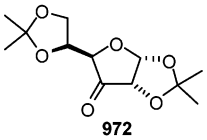
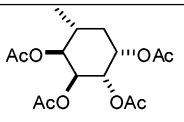
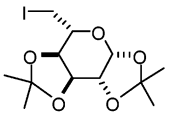
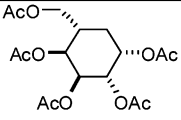
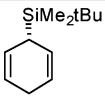
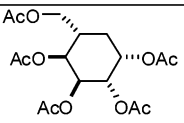
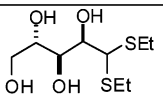
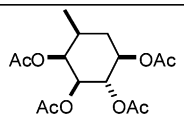
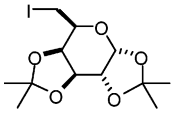
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 ***α*–D-*allo***	 **790**	17	22	332
 ***α*–D-*allo***	 **1264**	17	5	442
 ***β*–D-*allo***	 **790**	15	31	332
 ***β*–L-*allo***	 **972**	14	<5	362
 ***β*-D-*altro***	 **811**	9	41	334
 **α-L-*altro***	 **972**	14	9	361
 **α-L-*altro***	 **972**	16	<5	361, 362
 **6-deoxy-α-L-*altro***	 **1175**	7	14	424
 **β-L-*altro***	 **825**	10	24	340
 **β-L-*altro***	 **943**	12	<5	356, 357
 **β-D-*fuco***	 **1175**	7	<5	424

Table 9. Continued

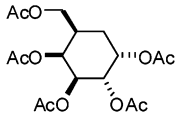
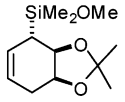
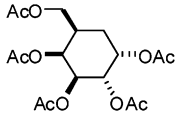
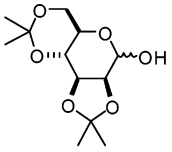
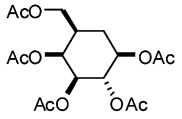
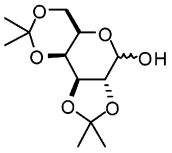
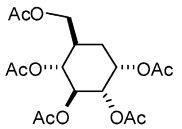
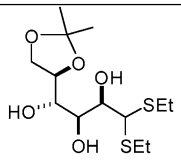
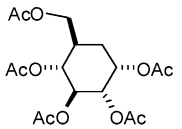
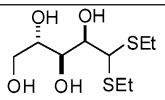
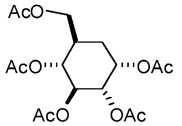
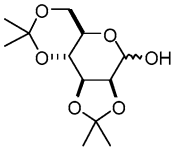
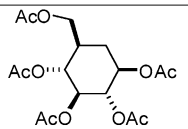
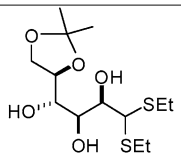
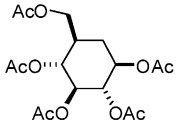
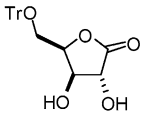
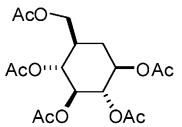
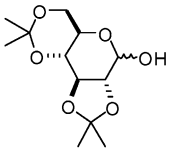
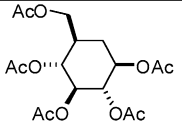
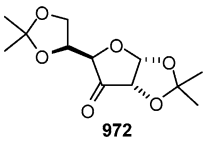
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 α-D-*galacto*	 **836**	6	29	340
 α-D-*galacto*	 **1264**	15	<5	443
 β-D-*galacto*	 **1306b**	11	7	446
 α-D-*gluco*	 **915**	11	<5	353
 α-D-*gluco*	 **943**	12	<5	356, 357
 α-D-*gluco*	 **1264**	14	<5	443
 β-D-*gluco*	 **915**	11	7	353
 β-D-*gluco*	 **1132**	12	20	415
 β-D-*gluco*	 **1306a**	11	<5	446
 β-D-*gluco*	 **972**	14	<5	361, 362

Table 9. Continued

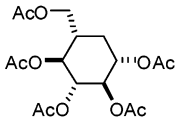
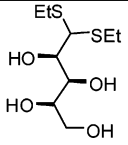
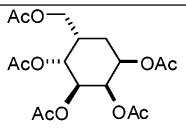
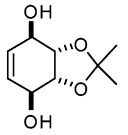
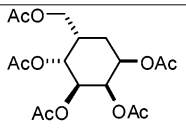
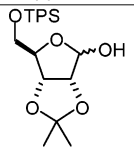
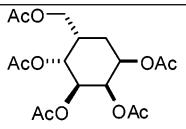
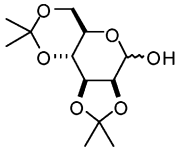
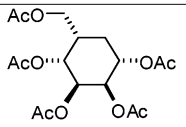
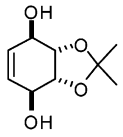
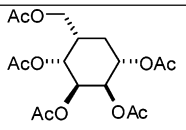
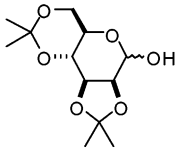
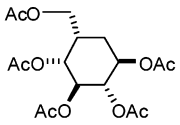
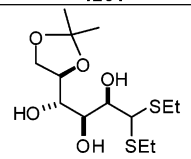
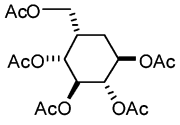
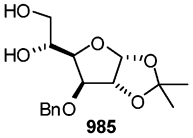
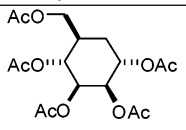
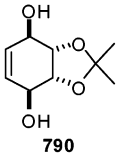
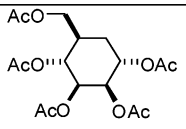
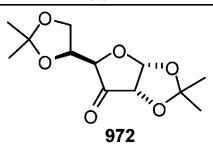
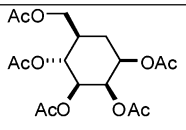
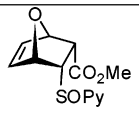
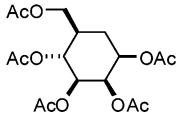
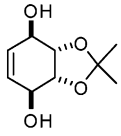
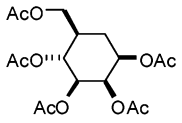
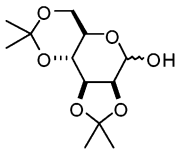
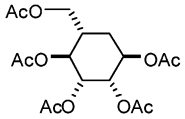
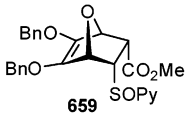
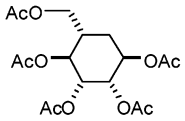
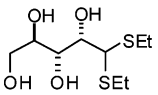
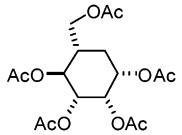
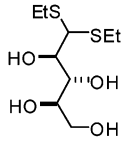
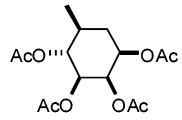
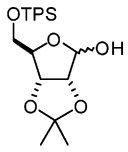
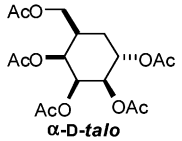
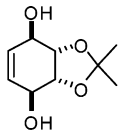
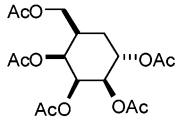
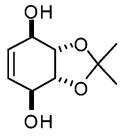
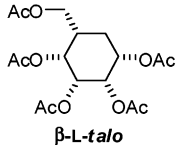
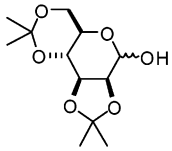
Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 **β–L-*gluco***	 **958**	12	<5	207b
 **α-L-*gulo***	 **790**	11	36	332, 333
 **α-L-*gulo***	 **1158**	9	8	437
 **α-L-*gulo***	 **1264**	14	<5	442
 **β-L-*gulo***	 **790**	8	44	332, 333
 **β-L-*gulo***	 **1264**	12	<5	443
 **β-L-*ido***	 **915**	11	<5	353
 **β-L-*ido***	 **985**	12	<5	363
 **α-D-*manno***	 **790**	12	42	332
 **α-D-*manno***	 **972**	13	<5	361, 362
 **β-D-*manno***	 **653**	16	8	290

Table 9. Continued

Carbapyranose	Starting material	Number of steps	Overall yield (%)	Reference
 β-D-*manno*	 **790**	11	43	332, 333
 β-D-*manno*	 **1264**	13	6	440
 α-L-manno	 **659**	11	<5	290
 α-L-manno	 **950**	15	5	207b
 β-L-*manno*	 **956**	15	<5	207
 β-D-*rhamno*	 **1158**	9	11	437
 α-D-*talo*	 **790**	10	41	332,333
 β-D-*talo*	 **790**	10	41	332, 333
 β-L-*talo*	 **1264**	11	<5	443

9. Acknowledgments

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10. References

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