ADVANCES IN THE ENANTIOSELECTIVE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES

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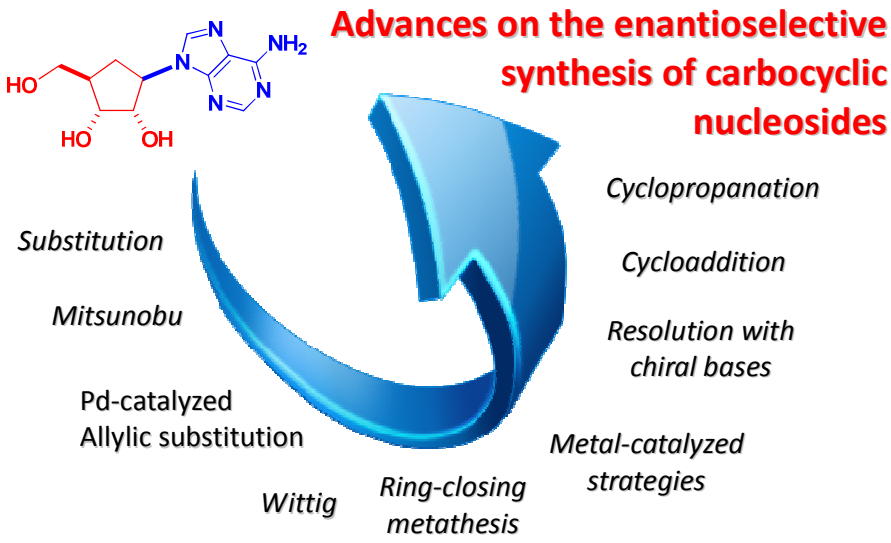


Abstract

Carbocyclic nucleosides are nucleoside analogues in which the furanosidic moiety has been replaced by a carbocycle. Several members of this family have been isolated from natural sources and include a 5-membered ring carbocycle. The aim of this review is to examine critically the different methodologies for the enantioselective construction of 3- to 6-membered rings, with a particular focus on 5-membered rings and their modifications, with emphasis on the synthesis of structurally useful carbocyclic nucleosides. The procedures for bonding the heterocyclic moiety and the carbohydrate are treated separately. The methods for synthesising the carbocyclic moiety mainly focus on the construction of the cycle, although precise details about the functionalisation are provided in some cases. The selected methods aim to provide an overview of the synthesis of carbocycles related to the synthesis of carbocyclic nucleosides. The methods of synthesis of 5-membered rings are classified into two types: methods in which the cyclopentane ring is formed by ring closing reactions (C=C and C-C formation) and methods that start from preformed 5-membered rings, based mainly in cycloaddition reactions. With respect to the methods of synthesis of 3-, 4- and 6-membered ring carbocyclic nucleosides, a selection of the more relevant enantioselective procedures is presented in a systematic manner.

1. INTRODUCTION

The synthesis of modified nucleosides, and in particular the preparation of their carbocyclic counterparts, is an important topic in medicinal chemistry. The substitution of the endocyclic oxygen atom by a CH_2 moiety increases not only the chemical stability of the *N*-glycosidic bond but also makes these derivatives metabolically resistant to the action of several enzymes such as pyrimidine and purine nucleoside phosphorylases. Some 5-membered carbocyclic nucleosides have been isolated from natural sources and exhibit significant biological activity (Figure 1). Only a limited number of these nucleosides, however, have been developed into drugs, due either to high toxicity or low activity that is, in part, attributed to their conformational flexibility. These limitations have motivated the search for new carbocyclic nucleoside analogues with improved activity/toxicity profiles. Recently, the emergence of drug-resistant and pandemic viruses (HIV, H1N1, avian influenza H5N1, etc.) has spurred the synthetic community to seek flexible methodologies that might result in easy access to new generations of more efficient and selective nucleoside drugs. Many different synthetic approaches for the enantioselective synthesis of 5-membered rings as well as the synthesis of 3-, 4- and 6-membered rings have been reported. Moreover, the specific structural characteristics of nucleosides and the possibility of late-stage derivatisation of the aromatic ring have enabled the construction of a large library of compounds with valuable chemical diversity. Several reviews covering different aspects of carbocyclic nucleosides, such as their syntheses and biological properties,[1,2] or more specialised aspects of their chemistry such as their synthesis using ring- losing metathesis reactions,[1] have been published during the last decade. Indeed, a recent review describes the synthesis and the biological properties of the lead compounds of this family and derivatives thereof but primarily focuses on their antiviral activities.[3] The last general review covering the chemistry of carbocyclic nucleosides was published in 1998.[4] The aim of this review is to critically examine the different methodologies for the enantioselective construction of 3- to 6-membered rings, with a specific focus on 5-

membered rings, and to ecamine modifications of these rings with emphasis on the synthesis of structurally useful carbocyclic nucleoside constructs. The preparation of relevant carbocyclic nucleosides will be presented as examples of efficient synthetic protocols.

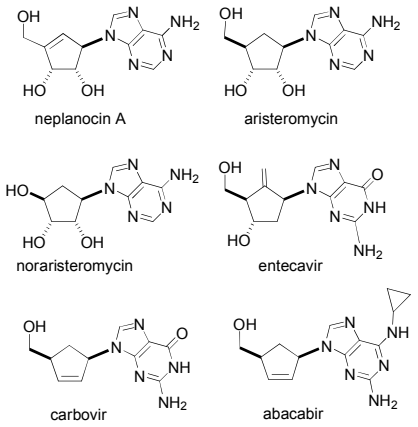
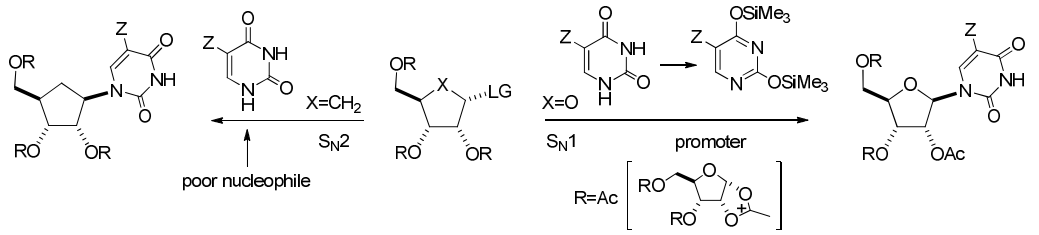


Figure 1. Selected examples of relevant carbocyclic nucleosides.

1. METHODS FOR COUPLING THE HETEROCYCLIC BASE WITH THE CARBOCYCLIC PSEUDOSUGAR

In nucleoside chemistry, the attachment of the nucleobase to the furanose ring is essentially an S_N1 process in which the key variables are the leaving group/promoter pair, the conformation of the oxonium cation intermediate and the presence of participating groups at the C-2 position, which usually controls the stereochemical course of the glycosylation. One problem is the low nucleophilicity and solubility of nucleobases in organic solvents. This problem is typically circumvented through the use of silyl derivatives (Scheme 1, X=O). For carbocyclic nucleosides, however, the attachment of the nucleobase to the carbocycle ($X=CH_2$) occurs through an S_N2 process, which also has the limitation of having low nucleophilicity for nucleobases. In this case the silylated bases are not nucleophilic enough. For this reason, procedures that do not require good nucleophiles, such as Mitsunobu reactions and palladium-catalysed allylic aminations, or even the generation of heterocyclic bases from cyclopentyl amines, are the procedures of choice.



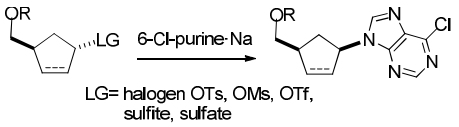
Scheme 1. Introduction of the base in nucleosides *versus* carbocyclic nucleosides.

In this context, the synthesis of carbocyclic nucleosides involves 2 basic approaches: a convergent synthesis, in which a cyclopentyl derivative is condensed with an intact nucleobase, and a linear route, in which the heterocyclic base is generated from a cyclopentyl amine derivative.

2.1. Convergent synthesis. Methods based on nucleophilic substitution/addition.

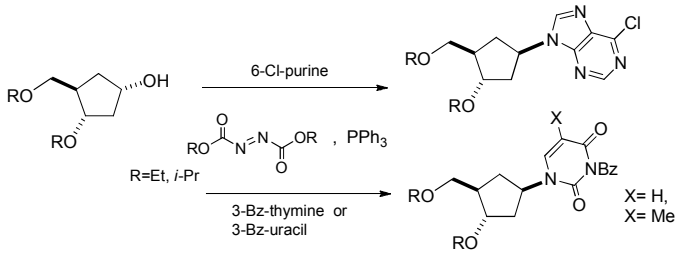
There are 3 main procedures based on nucleophilic substitution/addition: i) direct S_N2 reaction, ii) palladium-catalysed allylic substitution and, iii) conjugate addition. General trends in these reactions are the use of 6-chloropurine instead of adenine and 4,6-dichloropurine instead of guanine, due to their greater solubility in organic solvents. As for pyrimidinic bases, uracil and thymine are generally protected at the *N*-3 position to prevent competing reactions at this site.

i) Direct nucleophilic substitution using nucleic base salts is usually limited to purinic bases due to the decreased nucleophilicity of pyrimidinic bases (Scheme 2). The reaction entails the displacement of halides, sulphonate esters (OTs, OMs and OTf) or sulphite and sulphate derivatives, and takes occurs with inversion of configuration at the carbon linked to the leaving group.



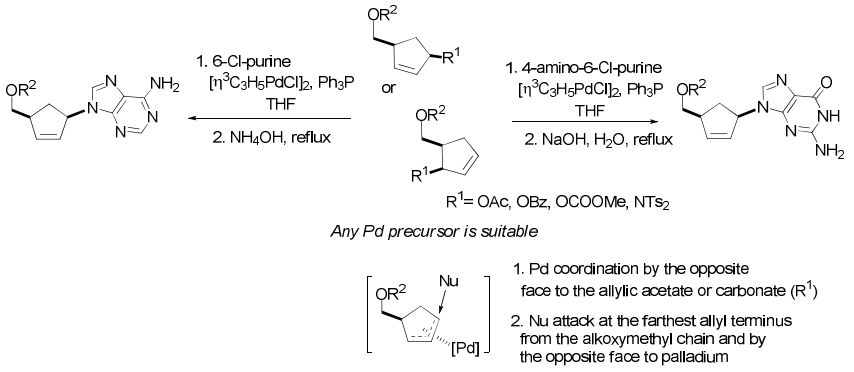
Scheme 2. Direct nucleophilic substitution

The Mitsunobu reaction is widely used in nucleoside chemistry and comprises the substitution of alcohols with acidic nucleophiles in the presence of diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), and triphenylphosphine. The acidity of the protons bonded to nitrogen atoms makes nucleic bases appropriate for this reaction. Both pyrimidinic and purinic bases are successfully used, and the reaction occurs with inversion of configuration (Scheme 3).



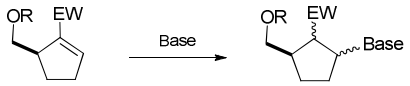
Scheme 3. Coupling the base and the carbocycle via a Mitsunobu reaction.

ii) Palladium-catalysed allylic substitution allows a very efficient introduction of nucleic bases into cyclopentenes bearing an ester, carbonate or ditosylimide moiety at the allylic position. The regioselectivity of the reaction is governed by steric factors and by the nature of the catalyst, while the stereochemistry also depends on the nature of the nucleophile. For nucleic bases, the reaction occurs with retention of configuration due to a double inversion mechanism (Scheme 4). Pd/PPh_3 complexes are commonly used as a catalytic system when chiral substrates are used, but chiral ligands can also be used for desymmetrisation processes, which usually start from *meso* cyclopent-4-ene-1,3-diyl diacetate (See Schemes 22 and 23).



Scheme 4. Synthesis of carbocyclic nucleosides by Pd-catalysed allylic amination.

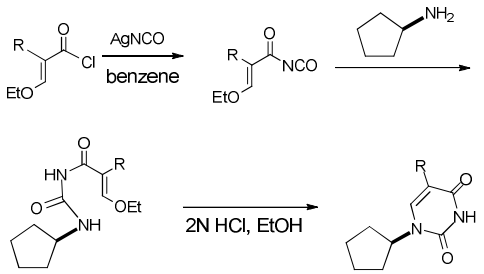
iii) Conjugate addition. Nucleic bases can be introduced by Michael addition to an activated alkene, although very few examples of this approach have been reported.



Scheme 5. Introduction of nucleic bases by Michael addition.

2.2. Linear routes. Base construction from cyclopentylamines

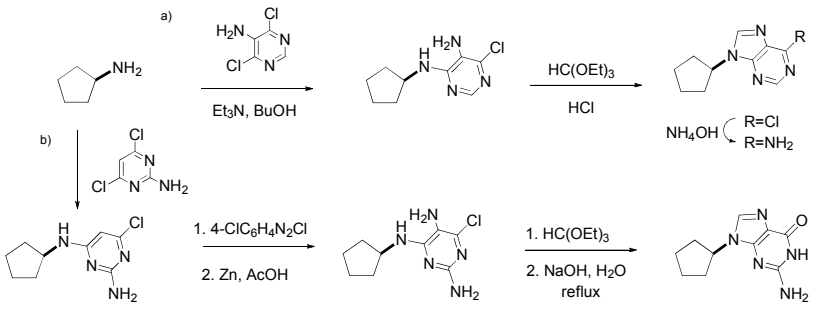
iv) Pyrimidinic bases. The amino group in a carbocyclic amine can become the *N*-9 site of a purine moiety or the *N*-1 of a pyrimidine in the final nucleoside. There are well-defined strategies for building uracil and thymine from an amino group. These strategies are based on the reaction of acylisocyanate, or a related carbamate, which can be obtained from (*E*)-3-ethoxy-methyl-acryloyl chloride with silver isocyanate, with an aminocycloalkane to give a urea intermediate that then undergoes cyclizsation induced by acid or base[5] (Scheme 6).



Scheme 6. Synthesis of uracil and thymine from an amino group.

v) The synthesis of purine derivatives is typically accomplished by coupling the cyclopentylamine with a 5-amino-4,6-dichloropyrimidine, which is followed by the construction of the imidazole ring through a reaction with triethyl orthoformate (Scheme 7a).[6] Adenine analogues are then obtained by nucleophilic substitution of chloride in the 6-chloropurine derivative with ammonia. Guanine derivatives are prepared by a similar sequence (Scheme 7b) that involves condensation of the cyclopentylamine with 2-amino-4,6-dichloropyrimidine, formation of the diazo compound through a reaction with benzene diazonium chloride and reduction with zinc to generate the diamino derivative. Finally, the

reaction with ethyl orthoformate and sodium hydroxide completes the formation of the guanine moiety.



Scheme 7. Construction of adenine and guanine moieties from an amino group

3. METHODS FOR CONSTRUCTING AND MODIFYING THE CARBOCYCLE

3.1 5-membered ring

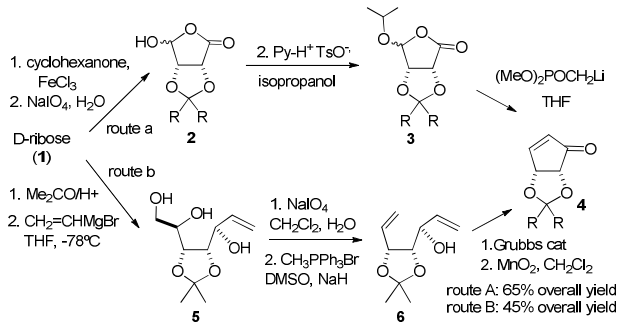
Cyclopentane nucleosides are the most widely studied. There are many approaches for the enantioselective construction of the cyclopentane ring but most of these approaches are based on the use of compounds from the chiral pool, from which a set of key intermediates can be obtained. Cyclopentadiene easily undergoes cycloaddition reactions, particularly Diels-Alder reactions involving singlet oxygen, tosyl cyanide and other reagents, threby yielding versatile intermediates. Recently, some transition metal-catalysed reactions have also been successfully used, particularly ring-closing metathesis (RCM), which has emerged as a powerful tool for the construction of carbocycles. Taking into account these considerations, this section focuses on methods for synthesising cyclopentanes and is organised as follows: a) methods based on ring-closing reactions and, b) methods based on cyclopentadiene as a starting material.

3.1.1 Methods based on ring-closing reactions

Ring-closing processes by formation of double bonds. Wittig *versus* metathesis reactions. Wittig-type reactions and metathesis reactions are powerful methodologies for cyclopentene ring formation. The initial procedures based on Wittig-type reactions have been progressively substituted by ring-closing metathesis reactions (RCM) which offer a general, efficient and

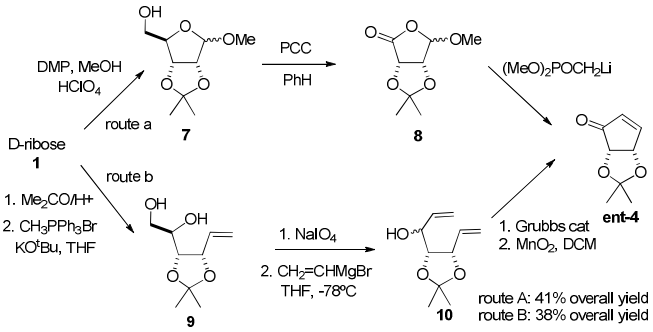
modular methodology for the preparation of key intermediates from appropriate building blocks. However, although the chiral version of RCM has been developed, there are no examples of this application in the synthesis of carbocyclic nucleosides. Thus, RCM and Wittig type reactions are used in the enantioselective synthesis of carbocycles from appropriate precursors obtained from the chiral pool or by using chiral auxiliaries.

In this context, cyclopentenones have been strategic intermediates in the field because of the ease with which they can be functionalised. In particular, cyclopentanones **4** and **ent-4** (Schemes 8 and 9) are among the most versatile synthons for synthesising carbocyclic nucleosides and several reports describe their synthesis using Wittig-type and RCM reactions. Thus, **4** has been synthesised from either D-ribonolactone[7] D-ribose[8,9] or D-isoascorbic acid.[10] In Schemes 8 and 9 the synthesis of **4** and **ent-4** from D-ribose using a Wittig-type (route a)[7,8] or RCM (route b)[9,10] reactions as key steps is presented. The synthesis of **4** begins through the reaction of D-ribose with cyclohexanone in the presence of iron trichloride followed by reaction with sodium periodate to produce compound **2**, from which compound **3** was obtained by treatment with isopropanol in an acidic medium. The reaction of **3** with lithium phosphonate with concomitant ring- losing through a Wittig-Wadsworth-Emmons reaction gave **4** in 65% overall yield. The synthesis utilising RCM as a key step begins with a partial protection of the D-ribose followed by reaction with vinyl magnesium bromide to give **5**. Further cleavage of the diol followed by olefination of the resulting aldehyde afforded **6**, from which RCM followed by oxidation of the allyl alcohol yielded **4** in 45% overall yield.



Scheme 8. Synthesis of synthon **4** by Wittig and RCM as key reactions

The enantiomer **ent-4** was prepared following a related strategy starting from D-ribose. Thus, in the Wittig approach, partially protected D-ribose **7** was converted into **8** by oxidation with PCC involving cleavage of the C4-C5 bond. Lactone **8**, which is pseudoenantiomeric with **3**, was treated with lithium phosphonate with concomitant ring-closing to produce **ent-4** in 41% yield in only 3 steps (Scheme 9, route a). Compound ent-**4** was also prepared from D-ribose using a RCM reaction as a key step through a reaction sequence inverse to the sequence used in Scheme 8. Thus, in this case the synthesis began with olefination of 2,3-*O*-isopropylidene-D-ribose affording **9**, which was later treated with sodium periodate and the resulting aldehyde was reacted with vinylmagnesium bromide to produce **10**. Ring-closing metathesis followed by oxidation provided compound **ent-4** in 38% overall yield (Scheme 9, route b).

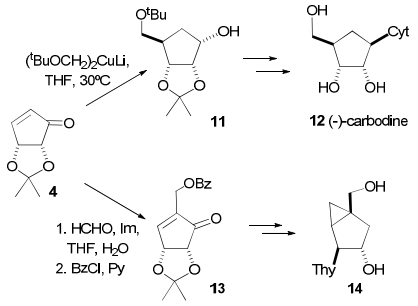


Scheme 9. Synthesis of synthon **ent-4** by Wittig and RCM as key reactions

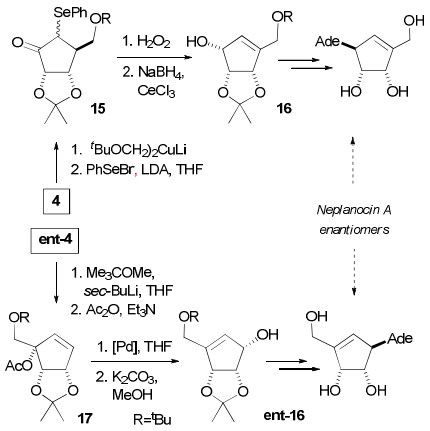
Compound **4** has a rich reactivity determined by the enone system, which, together with the excellent control of stereoselectivity due to the presence of the bicycle, makes this compound a versatile intermediate in the synthesis of carbocyclic nucleosides. Examples of the easy

functionalisation of compounds **4** and **ent-4** to produce important precursors of carbocyclic nucleosides such as **11**, **13**, **16** and **ent-16**, are presented in Schemes 10 and 11. Therefore, the conjugate addition of an alkylcuprate to enone **4** and subsequent stereoselective reduction produced **11**. Replacement of the hydroxyl for an amino group and construction of the cytosine moiety produced (-)- arbodine **12**.[11] Following a similar approach adenine was directly introduced through a S_N2 type reaction to produce arysteromicin. Alternatively, the reaction of **4** with formadehyde and imidazole as a base afforded **13** by means of a Bayllis-Hillman reaction. Compound **13** was then transformed into the conformationally restricted nucleoside **14**.[12]

In a different functionalisation, a tandem cuprate addition to compound **4** followed by selenenylation of the enolate intermediate produced **15** (Scheme 11). Oxidation of **15** regenerated the enone, and further reduction of the carbonyl group produced the key intermediate **16**. Alternatively, addition to the carbonyl in **ent-4** and acetylation produced **17**, which was transformed into **ent-16** by palladium- atalysed isomerisation and hydrolysis. In this manner, both enantiomers **16** and **ent-16** are accessible from **4** and **ent-4**, respectively, and both enantiomers of neplanocin A were obtained from these compounds.[7]



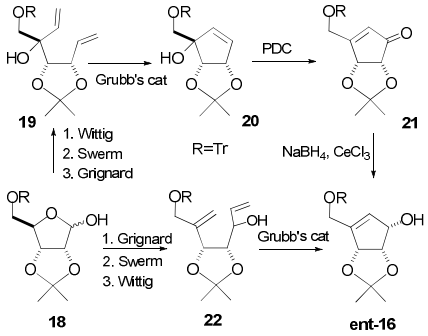
Scheme 10. Useful transformations from synthon **4**



Scheme 11. Synthesis of both neplanocin A enantiomers from **4** and **ent-4**

Two different approaches to **ent-16**, and, consequently, to neplanocin A, that are also based on RCM as a key step are shown in Scheme 12. In these examples, all carbons of the starting D-ribose were incorporated in the final product. The synthesis started from protected D-ribose **18**, which was treated with vinylmagnesium chloride (Grignard), DCC/DMSO (Swerm oxidation) and methylentriphenylphosphorane (Wittig) to provide **22**. Compound **19** could be obtained by simply inverting the order of these reactions. Compound **22** directly afforded **ent-16** by RCM.[13] Reaction of diene **19** in the presence of Grubbs catalyst yielded cyclopentene **20**, which was converted into **21** by oxidation with PDC (a related transformation using palladium chemistry is presented in Scheme 11). Stereoselective reduction of **21** afforded **ent-16**.[14]

Thus, the diene **19**, which was obtained from D-ribose by vinylmagnesium bromide addition, oxidation, and Wittig reaction, was subsequently treated with the Grubbs catalyst to produce the allylic alcohol **ent-16** (epimeric mixture, see Scheme 11), which was efficiently converted into the key D-cyclopentenone intermediate **20** by oxidation with manganese dioxide. For a synthesis of an **ent-16** derivative based on an intramolecular aldol reaction see Scheme 16 as well.

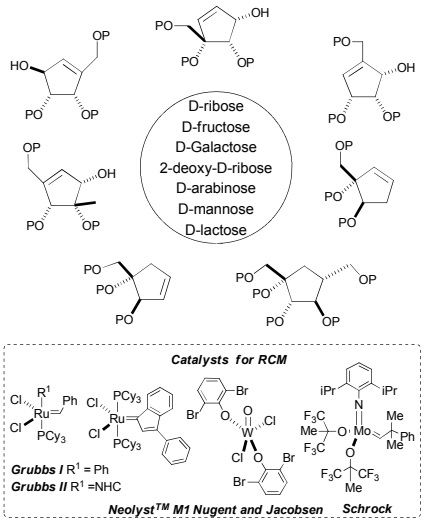


Scheme 12. Synthesis of **ent-16** from D-ribose using RCM as a key step.

Many others carbocyclic intermediates have been prepared from carbohydrates using RCM as the key step. Scheme 13 summarises the carbohydrate precursors typically employed for these transformations as well as the main key intermediates obtained.[1] These intermediates are further elaborated to the final carbocyclic nucleoside derivatives. Carbohydrate precursors include pentoses such as D-ribose,[10,15,16] 2-deoxy-D-ribose,[17] and D-xylose[15] and hexoses such as D-fructose,[18] D-glucose,[19] D-galactose,[15,20] D-mannose,[15] and D-lactose.[21]

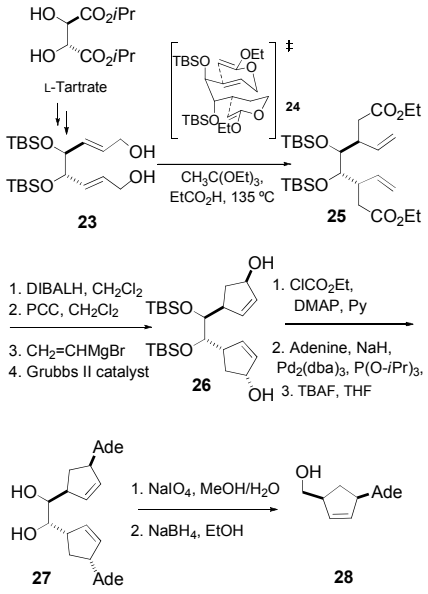
The transition metal catalysts usually employed in RCM for the synthesis of 5-membered carbosugar structures are traditionally molybdenum- and tungsten-based catalysts, such as the catalysts developed by Schrock, Nugent and Jacobsen, respectively, and the ruthenium-based catalysts developed by Grubbs (Scheme 13). Although early reports describe the preparation of highly functionalised cyclopentene derivatives by RCM reactions using Schrock catalyst from sterically demanding alkenes derived from D-arabinose and D-mannose,[22] recent improvements of ruthenium complexes have broadened the scope of this powerful reaction and therefore have reduced interest in other types of catalysts.

An interesting procedure for preparing 2',3'-dideoxynucleoside drugs such as carbovir using a RCM reaction as a key step starting from a non-carbohydrate precursor is shown in Scheme14. Starting from L-tartrate[23] and following a synthetic route that involves the initial preparation of bis-allylic alcohol **23**, the γ,δ-unsaturated ethyl ester **25** was obtained by a



Scheme 13. Key intermediates obtained by RCM from carbohydrate starting materials.

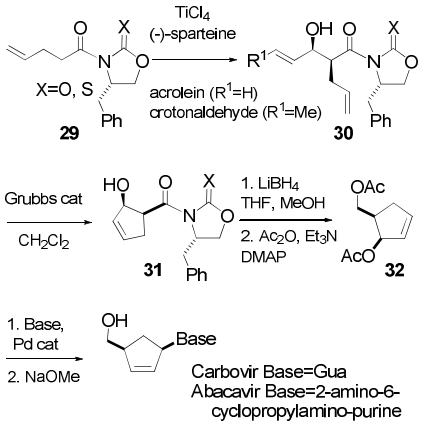
double [3,3]-sigmatropic rearrangement after reaction with ethyl orthoacetate. Subsequent ester reduction, oxidation to aldehyde and vinylmagnesium addition followed by RCM produced **26**. Adenine was introduced using palladium chemistry to provide **27** and the cleavage of the diol and reduction afforded the nucleoside **28**.



Scheme 14. Synthesis of the carbovir analogue **28** from L-tartrate.

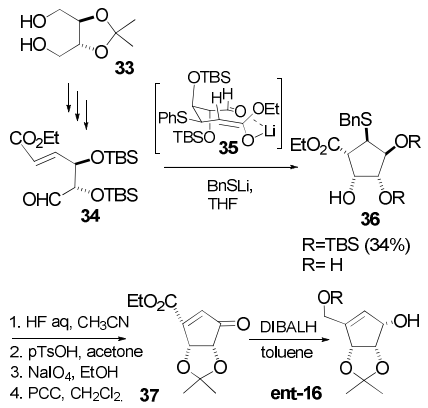
Some reports describe the preparation of chiral synthons for RCM by asymmetric synthesis. Thus, an aldol reaction involving a chlorotitanium enolate derived from **29** bearing a

(tio)oxazolidinone as a chiral auxiliary produced **30**, and underwent RCM to obtain **31**. Removal of the chiral auxiliary and acetylation of the resulting diol afforded **32**, which was suitable for base (guanosine and cyclopropyl-adenine) introduction using a Pd(0)-mediated coupling sequence to produce carbovir and abacavir (Scheme 15).[24]



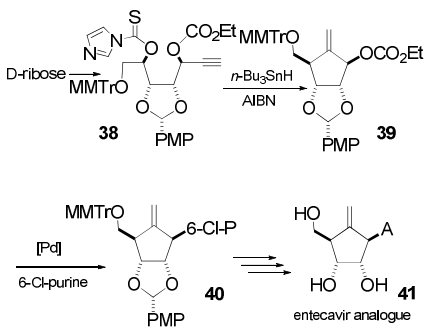
Scheme 15. Use of a chiral auxiliary in the synthesis of carbovir and abacavir via RCM.

Ring-closing by aldol reaction. Despite the usefulness of the intramolecular aldol-type reaction for preparing 5-membered rings, there are only a few reports of the use of this method in the synthesis of carbocyclic nucleosides. An example of this reaction to produce the useful intermediate **ent-16** is presented in Scheme 16. Thus, the diol **33** was elaborated to provide the aldehyde **34**, which was treated with lithium benzylsulphide to produce compound **36** as the major isomer through a Michael-type reaction. This reaction initially leads to the enolate **35**, which undergoes an intramolecular aldol reaction. Protecting group manipulation in **36** followed by oxidation of the benzyl thioether produced the corresponding sulphoxide, wich underwent elimination upon heating to afford the unsaturated ester. Oxidation of the remaining alcohol yielded compound **37**, which was finally reduced to obtain the key synthon **ent-16**.[25]



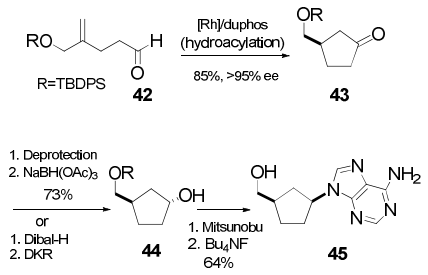
Scheme 16. Synthesis of the key synthon **ent-16** through an aldol reaction.

Ring-closing based on radical cyclisation reactions. There are only a few reports describing the use of radical cyclisation reactions for synthesising cyclopentanes. An example of the synthesis of an entecavir analogue using a radical process is presented in Scheme 17. The key thiocarbamate **38**, which was obtained from D-ribose in 5 steps, was treated with tributyltin hydride to generate a radical at the thiocarbamate position, which reacted regioselectively with the triple bond to produce the cyclopentane **39**. This compound possesses an exocyclic double bond and a group carbonate at the allylic position, making it suitable for introducing the base using palladium-catalysed reactions. Therefore, the reaction of **39** with 6-chloropurine using a Pd-catalyst selectively produced compound **40**. Elaboration of the nucleobase and removal of protecting groups yielded 5'-methylene arysteromicin, **41**, which is a nucleoside analogue of entecavir.[26]



Scheme 17. Radical-cyclisation strategy to exo-methylene derivatives from D-ribose.

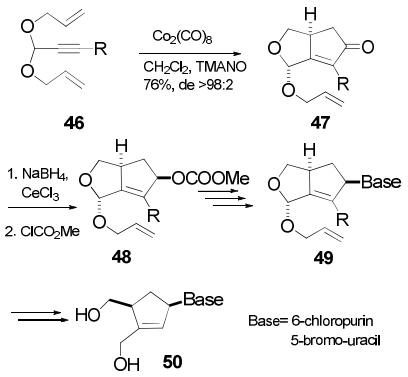
Ring-closing methods based on transition metal-catalysed reactions. There are very few methods for enantioselective synthesis of carbocyclic nucleoside based on reactions catalysed using transition metals, with the exception of ruthenium- atalysed RCM. An efficient procedure is based on a rhodium- atalysed hydroacylation reaction, which consists of the addition of an aldehyde to an alkene to obtain a ketone with full atom economy. Thus, an asymmetric intramolecular hydroacylation reaction was successfully applied to the silylated 4-hydroxymethyl-pent-4-enal (**42**) using Rh/duphos as a catalytic system, which achieve enantioselectivities greater than 95% in the synthesis of cyclopentanone **43** (Scheme 18).[27] Deprotection and reduction with $NaBH(OAc)_3$ provided alcohol **44** in a stereoselective manner. Primary hydroxyl protection, introduction of the base (adenine) by Mitsunobu reaction and deprotection afforded the nucleoside **45** in a practically enantiomerically pure form. Both enantiomers are accessible using this procedure.



Scheme 18. Synthesis of **45** by Rh-catalysed enantioselective hydroacylation as the key step.

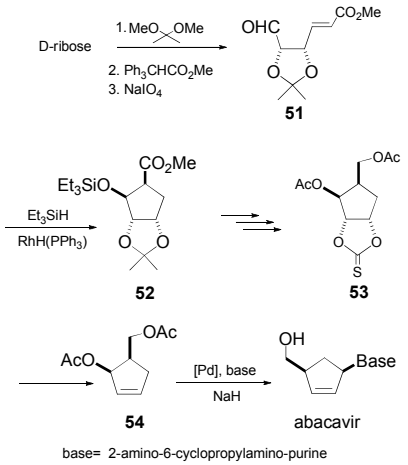
The Pauson-Khand reaction entails the Co-catalysed cyclisation of alkenes and alkynes to give cyclopentenones. This reaction was used as a key step in the synthesis of nucleoside **50**, which started by treating propynal derivatives with allyl alcohol in an acid medium to obtain the acetal **46**, which was transformed into the cyclopentanone **47** upon treatment with cobalt octacarbonyl (Scheme 19). Ketone reduction and acetylation produced compound **48**, followed by introduction of the base (6-choro-purin, 5-bromouracil) by palladium-catalysed allylic substitution to yield **49**. The hydrolysis of the acetal and reduction of the resulting

aldehyde provides the target nucleoside **50**.[28] The use of catecholborane allowed a kinetic resolution during the ketone reduction step.



Scheme 19. Synthesis of **50** based on a Pauson-Khand reaction.

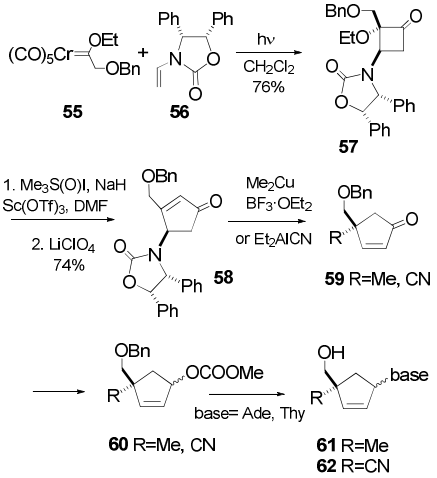
Another interesting procedure based on the use of transition metals is the tandem rhodium-catalysed hydrosilylation-aldol reaction. The preparation of the key synthon began from D-ribose as its 2,3-*O*-isopropylidene derivative, and the subsequent Wittig olefination produced a diol that was cleaved by reaction with sodium periodate to generate the aldehyde **51** (Scheme 20). The cyclopentane **52** was generated in 81% yield by a tandem hydrosilylation-intramolecular aldol reaction. Next, functional group manipulations produced **53** and



Scheme 20. Hydrosilylation-intramolecular aldol sequence for the preparation of 2',3'-dideoxy carbocyclic nucleosides.

cyclopentane **54**, which was suitable for palladium- atalysed allylic substitution. Therefore, the reaction of **54** with 2-amino-6- y lopropylamino-purine in the presence of a palladium catalyst yielded, after hydrolysis, the nucleoside abacavir.[29] Similarly, carbovir was prepared using 2-amino-6- hloropurin as the base.

Fischer carbenes have also been used in the preparation of carbocyclic nucleosides. This is a conceptually different approach because, in the key step, the transition metal acts as a reagent and not as a catalyst. In an asymmetric version, the chiral vinyl oxazolidinone **56** was photolysed in the presence of carbene **55** to afford the cyclobutanone **57**, from which cyclobutane (See section 3.2, Scheme 34) and cyclopentane nucleosides were prepared. Thus, the reaction of **57** with $Me_3S(O)I$ in the presence of NaH and $Sc(OTf)_3$ resulted in ring expansion to obtain, after the elimination of ethanol, the cyclopentanone **58**. From **58**, stereoeselective conjugate addition of a methyl group ($Me_2Cu/BF_3{\cdot}OEt_2$), or a nitrile (Et_2AlCN), followed by elimination of oxazolidinone (LDA) produced **59** (R=Me, CN) (Scheme 21). The reduction of the ketone was not stereoselective and the diastereomers were separated by chromatography. The subsequent preparation of the carbonate **60** allowed an easy introduction of adenine and thymine by palladium- atalysed allylic substitution. The



Scheme 21. Synthesis of 2,'3'-dideoxy nucleosides using a chiral auxiliary.

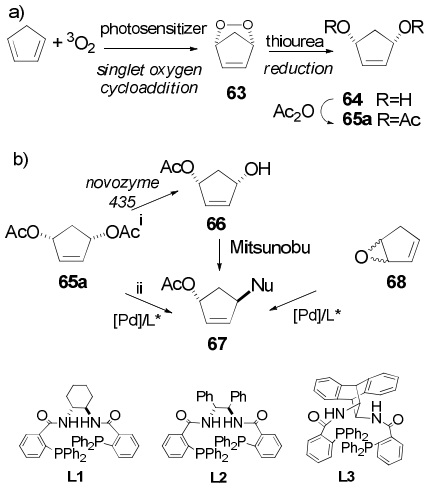
final removal of the benzyl group produced nucleosides **61** and **62**. Using the diastereomeric mixture of carbonates and Trost's ligand L1 (see Scheme 22), only the β derivative reacts and the α-derivative remains intact.[30] Neplanocin A, carbovir and aristeromicin have been also prepared using this procedure.

3.1.2. Synthesis of the carbocyclic ring using cyclopentadiene and cyclopentene as a starting material

Using [4+2] cycloaddition reactions as the key step. In this section, we will focus on synthetic approaches based on transformations from cyclopentadiene and, especifically, on cycloaddition reactions. The availability of cyclopentadiene and its specific chemical properties, which enable functionalisation in almost all positions of the ring, have made this compound a widely used starting material in the synthesis of carbocyclic nucleosides. Furthermore, cyclopentadiene can undergo Diels-Alder reactions with various types of dienophiles, extending its application to the synthesis of carbocyclic nucleosides. The bicyclic cycloadducts thus obtained can be subsequently ring-opened to give stereodefined *cis* substituted cyclopentene derivatives appropriate for nucleoside synthesis. Diels-Alder reactions with hetero-dienophiles such as singlet oxygen, tosyl cyanide, chlorosulphonylisocyanate, acylnitrosoderivatives and iminium salts and even [2+2] cycloadditions have been reported.

a. Singlet oxygen as dienophile. Synthesis of cyclopent-4-ene-1,3-diol. A strategic compound in the synthesis of carbocyclic nucleosides is cyclopent-4-ene-1,3-diol (**64**), which is obtained from cyclopentadiene by cycloaddition of singlet oxygen (generated from molecular oxygen with a photosensitizser such as rose bengal and light) to produce **63**, followed by reduction with thiourea (Scheme 22a). Once di-acylated, the *meso*-diester **65a** becomes one of the most attractive starting materials for preparing carbocyclonucleosides. There are two main strategies for desymmetrisation of *meso*-diester: a) enzymatic catalysis (Scheme 22b, route i)

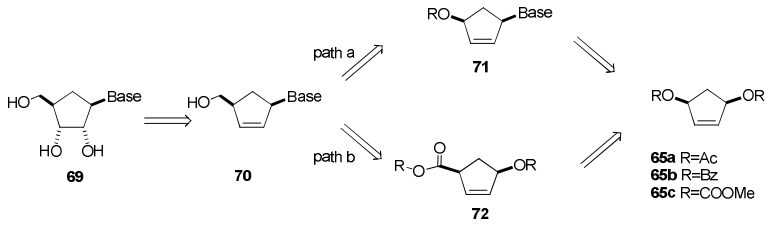
and b) palladium- atalysed asymmetric allylic substitution (route ii). Enzymatic desymmetrisation of the diacetyl derivative **65a** with different enzymes produces **66** with excellent enantioselectivity.[31] The reaction of **66** with a nucleic base under Mitsunobu conditions affords **67**. The diacetate **65a** is also a suitable starting material to introduce the base using palladium chemistry.[32] The use of Pd/ **L1-L3** chiral ligands produces an efficient desymmetrisation of **65a** to give **67** with excellent enantioselectivity. Benzoates (**65b**)and carbonates (**65c**) can be used in place of acetates (**65a**). Epoxide **68** is also an alternative starting material (Scheme 22).



Scheme 22. Synthesis of diol **64** and desymmetrisation of **65a**.

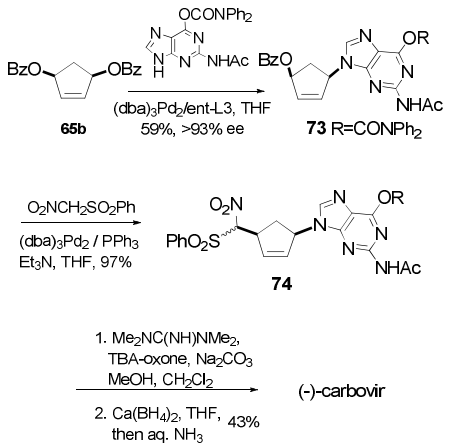
In both approaches the hydroxymethyl chain characteristic of nucleosides must be introduced from **67** in a subsequent step. This chain can also be introduced by palladium-catalysed allylic alkylation using the appropriate reagent. In this context, Scheme 23 outlines the 2 possible strategies for the synthesis of the carbocyclonucleosides **69** and **70** from the *meso*-diester **65**. Either the base to give **71** or the C-1 fragment to give **72** can be introduced in the first step, which provides great flexibility to the synthesis. Once the first nucleophile is introduced, the compound becomes chiral and a chiral catalyst is not required to introduce the second nucleophile, although in general it provides improved results.

The mechanism of the palladium- atalysed allylic substitution with soft nucleophiles entails a double inversion process that involves retention of configuration (See Introduction, Scheme 4). For the *meso*-diesters, the desymmetrisation determines which acetoxy substituent is replaced first, but the 2 allylic substitution processes for installing the base and hydroxymethyl chain guarantee that the relative configuration of the substituents in the cyclopentane ring will be *cis*, which is the case in most biologically active nucleosides. The most relevant carbocycle nucleosides have been prepared using this methodology.



Scheme 23. Synthesis of nucleosides by Pd-catalysed desymmetrisation of **65**

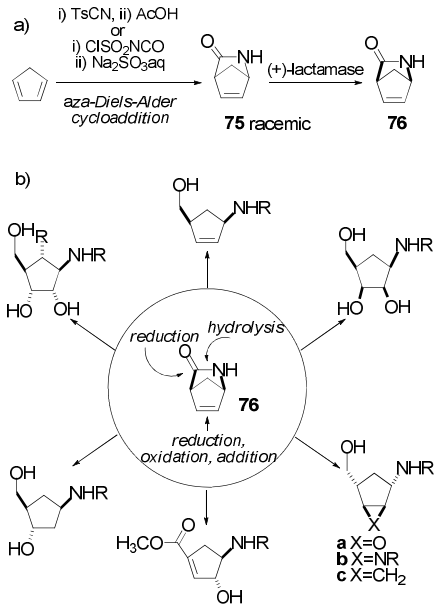
A straightforward synthesis of (-)-carbovir based on this approach is shown in Scheme 1.[32] In this synthesis, the nucleic base was introduced first and protected guanine was directly used as nucleophile. However, due to the low solubility of guanine analogues allylic substitution results troublesome. The results are improved using the diphenylcarbamate derivative Pd/L3 as a catalytic system, and amine bases such as 1,2,2,6,6,-pentamethylpiperidine (Scheme 24). Under these conditions, the nucleoside **73** was obtained in 59% yield and with excellent enantioselectivity. A second palladium-catalysed allylic substitution with phenylsulphonylnitromethane in the presence of triethylamine gave **74** almost quantitatively as a diastereomeric mixture. Chemoselective oxidation with tetrabutylammonium oxone buffered with sodium carbonate gave the methyl ester, which was further reduced with calcium borohydride, followed by aqueous ammonia work-up to remove the protecting groups to produce (-)-carbovir. This methodology was also applied to the synthesis of (-)-neplanocin.



Scheme 24. Synthesis of carbovir from **65b** using a double Pd-catalysed allylic substitution.

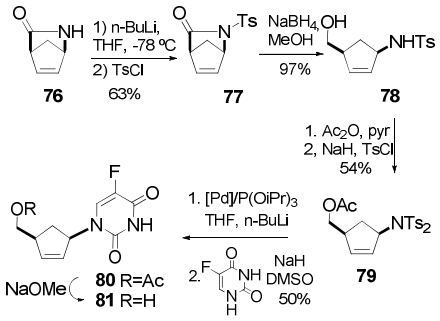
b. *Aza Diels-Alder cycloaddition reactions by addition of sulphonyl cyanides and isocyanates. Bicyclic lactams as intermediates.* One of the most popular cycloadducts for synthesising carbocyclic nucleosides is 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH, or Vince lactam, **76**), which is efficiently synthesised from an aza-Diels-Alder cycloaddition reaction between cyclopentadiene and tosyl cyanide or chlorosulphonyl isocyanate, followed by either acid or base hydrolysis (Scheme 25a). When chlorosulphonyl isocyanate is used, the product of the thermodynamic control results from a [4+2] cycloaddition while when the reaction is conducted under kinetic control (-78ºC), the β-lactam, which results from a [2+2] cycloaddition, is mainly produced (See Scheme 31). The bicyclic lactam ABH has been used for the synthesis of carbocyclic nucleosides for more than 30 years, since Vince et al. realized the unique possibilities of this intermediate for synthesising carbocyclic nucleosides with the required *cis* orientation of the hydroxymethyl and nucleobase functions. A recent and excellent review collects the different modifications and applications of ABH.[33] Enzymatic resolution of ABH has been widely studied, and there are several enzymes that provide excellent enantioselectivity, enabling access to enantiopure carbocyclic nucleosides. Reductive cleavage of the lactam using sodium borohydride provides an amino-alcohol with the relative configuration defined. Transformations of the double bond prior to or after the reductive ring-opening can lead to the generation of functionalised carbocyclic structures

(Scheme 25b), from which carbocyclic nucleosides are easily obtained. Because an amine group is installed in the carbocycle the nucleic base is generally introduced through a linear route (see section 2.2).



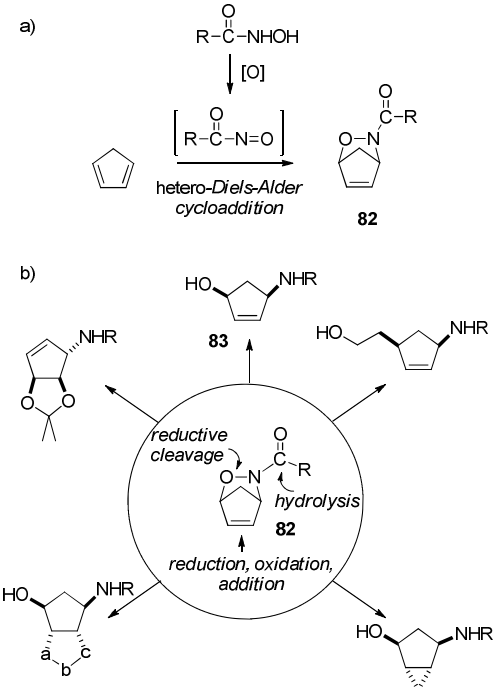
Scheme 25. Obtention of the bicyclic lactam ABH (**76**) by aza Diels-Alder cycloaddition and synthetic intermediates that can be obtained from it.

An example of the potential of this methodology is presented in Scheme 26. Interestingly, in this case the cylopentenyl ditosylimide **79**, obtained by derivatisation of bicyclic lactam **76**, was used as a substrate for the introduction of the base through a palladium-catalysed allylic substitution to produce nucleoside **80**, which yielded **81** after hydrolysis (Scheme 26).[34]



Scheme 26. Synthesis of pyrimidine carbocyclic nucleosides from ABH (**76**) through Pd-catalysed allylic substitution from cyclopentenyl ditosylimide

c) Aza Diels-Alder cycloaddition reactions by addition of nitrosocarbonyls. Acylnitroso Diels-Alder cycloadducts have also been explored as key intermediates for the synthesis of carbocyclic nucleosides, and most these nucleosides are 5'-*nor* analogues, which lacks the hydroxymethylene chain at the carbocyclic unit.[35]

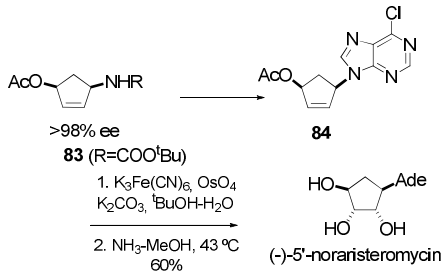


Scheme 27. Synthesis of the 2-oxa-3-azabicyclo[2.2.1]hept-5-ene (**82**) cycloadduct and synthetic intermediates obtained by derivatisation thereof.

Nitrosocarbonyls are highly reactive intermediates in hetero-Diels-Alder reactions (Scheme 27a). Cyclopentadiene efficiently traps these transient intermediates affording cyclopentene hetero Diels-Alder adducts **82** which, in turn, are suitable for multiple synthetic transformations, such as catalysed allylic substitution, dihydroxylation, aminohydroxylation and cycloaddition. Detachment of the acyl moiety and reductive cleavage of the N-O bond quantitatively affords the stereodefined *syn*-aminocyclopentenols (Scheme 27b), which can serve as nucleoside precursors through the assembly of purine or pyrimidine rings. The enantiomerically pure cycloadduct has also been synthesised, either through an auxiliary-base

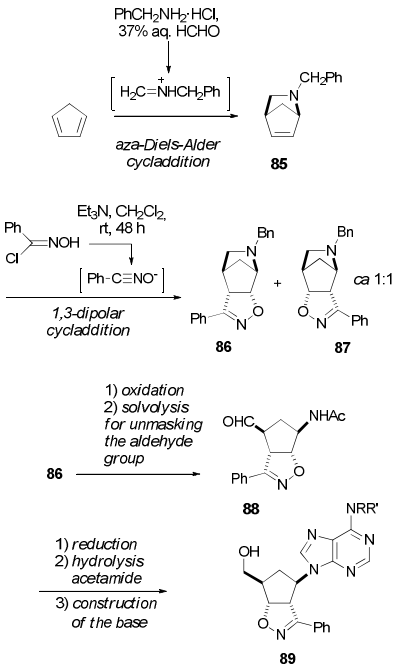
strategy using an hydroxamic acid derived from L-alanine[36] or through a more efficient enzymatic resolution process of **83** using lipases or hydrolases.[37]

The enantiomerically pure compound **83** (R=COO^{t}Bu) was used in the synthesis of carbocyclic nucleosides, such as noraristeromycin.[38] The key steps entails the condensation of the free amine resulting from Boc group removal in **83**, with 5-amino-4,6-dichloropyrimidine, and further elaboration of the imidazole ring to afford **84**. Stereoselective dihydroxylation and hydrolysis yield 5'-noraristeromycin (Scheme 28).



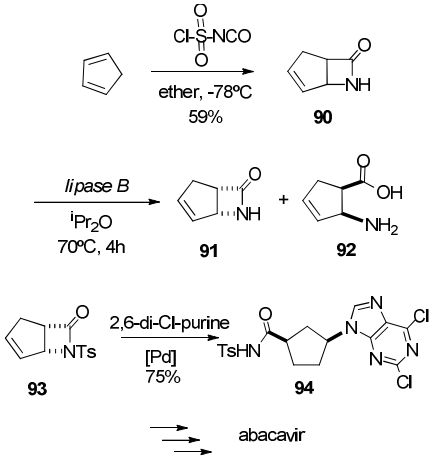
Scheme 28. Synthesis of noraristeromycin from **83**

d. Aza Diels-Alder reactions by the addition of iminium salts. A less explored approach to the synthesis of carbocyclic nucleosides involves the transformations of the 2-azanorbornene intermediate **85** derived from an aqueous aza-Diels-Alder cycloaddition between cyclopentadiene and iminium salts[39] generated in situ under Mannich-like conditions. The strategy was applied to the synthesis of oxazoline fused carbocyclic nucleosides **89**. which This synthesis is limited, however, by the low regiochemical control of the 1,3-dipolar cycloaddition and the non-stereoselective oxidation of the aza-methylene bridge to unmask the hydroxymethyl side chain (Scheme 29).



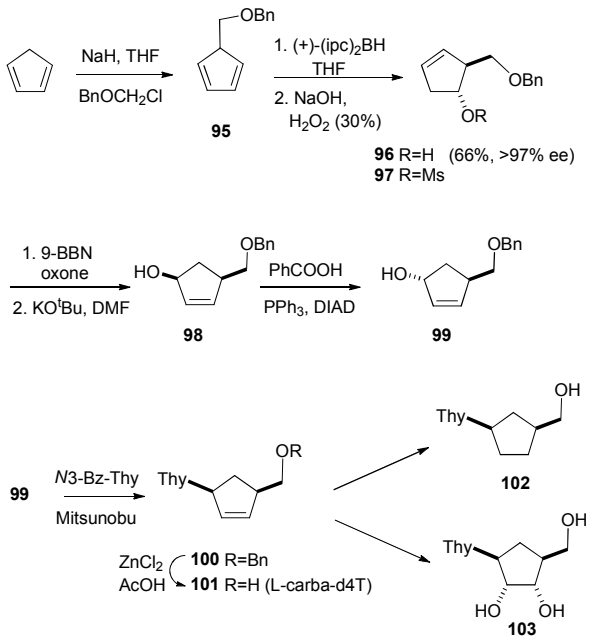
Scheme 29. Synthesis of isoxazoline-based carbocyclic nucleosides.

[2+2] cycloadditions. When the reaction of chlorosulphonyl isocyanate with cyclopentadiene was conducted under kinetic control (see also section b and Scheme 25), a [2+2] cycloaddition occured to afford the β-lactame **90** after reductive work-up (Scheme 30). Enzyme-catalysed hydrolysis of **90** afforded the lactam **91** and the amino acid **92** with high enantiomeric purity.[40] In general, in this case the base is also generated from the amino group. However, the allyl tosyl-imide **93** was envisioned as a suitable starting material for base introduction using palladium catalysis (see Scheme 26 for a related reaction). Thus, when **93** was treated with 2,6-dichloropurine tetrabutylammonium salt in the presence of $Pd_2(dba)_3/P(O^iPr)_3$ as a catalyst, the carbocyclic nucleoside **94** was obtained in 75% yield. Elaboration of the alkyl chain and elaboration of the base produced abacavir.



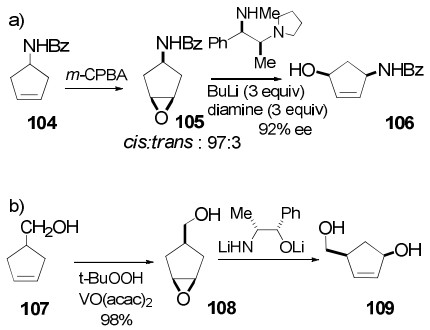
Scheme 30. Enzymatic kinetic resolution of adduct **90** and application in the synthesis of abacavir.

Derivatisation of cyclopentadiene other than cycloaddition. A different but direct approach to functionalised cyclopentanes from cyclopentadiene entailed an initial reaction with benzyl chloromethyl ether in a basic medium to produce **95**, which was converted into **96** in 66% yield with an enantiomeric excess greater than 97%, using an asymmetric hydroboration reaction with iso-pinocamphenylborane (Scheme 31). Compound **96** is a suitable synthon for the synthesis of a variety of carbocyclic nucleosides. Thus, mesylation of **96**, double bond hydroboration and elimination afforded **98**. The inversion of the hydroxyl in **98** under Mitsunobu conditions gave **99**, which was treated with N^3-benzoylthimine under Mitsunobu conditions to produce the carbocyclic nucleoside **100** and, finally, L-carba-d4T (**101**) after the removal of protecting groups.[41] Nucleosides **102** and **103** were also prepared in a straightforward manner from **100**. The acetyl derivative of compound **98** is a suitable synthon to introduce bases by palladium catalysis.



Scheme 31. Synthesis of carbocyclic nucleosides by asymmetric hydroboration of cyclopentadiene

Synthesis from cyclopentenes. Resolution of epoxides using chiral bases. In a straightforward approach to carbocyclic nucleosides, chiral bases were used for the desymmetrisation of epoxides. Aminocyclopentene **104** was treated with *meta*-chloroperbenzoic acid, which essentially provided the *meso* epoxide **105** through a NH-directed epoxidation. Resolution of the *meso*-epoxide using chiral lithium amides produced the hydroxyaminocyclopentane **106** with excellent enantioselectivity (Scheme 32). These compounds are appropriate starting materials for the preparation of carbocyclic nucleosides.[42] Similarly, the reduction and hydroxyl-directed epoxidation of cyclopentene **107** afforded epoxide **108**, which was then treated with a chiral base to produce cyclopentenol **109** in an enantiopure manner.[43] Using this procedure, nucleosides can be easily obtained by protection of the primary alcohol, activation of allylic alcohol and palladium-catalysed allylic substitution.



Scheme 32. Synthesis of carbocyclic nucleosides precursors by desymmetrisation of epoxides using chiral bases

3.2. 4-Membered ring carbocyclic nucleosides

The synthesis of cyclobutane *carba*-nucleosides has been inspired by the unique structure and broad-spectrum antiviral activity of the natural nucleoside oxetanocin (Figure 2).

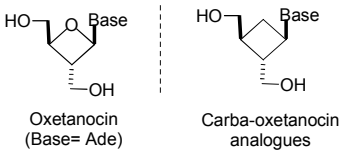
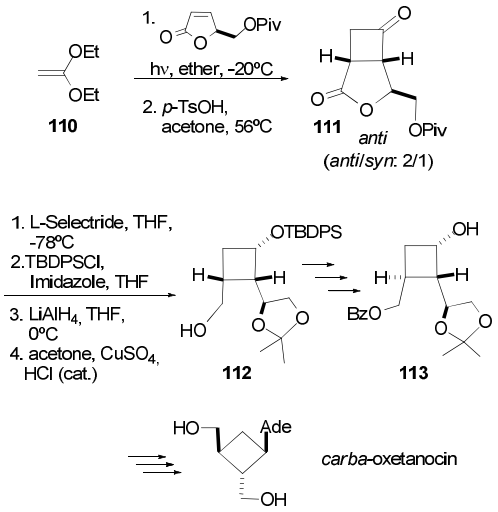


Figure 2. Structures of four-membered ring nucleosides

Photochemically induced [2+2] cycloaddition is the most general procedure for synthesising cyclobutanes. The need for appropriately functionalised enantiopure compounds has oriented the synthesis of oxetanocin analogues to the use of chiral alkenes or the kinetic resolution of cycloadducts.

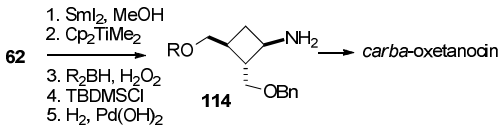


Scheme 33. Synthesis of *carba*-oxetanocin by [2+2] cycloaddition using an alkene from the chiral pool

The synthesis of the *carba*-oxetanocin analogues, as shown in Scheme 34, involves the use of chiral alkenes. By this route, the cyclobutane construction was performed by a regio- and diastereoselective [2+2] photocycloaddition of 1,1-diethoxyethylene (**110**) to the chiral 5-

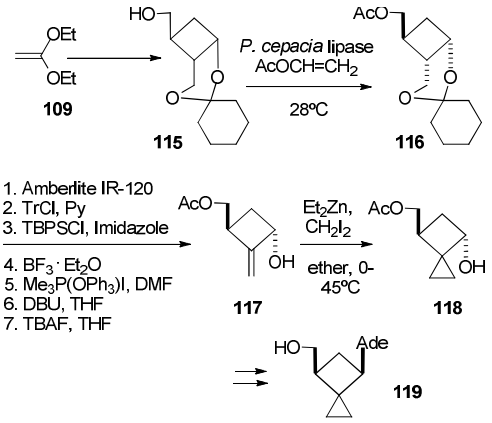
pivaloyloxymethyl-2(5*H*)-furarone,[44] an alkene that displays good facial selectivity in photochemical reactions, to produce **111** (Scheme 33). Further stereoselective reduction of the ketone and functional groups manipulation provided **112**. Epimerisation of the benzoyloxymethyl chain, elaboration of the dioxolane ring and nucleobase introduction afforded *carba*-oxetanocin.

A different approach to obtain the optically active cyclobutane, involves the photolysis of a chromium carbene complex with optically active ene- arbamates to give **62** (See Scheme 21), from which amino cyclobutane **114** was obtained following the reaction sequence shown in Scheme 34. Compound **114** was then transformed into *carba*-oxetanocin by building the adenine moiety from the amino group and removing the protecting groups.[45]



Scheme 34. Synthesis of carba-oxetanocin from **62**.

The second approach involves the resolution of the previously formed racemic cyclobutane derivative. The cyclobutane **115** was obtained again from 1,1-diethoxyethylene via a [2+2] photocycloaddition and was resolved using *pseudomonas cepacia* lipase to produce the enantiomerically pure **116** (Scheme 35).[46] Protecting group manipulation, iodination and DBU-mediated elimination yielded the methylene cyclobutane **117**, from which the spiro framework **118** was obtained via cyclopropanation. Nucleoside **119** was obtained from **118** through a reaction with adenine under Mitsunobu conditions.



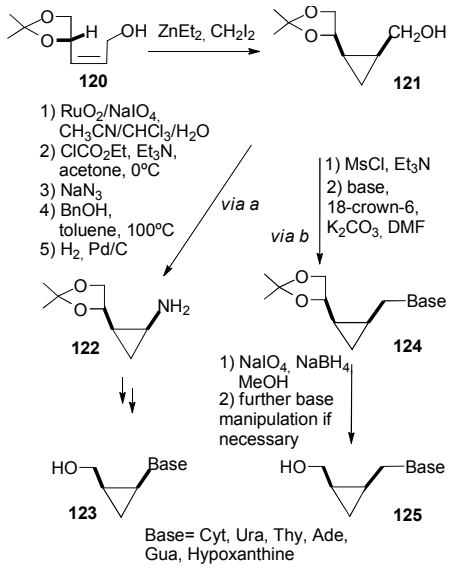
Scheme 35. Synthesis of oxetanocin analogues via diastereoselective [2+2] cycloaddition and enzymatic resolution

3.3. 3-Membered ring carbocyclic nucleosides

Three-membered carbocyclic nucleosides in which the base moiety is directly attached to the ring can be considered as ring-contracted analogues of *carba*-oxetanocin. Cyclopropanation is the method of choice for obtaining these analogues, and most reports address the synthesis of the alkene precursor to obtain appropriately functionalised cyclopropanes.

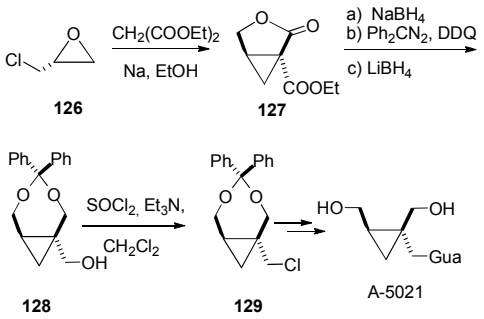
In this regard, the classical asymmetric synthesis of D- and L-cyclopropyl nucleosides uses protected mannitol as a chiral source, which has become a general synthetic strategy.[47] Thus, 1,2:5,6-di-*O*-isopropylidene-D-mannitol was converted into the allyl alcohol **120** by a standard oxidative cleavage/Wittig reaction/reduction sequence. The cyclopropyl ring was installed using Simmons-Smith cyclopropanation to yield the key intermediate **121** (Scheme 36). The subsequent oxidation to acid, Curtius rearrangement of the acyl azide and deprotection yielded the cyclopropyl amine derivative **122** (via a). The target D-nucleosides **123** were obtained by a linear methodology. L-Cyclopropyl nucleosides were synthesised in a similar fashion using L-gulonic γ-lactone as a chiral starting material. However, most likely due to the lack of biological activity exhibited by these nucleosides, no further significant contributions to the synthesis of this type of structures have been made since 2000.

Conversely, nucleosides with a spacer between the base and the ring exhibit interesting biological properties. The strategy explained previously was also used to obtain this type of cyclopropyl methyl nucleosides from the key intermediate **121** shown in Scheme 37.[48] Mesylation of alcohol **121** and condensation with various purine and pyrimidine bases via S_N2 reaction produced nucleosides **124**. Further oxidative cleavage and reduction to generate the hdyroxymethyl chain provided the target nucleoside **125** (via b).



Scheme 36. Asymmetric synthesis of cyclopropyl nucleosides

A chiral starting material such as enantiopure epichlorhydrine was used in the synthesis of the antiherpetic carbocyclic nucleoside A-5021,[49] and structurally related derivatives (Scheme 37). Therefore, lactone **127** was obtained with high optical purity (>97% ee), from (*R)*-(-)-epichlorhydrin (**126**) through condensation with diethyl malonate. Lactone and ester reduction, and diol protection afforded **128**. This compound was transformed into the key halomethyl intermediate **129**, which was condensed with the base moiety via classic S_N2 reaction to produce the corresponding bis-hydroxymethyl nucleoside A-5021.



Scheme 37. Synthesis of A-5021

3.4. 6-Membered ring carbocyclic nucleosides

With the exception of the C-3-hydroxyl cyclohexenyl derivatives shown in Figure 3, which exhibit anti-herpes virus activity, 6-membered *carba*-nucleosides do not display biological activity. Nearly all activity was abolished when the oxygen atom was replaced by a methylene group in the 6-membered nucleosides. A conformational change was the decisive factor responsible for this inactivity against viruses.

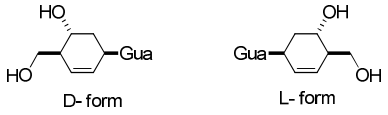
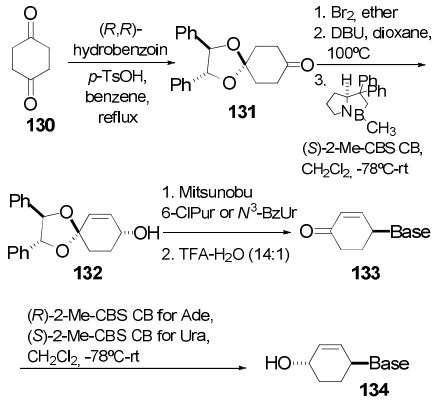


Figure 3. Biologically active 6-membered carbocyclic nucleosides

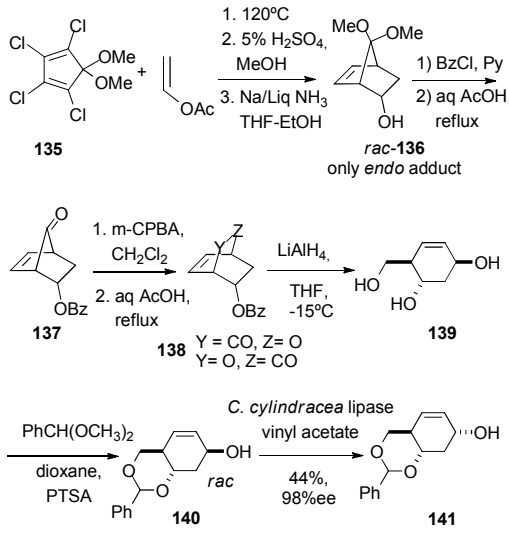
The enantioselective synthesis of structurally related nucleosides has been performed by using chiral auxiliaries or by enzymatic kinetic resolution.



Scheme 38. Synthesis of cyclohexenyl nucleosides using the hydrobenzoin moiety as a chiral auxiliary

An enantiodivergent approach to D- and L-hydroxycyclohexenyl nucleosides has been designed starting from a common intermediate **131** which bears a hydrobenzoin moiety as a chiral auxiliary.[50] The synthesis initially involves the installation of a double bond and the selective reduction of the ketone to give **132** (Scheme 38). Then, the nucleobase is introduced with either inversion (Mitsunobu methodology) or retention (Pd- atalysed allylic substitution). Stereoselective reduction of the carbonyl group delivers the target cyclohexene nucleosides **134**. The methodology of synthesis of 5-membered rings using chiral auxiliaires described in Scheme 15, has been also appolied to synthesis of 6-membered rings.[24a]

Other approaches to obtain cyclohexenyl structures are based on Diels-Alder methodology. For example, the synthesis of precursors of the corresponding nucleosides involves the Diels-Alder reaction of commercially available 5,5-dimethoxy-1,2,3,4-tetrachlorocyclo-pentadiene (**135**) and vinyl acetate to give the adduct racemic **136** (Scheme 39), which was transformed into **139** by ketal hydrolysis, Baeyer-Villiger reaction and lactone reduction. The enzymatic resolution of the benzylidene protected intermediate **140** afforded enantiomerically pure compound **141** from which cyclohexenyl nucleosides were obtained.[51]



Scheme 39. Synthesis of cyclohexenyl nucleosides by Diels Alder approach

4. CONCLUSIONS

The synthesis of carbocyclic nucleosides remains an active field of research in medicinal chemistry. Five-membered ring carbocycle nucleosides are by far the most studied. Currently, an important number of reliable synthetic protocols for both the synthesis of the carbocycle and base introduction are available to researchers and it can be used to synthesise a large number of carbocylic nucleosides with many structural modifications. Methods for base introduction are summarised in Scheme 40. Palladium- atalysed allylic substitution, the Mitsunobu reaction and the construction of the heterocyclic base from amino- y lopentanes are the most successful procedures. The selection of the most convenient procedure depends on the nucleic base (purin or pyrimidine) and on the presence of amino or hydroxyl groups in the formed carbocycle. The amino group must have, in general, the correct configuration, while the configuration of the hydroxyl group can be retained or inverted depending on the procedure used.

The methods of synthesis of cyclopentyl nucleosides can be classified in 2 groups: a) those involving ring closing and b) those that start from compounds with a 5-membered ring, such as cyclopentadiene and cyclopentene. Ring closing can be performed by generating a double or a single bond. Methods generating a double bond are more general and the initial methods based on the Wittig reaction, have been progressively substituted by ring- losing metathesis, mainly using Grubbs catalysts. Starting materials from the chiral pool are mainly used (Scheme 41ia). A variety of procedures for synthesising cyclopentanes through the generation of C-C bonds have been reported. These methods involve radical reactions and primarily transition metal- atalysed reactions. Most of these methods start from compounds of the chiral pool, and few describe the use of chiral catalysts (Scheme 41ib).

Among the compounds that do not belong to the chiral pool, cyclopentadiene is the most widely used. The cycloaddition [4+2] of several heterodienophiles produces a set of achiral

bicycle derivatives that are kinetically resolved by enzymatic catalysis (Scheme 41iia-d). Elaboration of these bicycles produces functionalised cyclopentenes that are suitables for the synthesis of carbocyclic nucleosides. A particular case is the cycloaddition of chlorosulphonylisocyanate, which can evolve through a [4+2] or [2+2] process depending on wether the reaction is under thermodynamic or kinetic control (Scheme 41iid, e). The [4+2] process produces Vince lactam (ABH), which has been one of the most successful intermediates in the synthesis of carbocyclic nucleosides. A limitation of the approaches based on cycladdition to cyclopentadiene is that the base must be introduced from the amino group present in the carbocycle obtained. However, there are efficient protocols for introducing both pyrimidinic and purinic bases and, moreover, modifications allowing the direct introduction of bases by palladium- atalysed allylic alkylation have been developed (See Schemes 26 and 31).

Important intermediates in the synthesis of cyclopentyl nucleosides were obtained in a straightforward manner from cyclopentadiene by employing an asymmetric hydroboration as a key step (Scheme 41ii,f) and from cyclopentene by a stereoselective-directed epoxidation to form a meso epoxide and further resolution using a chiral base (Scheme XXiig).

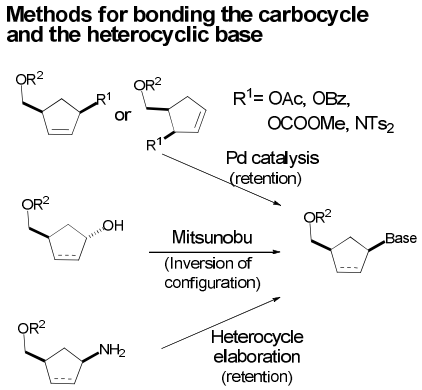
As mentioned previously, the synthesis of carbocyclic nucleosides of four, three and six membered-ring has been less well explored. The synthesis of the cyclobutane fragment of cyclobutyl nucleosides relies on the photochemical cycloaddition of ketene acetals to chiral alkenes proceeding from the chiral pool (Scheme 42). If the alkene is not chiral a kinetic resolution by enzymatic catalysis is required.

The synthesis of the cyclopropane moiety in cyclopropyl nucleosides commonly involves the cycloaddition [2+1] of a carbene to a chiral alkene, and the Simmons-Smith procedure is the most widely used procedure to generate the carbene.

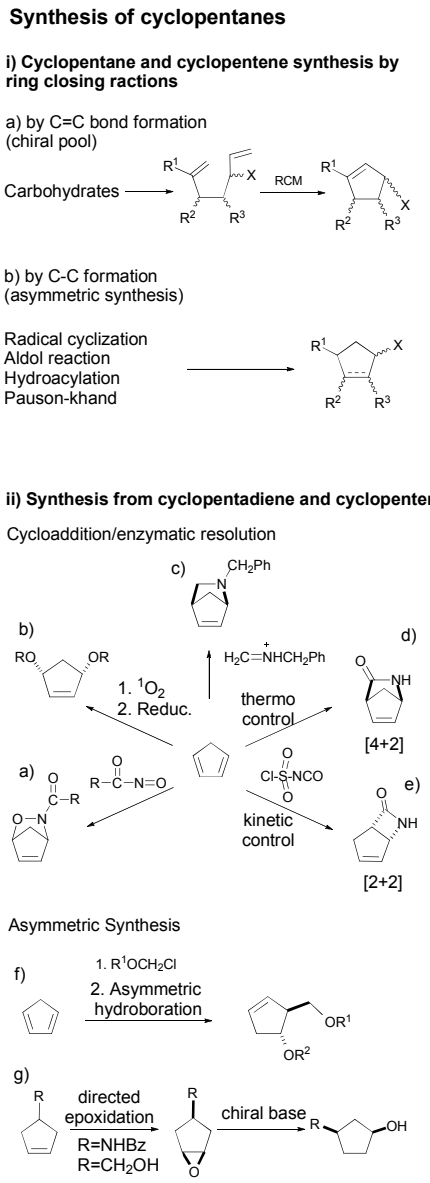
The cyclohexane moiety of cyclohexyl nucleosides has been synthesised via different procedures starting from carbohydrates or from cyclohexane derivatives, in which the

chirality is introduced through chiral auxiliaries or through kinetic resolution by enzymatic catalysis.

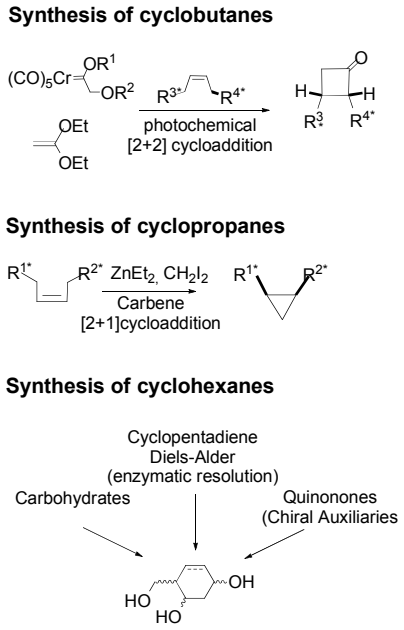
Therefore, there are a number of synthetic procedures that are effective for the synthesis of carbocyclic nucleosides that allow the preparation of the most important members of this family of compounds, as well as corresponding derivatives. Asymmetric processes based on transition metals are still scarce, and the use organocatalysts to obtain carbocyclic nucleosides remains to be explored.



Scheme 40. Relevant procedures for linking the base and the carbocycle



Scheme 41. Methods of synthesis of cyclopentanes



Scheme 42. Selected methods of synthesis of 3-, 4- and 6-membered ring carbocycles

5. AC KNOWLEDGEMETS

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Key learning points

-Methods for linking the nucleic bases and the carbocycles. Substitution *versus* glycosylation. Alternative procedures for nucleophilic substitution with nucleic bases: Mitsunobu reaction and palladium-catalysed allylic substitution. Differences between purinic and pyrimidinic bases.

-General strategies for the enantioselective construction of 5-membered rings. Key reactions based on ring-closing reactions or on cycloaddition reactions from cyclopentadiene and heterodienophiles.

- Chiral pool *vs* enantioselective synthesis *vs* resolution of racemates. Selecting the appropriate procedure.

-Methods for constructing 3, 4 and 6 carbocycles precursors of nucleosides

-Functionalization of key intermediates for providing the key nucleosides and structural modifications.