DOI: 10.1002/ejoc.200800238

Recent Advances in the Chemistry of Aminocyclitols

Antonio Delgado*[a,b]

Keywords: Aminocyclitols / Cyclitols / Natural products / Synthetic methodology / Stereocontrol / Disatereoselectivity / Functional group interconversion

Aminocyclitols are a group of natural products with remarkable biological activities. Over the last years, significant efforts have been made to develop synthetic methodologies directed not only towards their total synthesis but also towards the design of structural analogues with improved or novel biological properties. The aim of this review is to provide the reader with a concise update of the most relevant methods for the synthesis of aminocyclitols described in the literature. The review is organized according to the methodologies used for the construction of the aminocyclitol framework. These methodologies include chemoenzymatic approaches, intramolecular cyclizations, reactions of cyclitol derivatives with nitrogen nucleophiles, and rearrangement reactions.

1. Introduction

Aminocyclitols are a group of natural products of significant relevance in medicinal chemistry, as they are structural components of a variety of antibiotics,[1] glycosidase inhibitors,[2–4] and other families of biologically active compounds.[5] From a structural point of view, aminocyclitols are cycloalkanes containing at least one free or one substituted amino group and three additional hydroxy groups on the ring atoms.[6] Because of their close structural relationship with sugars, aminocyclitols are also regarded as aminocarbasugars.[7]

Natural aminocyclitols are secondary metabolites found as structural subunits in some complex natural products, such as validamycins, a family of antibiotics isolated from the fermentation culture of *Streptomyces hygroscopicus*.[8] A validamycin is composed of one valienamine unit, together with an additional unit variously of validamine, valiolamine, or hydroxyvalidamine. The α-amylase inhibitor acarbose is another complex natural product containing an aminocyclitol unit (valienamine), linked in this case to a trisaccharide (Figure 1).

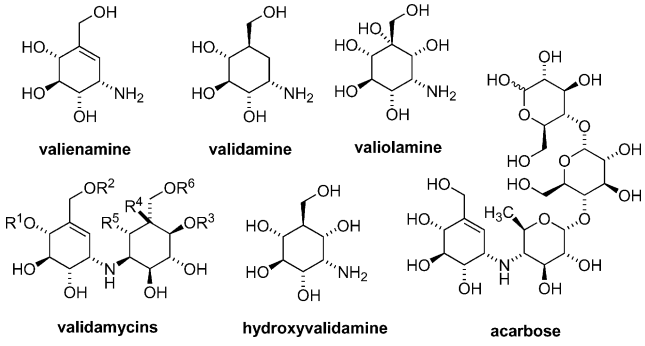


Figure 1. C7N aminocyclitols isolated from natural sources.

The above aminocyclitols are also known as C7N aminocyclitols,[9] due to the presence of a characteristic hydroxymethyl side chain. However, simpler aminocyclitols of the inosamine type (aminocyclohexitols) and some 1,3-diaminocyclitols (Figure 2) are found in several natural products with antibiotic properties.[10] In this context, the development of resistance to antibiotics by pathogenic agents has boosted the design of structural analogues with improved biological profiles.

[a] Research Unit on BioActive Molecules (RUBAM), Departament de Química Orgànica Biològica, Institut d'Investigacions Químiques i Ambientals de Barcelona (IIQAB–C.S.I.C), Jordi Girona 18–26, 08034 Barcelona, Spain
[b] Universitat de Barcelona, Facultat de Farmàcia, Unitat de Química Farmacèutica (Unitat Associada al CSIC), Avgda. Juan XXIII, s/n, 08028 Barcelona, Spain

Antonio Delgado (Barcelona, 1958) obtained his PhD in Pharmacy in 1986 from the University of Barcelona, where since 1988 he has been Associate Professor of Organic Chemistry. After two years as postdoctoral fellow of the Spanish Research Council (CSIC) at Cornell University, he became a member of RUBAM (Research Unit on BioActive Molecules, CSIC). His research interests are the design, synthesis, and biological evaluation of new pharmacological tools as modulators of sphingolipid metabolism with potential therapeutic value. He is also interested in synthetic methodology, as well as in the use of combinatorial chemistry for the generation of small-size libraries. His academic activities are focused on medicinal chemistry, organic chemistry, and synthetic organic chemistry, and he is the co-author of three textbooks on these topics.

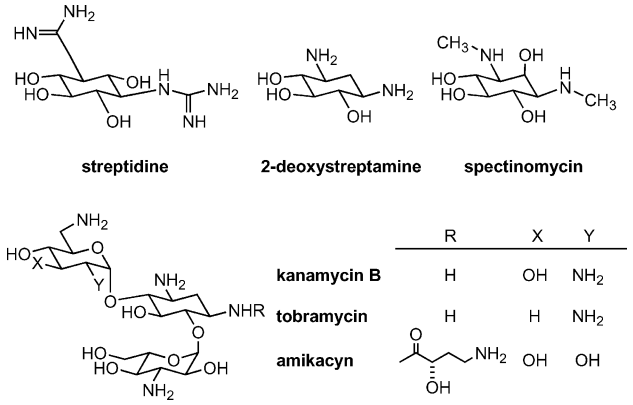


Figure 2. Natural products containing the 1,3-diaminocyclitol moiety.

In addition to the antibiotic properties of 1,3-diaminocyclitols, many of the known aminocyclitols are glycosidase inhibitors, due to their ability to act as carbohydrate mimics.[11] An important group of natural glycosidase inhibitors is to be found in a series of aminocyclopentitols represented by the mannostatin family of mannosidase inhibitors, the trehalase inhibitor trehazolin, and the chitinase inhibitor allosamidin (Figure 3). A lot of effort has been devoted to the total synthesis of these natural products and their analogues.[12] As glycosidases are involved in a variety of different biological processes, glycosidase inhibitors are suitable therapeutic targets for the development of new chemotherapeutic agents against viral infections, cancer, and diabetes, inter alia. In this context, some glycosidase inhibitors containing aminocyclohexitol cores have recently appeared on the market. This is the case with the α-glucosidase inhibitor voglibose (Figure 3), used for lowering postprandial blood glucose levels in people with diabetes mellitus type 2.

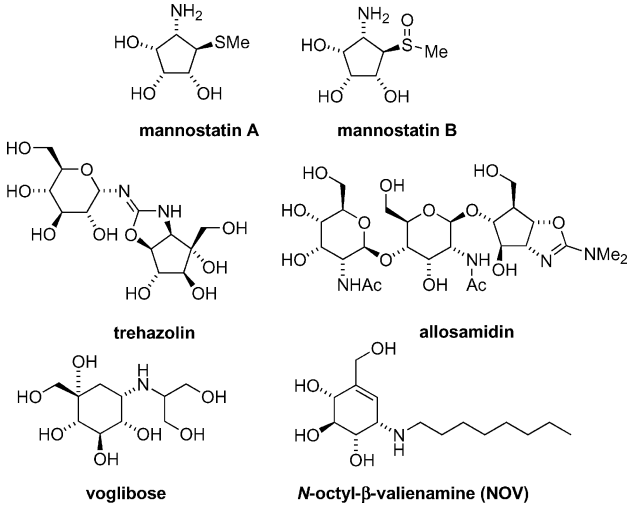


Figure 3. Natural and synthetic glycosidase inhibitors containing aminocyclitol cores.

More recently, the abilities of some aminocyclitols to interfere with sphingolipid metabolism[13] have paved the way for research into new potential therapeutic applications for this class of compounds. This is the case with *N*-octylvalienamine (NOV, Figure 3), currently under study for chemical chaperone therapy for the treatment of Gaucher's disease.[14] In addition, aminocyclitols are also candidates for the development of pharmacological tools for the study of the inositol phosphate cycle and related processes.[15] On the other hand, the 1,2-diaminoinositol framework has also been incorporated both into new salen asymmetric catalysts[16,17] and into new chelating agents.[18] Finally, aminocyclitols have also been found to serve as key intermediates in the synthesis of some natural products, such as those of the *Amarilladaceae* alkaloids.[19]

The aim of this review is to provide the reader with a concise update of the most significant synthetic methods for the synthesis of aminocyclitols described in the recent literature. Synthesis of *O*-glycosides derived from aminocyclitols, as well as biotechnological approaches, with the exception of some relevant chemoenzymatic methods, are not covered in this review.

2. Starting Materials

Most of the reported syntheses of aminocyclitols make use of the chiral pool as the main source of starting materials. Several natural products containing polyhydroxycyclohexane skeletons, such as *vibo*-quercitol, quinic acid, or cyclophellitol (Figure 4), have frequently been used as starting materials in the syntheses of aminocyclitol derivatives. Classical examples are to be found in the syntheses of valiolamine[20] and related amino-carbasugars[21] from quinic acid, the syntheses of (–)-valiolamine and (–)-1-epi-valiolamine from *vibo*-quercitol,[22] and the total syntheses of (+)-validamycin B and (+)-validoxylamine B from cyclophellitol derivatives.[23]

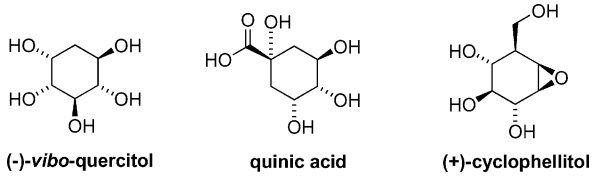
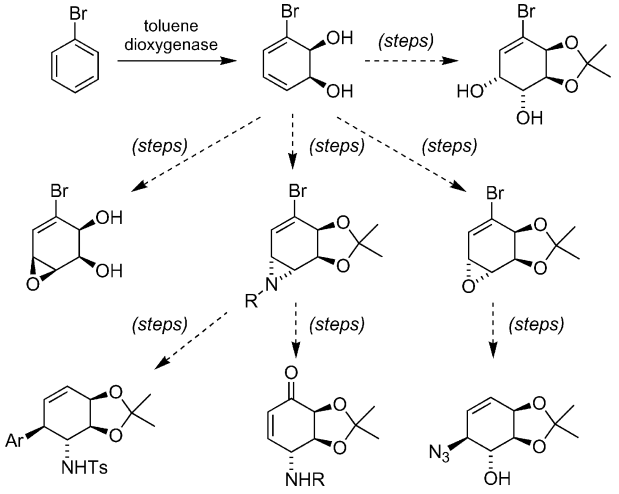


Figure 4. Natural products containing polyhydroxycyclohexane skeletons.

Carbohydrate derivatives are probably the most common starting materials, due to the well established protocols for their conversion into suitable functionalized carbocycles. Several general synthetic strategies have emerged along this line; they include: a) rearrangement reactions, such as the classical Ferrier rearrangement from methyl hex-5-enopyranosides,[24] or the Claisen rearrangement,[25] b) radical cyclizations,[26–28] c) cycloaddition reactions,[29] and d) ring-closing metathesis.[30]

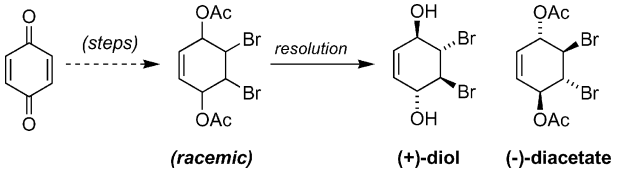
Examples of enantioselective syntheses leading to carbocycles are also known. Thus, it is worth mentioning the reported Pd-catalyzed asymmetric allylic alkylations for the enantioselective kinetic desymmetrization of achiral or racemic conduritols.[31,32]

Finally, several alternative protocols based on chemoenzymatic approaches have also gained relevance for the synthesis of cyclitol derivatives. This is the case with the enzymatic dihydroxylation of aromatic systems with *Pseudomonas putida*, in which the initially formed chiral bromodiols can act as precursors of a variety of functionalized cyclitols[33] (Scheme 1).



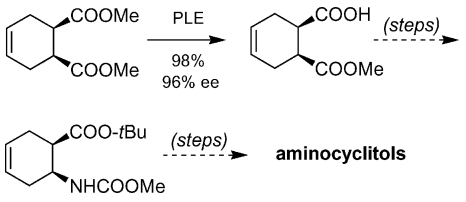
Scheme 1. Functionalized cyclitols obtained by enzymatic dihydroxylation of aromatic systems with *Pseudomonas putida*.

The enzymatic resolution of a racemic dibromo diacetoxy conduritol B derivative, obtained from *p*-benzoquinone, is another example of a chemoenzymatic approach to enantiopure cyclitol derived building blocks[34] (Scheme 2).



Scheme 2. Enzymatic resolution of a dibromo-diacetoxy-substituted conduritol B derivative.

In a related example, the enzymatic resolution of a cyclohexene *meso* diester has been used to obtain a chiral monoester that can be used as starting material for a multistep synthetic sequence leading ultimately to aminocyclitols. Thus, fortamine, the aminocyclitol moiety of the natural antibiotic fortimycin A, was synthesized from an enantiopure building block obtained by the above approach[35] (Scheme 3).

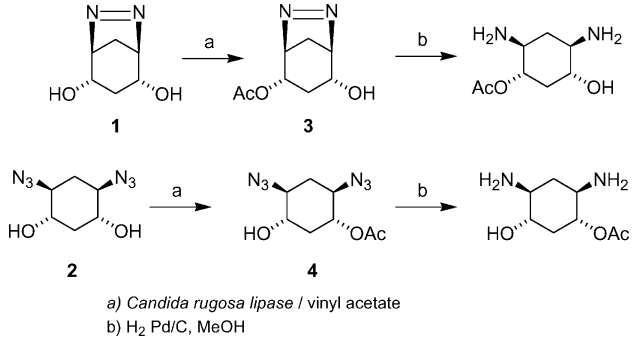


Scheme 3. Enzymatic desymmetrization of a *meso* diester.

Some of the most general synthetic approaches to aminocyclitols that have emerged over the last years are discussed in the following sections. They include the still relatively unexploited chemoenzymatic methods, the synthesis of aminocyclitols by intramolecular cyclization of suitable precursors, reactions between cyclitol derivatives and nitrogen nucleophiles, and a set of methods based on rearrangement reactions.

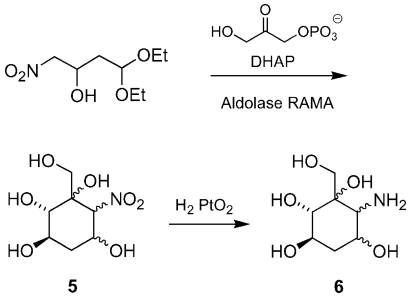
3. Chemoenzymatic Approaches

Despite the above examples of the use of enzymes for the enantioselective synthesis of stereochemically defined cyclitols, literature reports directed towards the direct formation of aminocyclitols by chemoenzymatic methods are still scarce. In this context, a recent account of the desymmetrization of the 2,5-dideoxystreptamine precursors **1** and **2** by enzymatic acylation in organic media is worth mentioning (Scheme 4).[36] The approach afforded the corresponding monoesters **3** and **4** in high enantiomeric excesses. These compounds were used as building blocks in the synthesis of 2,5-dideoxystreptamine precursors.



Scheme 4. Desymmetrization processes to provide 2,5-dideoxystreptamine precursors.

Another noteworthy contribution to the field is the nitroaldol-type intramolecular cyclization between a masked 3-hydroxy-4-nitrobutyraldehyde and dihydroxyacetone phosphate (DHAP) catalyzed by fructose-1,6-bisphosphate aldolase (RAMA, Scheme 5).[37] This transformation was applied to the synthesis of the diastereomeric mixture of nitrocyclitols **5**, which were separated and reduced to the corresponding aminocyclitols **6**, structural analogues of the glycosidase inhibitor valiolamine.

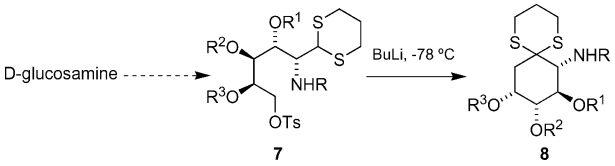


Scheme 5. Intramolecular chemoenzymatic nitroaldol condensation.

4. Intramolecular Cyclizations

4.1. Carbocyclization of Sugars Based on the 1,3-Dithiane Methodology

Starting from D-glucosamine, a series of diversely *O*-protected building blocks of general structure **7** containing a propane-1,3-diyl dithioacetal motif have been synthesized and successfully used in the synthesis of iminosugars and aminocyclitols.[38] Treatment of compounds **7** with *n*BuLi at low temperature afforded the corresponding *O*-protected aminocyclitol derivatives **8**, which have been used as advanced synthetic intermediates of a variety of aminocyclitols (Scheme 6).



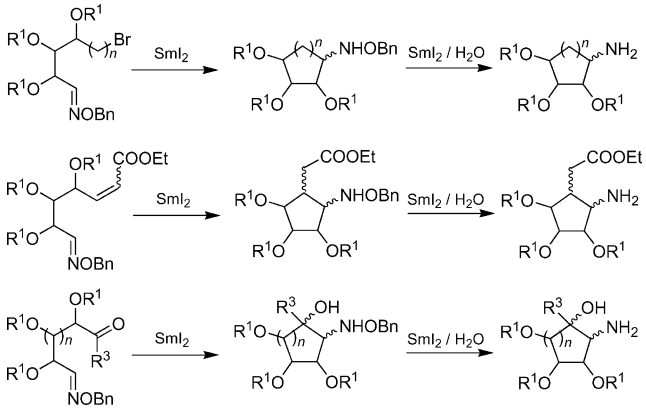
Scheme 6. Intramolecular cyclization of 1,3-dithianes.

In a recent work, this carbocyclization approach has also been implemented for the synthesis of C7N aminocyclitols (see Section 1) and aminocycloheptitols.[39] Oxidation of the primary hydroxy group of **9** to aldehyde **10**, followed by Corey–Chaykovsky epoxidation to **11** and intramolecular carbocyclization, thus led to a mixture of aminocyclitol precursors **12** and **13** as a result of the competition between 6-*exo* and 7-*endo* cyclization pathways (Scheme 7).

Interestingly, the cyclization course could be modified by judicious choice of protecting groups on the starting open-chain precursor. Thus, tri-*O*-benzyl-protected **11** ($R^1 = R^2 = R^3 = Bn$) led selectively to the six-membered aminocyclitol **12** under similar cyclization conditions. The fact that addition of LiBr substantially increases the ratio of cyclohexane vs. cycloheptane aminocyclitols is interpreted by the authors as an indication of the participation of a Li-chelated intermediate in this process.

4.2. Radical Cyclization of Oxime Ethers and Pinacol Coupling Reactions

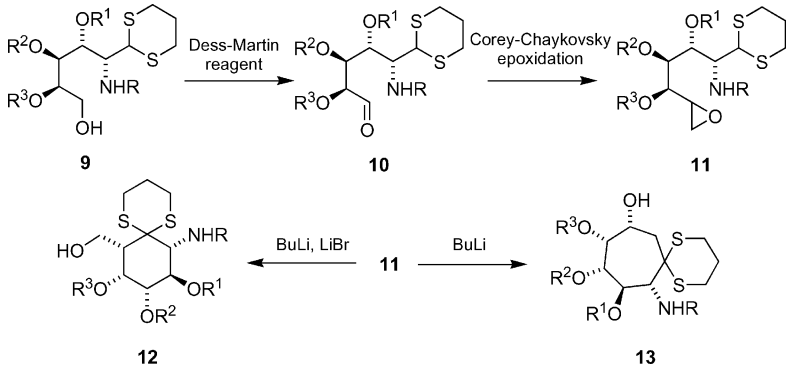
Tributyltin hydride- or samarium diiodide-based reductive couplings of polyhydroxylated oxime ethers functionalized at their terminal positions with bromide, α,β-unsaturated ester, aldehyde, or ketone groups have been reported to afford aminocyclopentitols ($n = 1$, Scheme 8) and aminocyclohexitols ($n = 2$, Scheme 8) in good yields and with high stereoselectivity under mild conditions.[27,40,41]



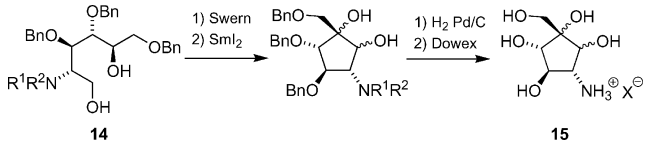
Scheme 8. Intramolecular radical cyclization of oxime ethers.

Application of this protocol to functionalized substrates derived from different carbohydrates allows access to a variety of aminocyclitols with defined regio- and stereochemistry. Moreover, the resulting *O*-benzylhydroxylamine intermediates can be further reduced in situ with excess SmI_2 in the presence of water to afford the corresponding amino alcohols in excellent yields (Scheme 8). The resulting polyhydroxylated aminocyclopentitols are structural motifs present in several natural products, such as the glycosidase inhibitors mannostatin A, trehazolin, and allosamidin, as well as the carbocyclic nucleosides aristeromycin and neplanocin A.

In a related approach, the amino polyol building block **14**, derived from D-glucosamine, was used in a SmI_2-promoted intramolecular pinacol coupling reaction to afford a diastereomeric mixture of the aminocyclopentitol core **15**, present in the hopanoid family of natural products[42] and also structurally close to those found in the trehalase inhibitor trehazolin (Scheme 9). Interestingly, this SmI_2-promoted pinacol coupling can be performed in a one-pot sequence after in situ Swern oxidation of the starting amino diol **14**, allowing its direct transformation into the corresponding aminocyclitols.



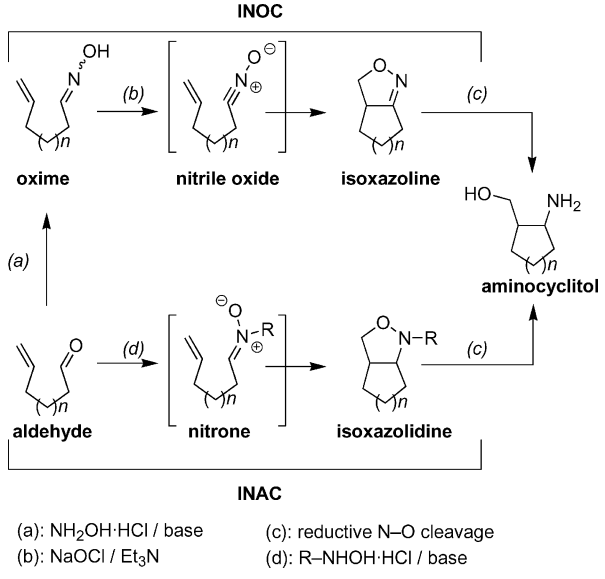
Scheme 7. Intramolecular 1,3-dithiane cyclization to afford C7N aminocyclitol (**12**) and aminocycloheptitol (**13**) precursors.



Scheme 9. Intramolecular pinacol coupling.

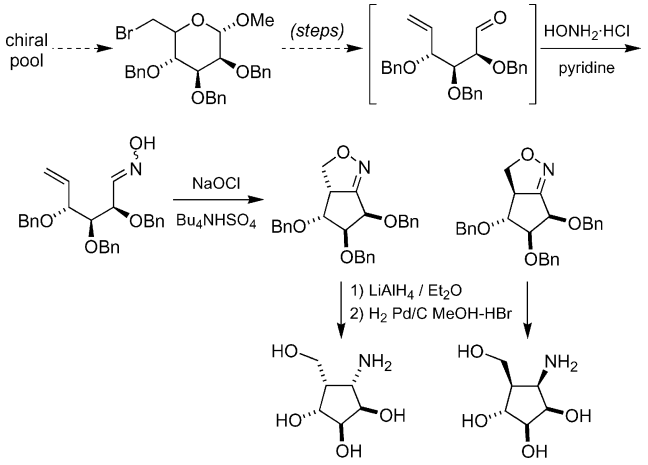
4.3. Intramolecular Nitrile Oxide–Alkene Cycloadditions (INOCs) and Intramolecular Nitrone–Alkene Cycloadditions (INACs)

These types of intramolecular cyclizations are versatile synthetic tools that have been used for the elaboration of functionalized aminocyclitols of different ring sizes from sugars.[43] Both nitrile oxides and nitrones can be generated from a common aldehyde precursor (Scheme 10). Nitrile oxides are therefore usually formed by treatment of the starting aldehyde with NH_2OH, oxidation of the resulting oxime with a chlorinated reagent (NCS, NaOCl, or chloramine-T), and base-induced elimination of HCl from the intermediate hydroximinoyl chloride.[44] Intramolecular [1,3]-dipolar cycloaddition of the transient nitrile oxide leads to a bicyclic fused isoxazoline, an advanced precursor of the target aminocyclitol through C=N reduction and simultaneous reductive cleavage of the N–O bond. On the other hand, treatment of the starting aldehyde with an *N*-substituted oxime, followed by treatment of the resulting nitrone under basic conditions, leads to a fused isoxazolidine system that, as above, leads to the target aminocyclitol by N–O bond reductive cleavage.



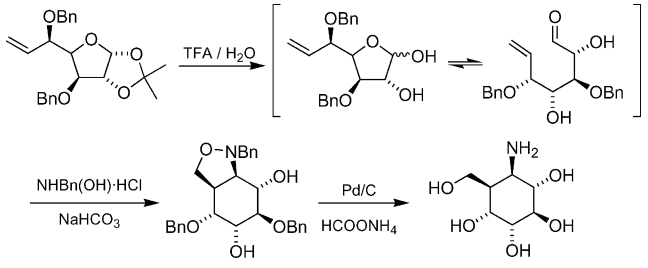
Scheme 10. General approaches to aminocyclitols based on INOC and INAC methodologies.

Relevant applications of both methodologies to the synthesis of aminocyclitols have been reported. The INOC approach, for example, has been used to explore new glycosidase inhibitors containing aminocyclopentitol scaffolds.[45] As can be observed in the example shown in Scheme 11, despite the fact that intramolecular cyclization gave rise to a diastereoisomeric mixture of isoxazolines, each of them afforded a single diastereomer upon reduction of the imine moiety. The high diastereoselectivity observed for this reduction step in systems of this kind has been interpreted on the basis of the configuration of the stereogenic center α to the C=N bond, as well as on the basis of the nature of the C(α) substituent.[46]



Scheme 11. Application of the INOC approach to the synthesis of aminocyclopentitols.

Intramolecular nitrone–alkene cycloadditions (INACs) have also been successfully applied to the production of aminocyclitols from chiral pool precursors.[47] As shown in Scheme 12, treatment of a starting D-glucose-derived allylic alcohol with TFA/H_2O afforded a transient hemiacetal that was treated directly with *N*-benzylhydroxylamine hydrochloride and $NaHCO_3$ to give a fused bicyclic isoxazolidine as a single diastereomer. This finding has been interpreted as a result of the in situ formation of an *N*-benzyl nitrone and a concomitant regio- and stereoselective INAC reaction to afford the observed product. In general, the stereochemical outcome of the process is dictated by the orientation of the alkoxy substituents in the sugar ring skeleton.

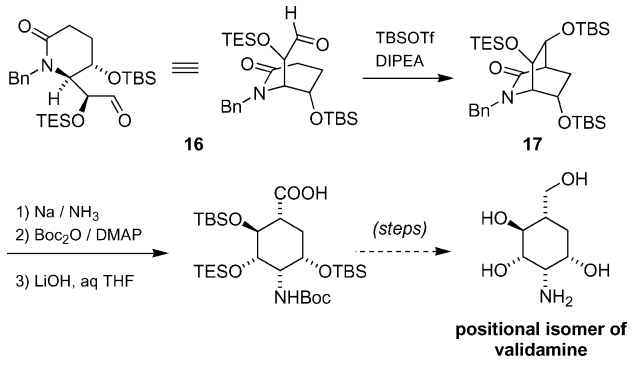


Scheme 12. Synthesis of aminocyclohexitols based on the INAC approach.

4.4. Intramolecular Aldol Reactions

Aldol-type reactions are among the most powerful synthetic methodologies for C–C bond formation. In the field of aminocyclitol chemistry, there are some illustrative examples of this general methodology. An intramolecular Mu-

kaiyama aldol reaction of aldehyde **16** in the presence of TBSOTf and DIPEA, for example, took place with enolization of the lactam group and silylative carbocyclization to yield the bicyclic system **17**.[48] The process afforded the *trans*-configured system with total stereocontrol (Scheme 13). This intermediate was further elaborated into a positional isomer of validamine.



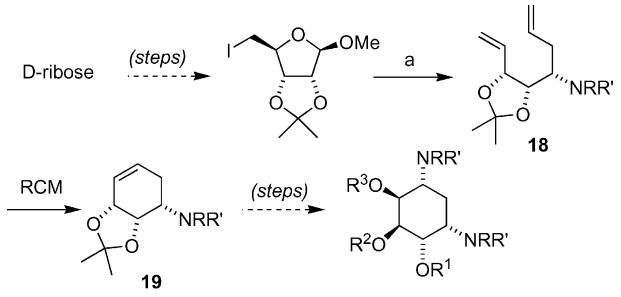
Scheme 13. Intramolecular Mukaiyama aldol reaction.

The nitroaldol condensation (Henry reaction) is a variant of the aldol reaction commonly used to generate β-nitro alcohols. These are versatile synthetic intermediates amenable to further transformations into a wide variety of functional groups.[49] The intramolecular version of this reaction has been successfully applied to the elaboration of nitro-substituted cycloalkanes in the context of the total synthesis of some natural products.[50,51] In particular, this reaction has been used in the synthesis of nitrocyclohexanol adducts starting from D-glucose[52] and also in the synthesis of inositols through subsequent removal of the nitro group under radical conditions (*n*-Bu_3SnH/AIBN).[53] For a chemoenzymatic version of this reaction and applications to the synthesis of aminocyclitols, see Section 3 and Scheme 5.

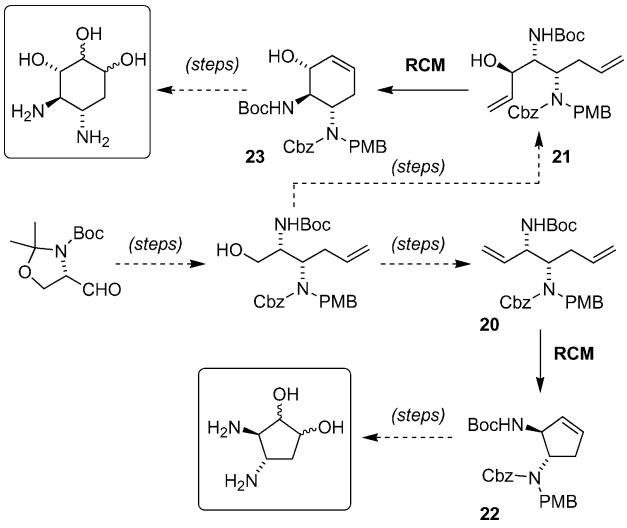
4.5. Ring-Closing Metathesis

Ring-closing metathesis (RCM) has quickly evolved as a suitable and versatile method for the synthesis of carbocycles from carbohydrates.[30] In the context of aminocyclitol chemistry, some interesting examples have been published over the last years. Thus, RCM of aminodiene **18** (Scheme 14), obtained by a multi-step sequence from a suitably protected furanoside, afforded conduramine **19**, a key intermediate in the synthesis of diaminocyclitols related to 2-deoxystreptamine aminoglycoside antibiotics.[54,55] Interestingly, by use of a suitable carbohydrate precursor, both enantiomers of the key conduramine intermediate **19** can be obtained.

In a similar approach, Garner's aldehyde, obtained from L-serine by a multistep sequence,[56] has been used as starting material for the elaboration of diaminodienes **20** and **21** (Scheme 15). These precursors were used in RCM reactions to provide diamino-cycloalkenols **22** and **23**,[57] which were further functionalized by diastereoselective olefin epoxidation or dihydroxylation to afford the target aminocyclitols (Scheme 15).

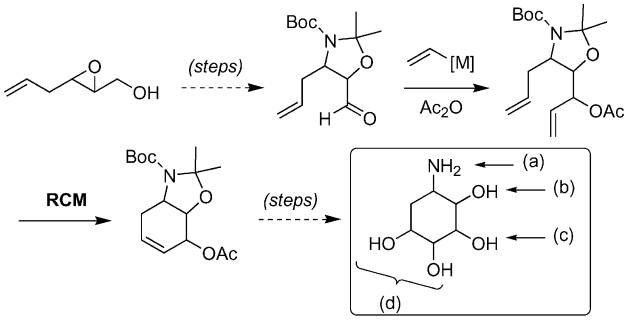


Scheme 14. Synthesis of conduramine **19** by ring-closing metathesis of aminodiene **18**.



Scheme 15. Synthesis of diaminocyclitols by ring-closing metathesis of diaminodienes.

In a very elegant example, RCM has been used in a multi-step synthesis of conduramines involving a Sharpless catalytic asymmetric epoxidation of (*E*)-2,5-hexadien-1-ol



Stereochemistry control

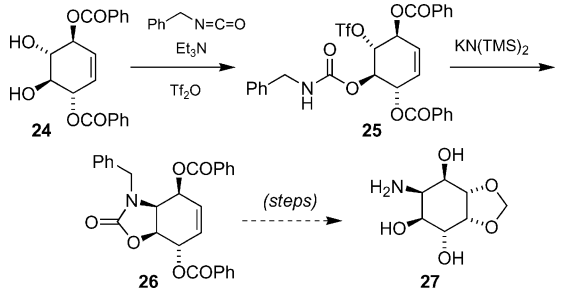
(a): 1) Sharpless epoxidation of (*E*)-2,5-hexadien-1-ol; 2) regio- and stereoselective epoxide opening with an amine precursor.
(b): Inversion / no inversion of the C2-hydroxyl after epoxide opening.
(c): Organometallic addition; Li reagents: *anti*; cuprates: *syn*
(d): *cis*-dihydroxylation: *anti* from oxazolidine *cis*; reversed stereochemistry from oxazolidine *trans*.

Scheme 16. Stereocontrolled synthesis of aminocyclitols by ring-closing metathesis and a combination of other organometallic-based methods.

followed by a diastereoselective addition of a vinylmetal reagent to an intermediate aldehyde (Scheme 16).[58] The double bond *cis*-dihydroxylation of the resulting conduramines allowed access to a family of aminocyclitols with full stereochemical control over the new stereogenic centers.

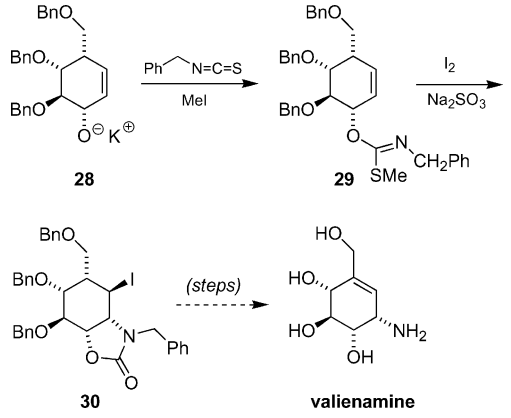
4.6. *N*-Alkylative Cyclization

Intramolecular cyclization of cyclitol carbamates or thiocarbamates with subsequent ring opening of an intermediate oxazolidinone has been used for the introduction of the amino functionality into aminocyclitols. Under suitable basic conditions, a nucleophilic nitrogen species can be generated in order to take part in a C–N bond-forming process through a stereocontrolled intramolecular S_N reaction. By this approach, treatment of diol **24** with benzyl isocyanate and subsequently with triflic anhydride, followed by treatment of the crude triflate **25** with bis(trimethylsilyl)-amide, afforded oxazolidinone **26**, a precursor of the target aminocyclitol **27** (Scheme 17).[32]



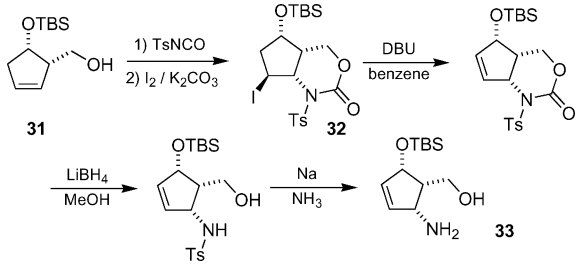
Scheme 17. Intramolecular cyclization of a cyclitol carbamate.

In a related approach, iodocyclization of carbonimidothioate **29**, obtained by condensation of the potassium salt **28** with *p*-methoxybenzyl isothiocyanate, followed by iodomethane quench led to oxazolidinone **30** after iodide treatment and aqueous sodium sulfite workup. This intermediate was further elaborated into valienamine[59] (Scheme 18).



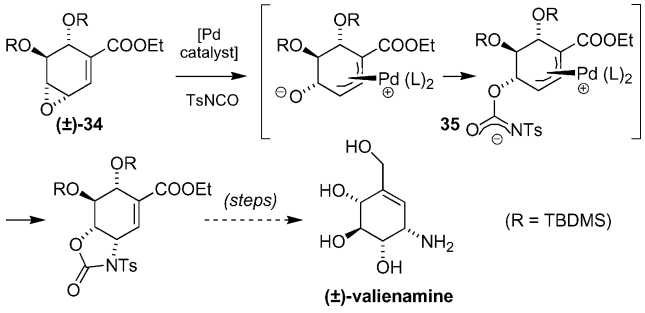
Scheme 18. Iodocyclization of **29** in the synthesis of an advanced intermediate of valienamine.

A conceptually similar protocol was used in the elaboration of the aminocyclopentitol moiety of the glycosidase inhibitor (+)-trehazolin (Scheme 19).[60] In this case, treatment of alcohol **31** with *p*-toluenesulfonyl isocyanate and subsequent iodocyclization generated iodide **32**, a precursor of the target aminocyclitol **33** after carbamate hydrolysis and functional group manipulation.



Scheme 19. Application of the iodocyclization reaction to the synthesis of aminocyclopentitols.

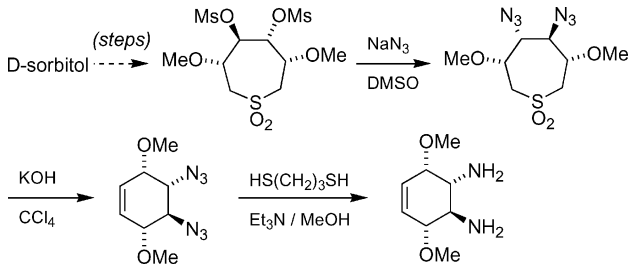
Finally, a more sophisticated approach was described by Trost et al. in the synthesis of (±)-valienamine.[61] In this case, the electrophilic species is the π-allyl system **35**, resulting from treatment of vinyl epoxide (±)-**34** with a Pd catalyst in the presence of tosyl isocyanate. The stereochemical control of the process is remarkable, since the overall transformation implies the ring opening of the epoxide (±)-**1** at the allylic position with retention of configuration (Scheme 20).



Scheme 20. Synthesis of valienamine through an intramolecular cyclization onto a Pd π-allyl system.

4.7. Transannular Cyclization

A method to obtain 2,3-diamino conduritols based on a Ramberg–Bäcklund reaction of a 4,5-diazidothiepane 1,1-dioxide has been described (Scheme 21).[62] The azido



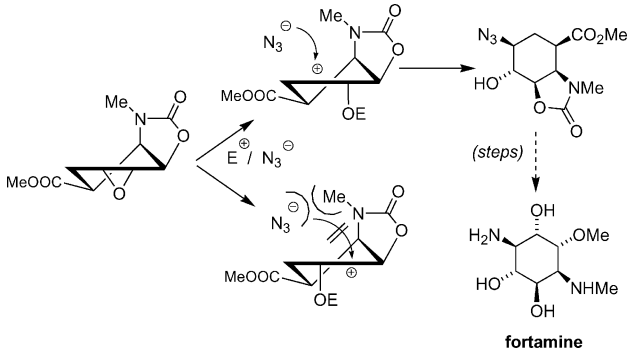
Scheme 21. Synthesis of conduramines by the Ramberg–Bäcklund reaction.

groups are introduced by nucleophilic displacement, with clean inversion of configuration, from a bis-mesyloxy intermediate originating from the chiral pool. Thus, since the stereochemistry of the heterocyclic system is dictated by the nature of the starting hexose used to elaborate the thiepane ring,[63] a variety of configurationally related diamino conduritols can be obtained by this methodology. More recently, a solid-phase version of the Ramberg–Bäcklund reaction leading to conduritols has been described.[64]

5. Treatment of Cyclitol Derivatives with Nitrogen Nucleophiles

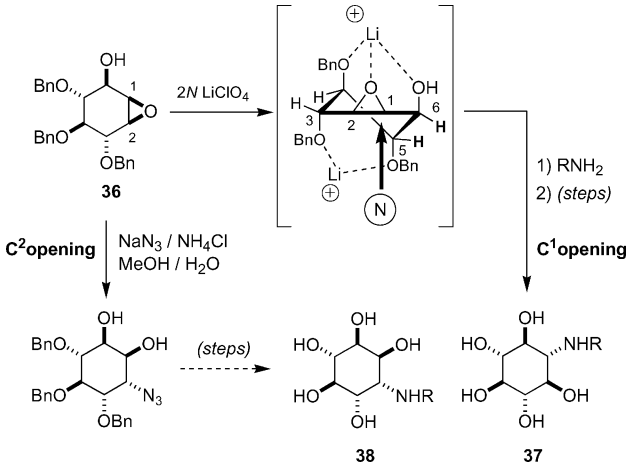
5.1. Ring Opening of Cyclitol Epoxides, Aziridines, and Cyclic Sulfites and Sulfates

Cyclohexane epoxides are an abundant group of natural products for which several synthetic strategies have been developed.[65] In this context, opening of cyclitol epoxides with nitrogen nucleophiles has been extensively reported in the literature. In general, reaction conditions require the use of excess nucleophile in the presence of a polar solvent at high temperature. Although the stereoselectivity of the epoxide opening is controlled by the well established Fürst–Platner rule,[66] which predicts *trans*-diaxial opening from the most stable chair conformation, the regiochemistry of the epoxide opening can be controlled in different ways. Thus, in one of the syntheses of fortamine,[35] the 1,4-diaminocyclitol moiety present in the aminoglycoside antibiotic fortimycin A, the stereochemical restrictions imposed by the starting substrate were crucial for the observed reaction outcome (Scheme 22).



Scheme 22. Synthesis of a fortamine precursor by epoxide opening in a stereochemically constrained system.

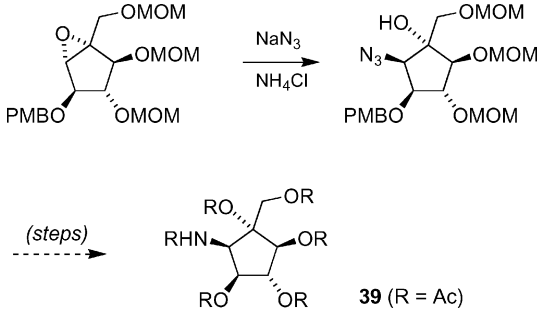
On the other hand, product formation can also be controlled by judicious choice of reaction conditions. The pioneering work of Calvani et al. on the chelation-controlled aminolysis and azidolysis of 1,2-epoxycyclohexanes bearing remote polar groups[67] inspired the use of $Yb(OTf)_3$[68] or $LiClO_4$,[69–71] allowing the regioselective opening of a fully *O*-protected conduritol B epoxide derivative (**36**, Scheme 23) through the operation of a "chelation-controlled" conformation to give, ultimately, aminocyclitols **37**. Interestingly, the regioisomeric adducts **38** were obtained under nonchelating conditions.[70] This methodology has proven very robust and efficient, since it has been successfully applied to the multi-gram scale synthesis of a series of building blocks for use in the production of combinatorial libraries of aminocyclitol systems.[72]



Scheme 23. Synthesis of aminocyclitols by regio- and stereoselective opening of conduritol B epoxide.

The more classical nonchelating conditions have been widely used for the selective *trans*-diaxial opening of related cyclitol epoxides with different nucleophiles.[21,34,73–75]

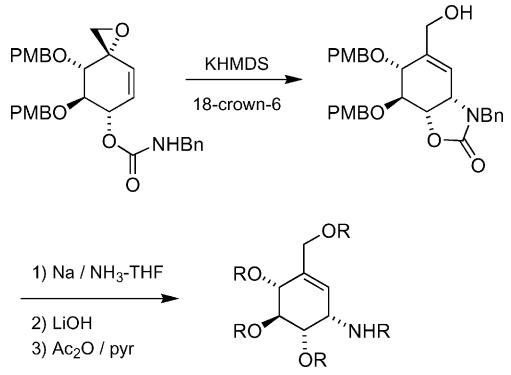
The reactivity of epoxides has also been applied to the synthesis of aminocyclitol analogues bearing the amino group as part of an exocyclic aminoalkyl substituent[28] and also to epoxy cyclopentanols in the course of a stereocontrolled synthesis of the aminocyclitol moiety of (+)-trehazolin (Scheme 24).[76]



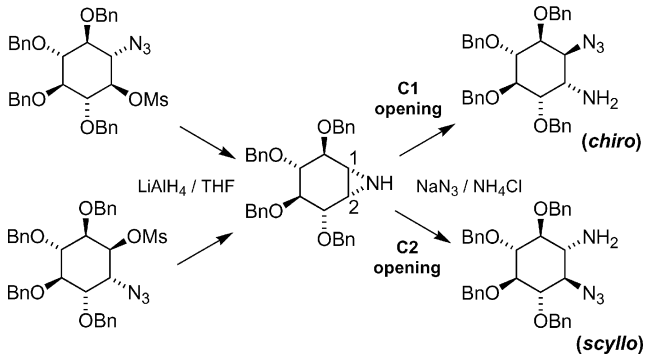
Scheme 24. Synthesis of aminocyclopentitols by epoxide opening.

In a very elegant approach, the hydroxymethyl side chain of (+)-valienamine has been introduced through an intramolecular *N*-alkylative cyclization of a carbamate precursor with simultaneous allylic displacement of a spiroepoxide[77] (Scheme 25). For additional examples of *N*-alkylative cyclizations, see Section 4.6.

The reactivity of aziridines, like that of epoxides, has been used to gain access to *trans*-1,2-diaminocyclitols with total stereochemical control. The required aziridines can be obtained easily by intramolecular displacement of transient vicinal *trans*-1-amino-2-mesylates originating from reduction of the corresponding azido mesylates[70] (Scheme 26).

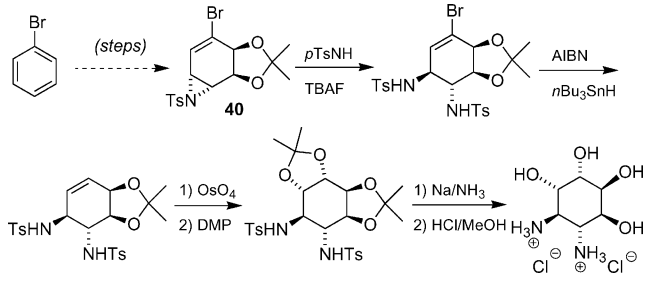


Scheme 25. Epoxide opening coupled with an intramolecular *N*-alkylative cyclization.



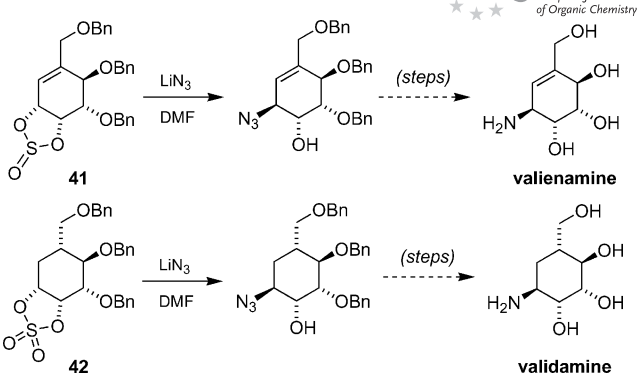
Scheme 26. Synthesis of a conduritol aziridine and steeocontrolled access to diaminocyclitols.

In this context, TBAF-catalyzed opening of *N*-tosyl-aziridine **40**[19] (see Section 2) with *p*-toluenesulfonamide has been applied to the synthesis of diamino-inositol derivatives[78] (Scheme 27), as well as to that of several *N*- and *O*-linked diinositols by iterative opening reactions of epoxides and aziridines.[16]



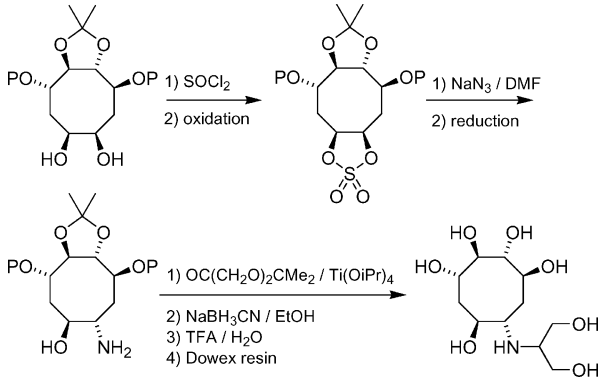
Scheme 27. Synthesis of diaminocyclitols by ring opening of a *N*-tosyl aziridine.

Cyclic sulfates based on vicinal diols can be regarded as equivalent to epoxides with enhanced reactivity profiles.[79] Their interesting properties, as well as those of related cyclic sulfites,[80] have been exploited in one of the syntheses of (+)-valienamine[81] and validamine.[82] Both the cyclic sulfite **41** and the cyclic sulfate **42** undergo regio- and stereospecific ring opening with azide ion to give the corresponding azido cyclitols in good yields (Scheme 28).



Scheme 28. Opening of cyclic sulfates and sulfites based on vicinal diols with azide.

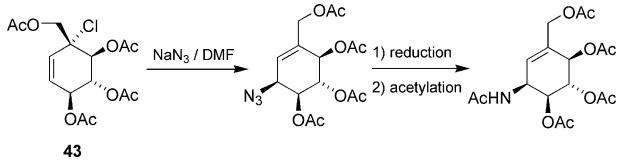
More recently, a cyclic sulfate precursor has been used in the synthesis of C8 amino carbasugars, designed as ring-enlarged inosamine analogues in the search for new glycomimetics with potential α-glucosidase activity[83] (Scheme 29).



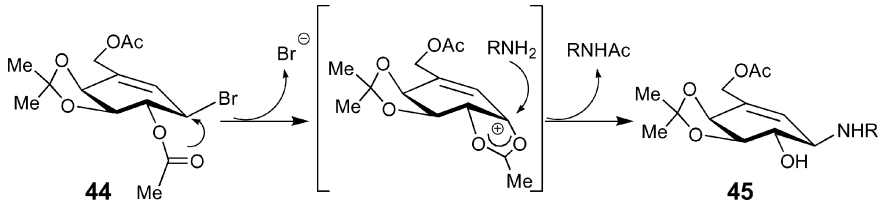
Scheme 29. Opening of a cyclic sulfate in the synthesis of ring-enlarged aminocyclitols.

5.2. Nucleophilic Displacement Reactions

Nucleophilic displacement of an activated inositol derivative by a nitrogen nucleophile is a widely used method for the synthesis of aminocyclitols. In a very straightforward approach, a racemic 1,2-diaminoinositol was obtained by nucleophilic S_N2 displacement from a protected inositol bismesylate.[84] A similar approach has been used in the synthesis of aminocarbasugars from precursors originating from rearrangement of norbornyl derivatives,[85] 2-deoxystreptamine analogues,[86] and several mono- and diazido and -amino inositols,[17,87] and also to prepare a deuterated



Scheme 30. Azidocyclitol by S_N2' displacement of an allylic chloride.

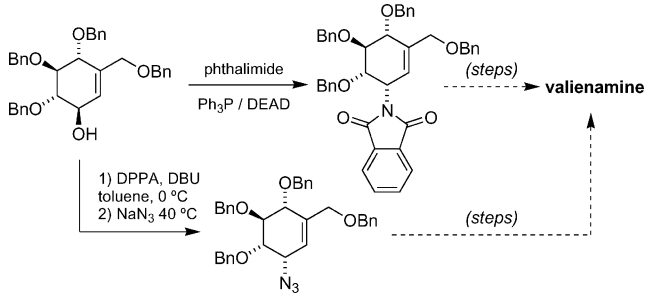


Scheme 31. Neighboring group participation in nucleophilic displacement reactions.

valiolol analogue for biochemical studies.[88] Examples of S_N2' displacements have also been described, as in the synthesis of peracetylated valienamine reported by Ogawa et al. from allylic chloride **43** and sodium azide (Scheme 30).[89]

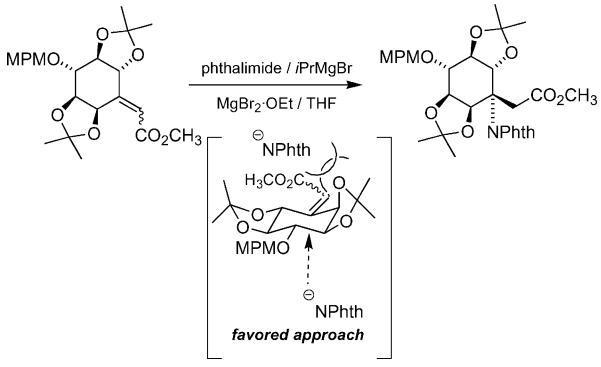
The stereochemical course of the nucleophilic displacement can be dramatically altered by neighboring group participation by a vicinal *trans* acetate. Thus, in the course of a synthesis of valienamine analogues,[90] aminolysis of bromoacetate **44** with different primary amines afforded amino alcohols **45** with clean stereochemical retention. The reaction outcome can be interpreted as the result of the formation of an acetoxonium ion intermediate through neighboring participation of the vicinal *trans* acetoxyl group. In addition, a single regioisomer was obtained as a result of nucleophilic attack at the allylic position of the acetoxonium ion (Scheme 31). The same mechanism has also been observed in the synthesis of (–)-1-epi-valiolamine from a tosylate precursor bearing a *trans*-α-acetoxy group.[22,91]

Reactions between alcohols and nitrogen nucleophiles under Mitsunobu conditions have also been reported. This approach has been successfully used in several syntheses of valienamine from suitable inositol precursors. The example shown in Scheme 32 is based on use of the classical DEAD/Ph_3P system to activate the hydroxy group and phthalimide as nucleophile.[92] A synthetically equivalent approach relies on the direct conversion of alcohols into azides by treatment with hydrazoic acid in the presence of Ph_3P/DEAD[93] or, alternatively, by treatment with diphenylphosphoryl azide (DPPA)[94] and NaN_3, as described by Chang et al. in an efficient synthesis of valienamine.[95] In each case, the process takes place with neat stereochemical inversion to afford the desired aminocyclitol precursor (Scheme 32).



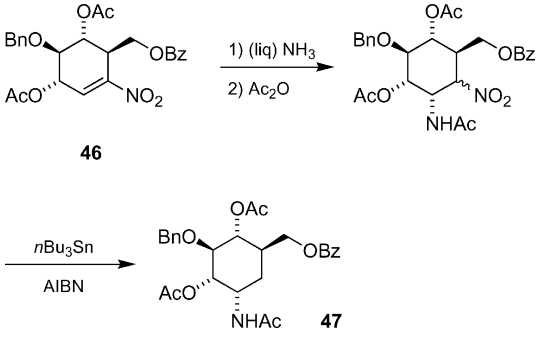
Scheme 32. Synthesis of valienamine precursors from a starting cyclitol through Mitsunobu reactions.

A Lewis-acid-catalyzed Michael-type nucleophilic addition of phthalimide to a protected cyclitol precursor has also been reported.[96] In this case, the stereochemical reaction outcome was interpreted in terms of the steric hindrance imposed by the axial acetonide group, which directs the nucleophilic attack from the less hindered face of the inositol system (Scheme 33).



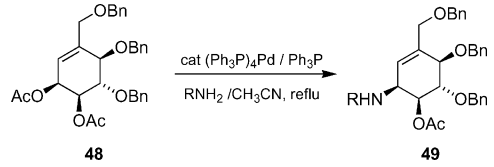
Scheme 33. Aminocyclitols by Michael addition of a nitrogen nucleophile.

A related Michael-type reaction with nitroolefin **46** has been reported. In this case, liquid ammonia is the nucleophilic species that undergoes conjugated addition to provide acetamide **47** after in situ acetylation. The nitro group was further removed by reduction under radical conditions (Scheme 34).[97]



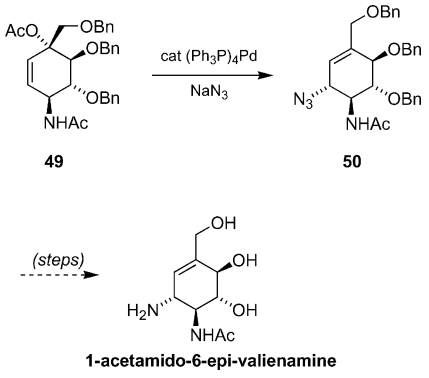
Scheme 34. Aminocyclitols by Michael addition to a nitroolefin cyclitol precursor.

Palladium-catalyzed allylic amination[98] has been successfully applied to the synthesis of various kinds of azido and aminocyclitol derivatives. Treatment, for example, of diacetate **48** with benzylamine in the presence of catalytic amounts of $Pd(PPh_3)_4$ and Ph_3P in acetonitrile at reflux afforded amine **49** (Scheme 35), a close precursor of valienamine. The resulting configuration is in agreement with the operation of a double inversion mechanism with overall retention, as expected.[99]



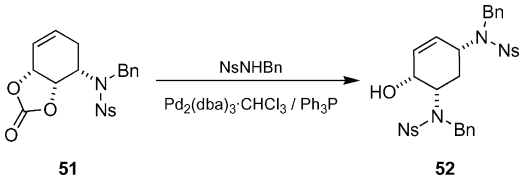
Scheme 35. Aminocyclitols by palladium-catalyzed allylic amination.

In a related process, the Pd-catalyzed reaction of sodium azide with a suitable allylic acetate to give allylic azide **50** has been reported. This compound is an advanced precursor of 1-acetamido-6-epi-valienamine (Scheme 36).[100]



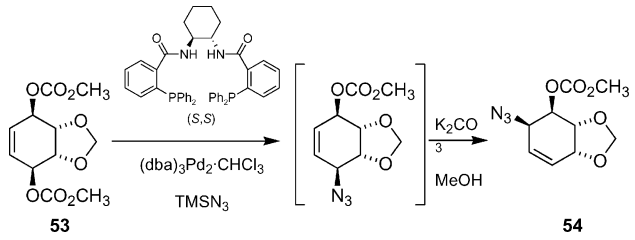
Scheme 36. Azidocyclitols by palladium-catalyzed allylic amination.

A similar approach from cyclic carbonate **51** and *N*-benzylnosylamide was used to obtain a series of 4,6-diaminocyclohexene derivatives **52** as precursors of the aminocyclitol core of aminoglycoside antibiotics of the 2-deoxystreptamine type[54,55] (Scheme 37). In addition, Pd-catalyzed allylic amination of a suitable substrate has been used to introduce an aminomethyl side chain onto a fully protected conduritol derivative.[28]



Scheme 37. Aminocyclitol precursor from an allylic cyclic carbonate through a palladium-catalyzed reaction.

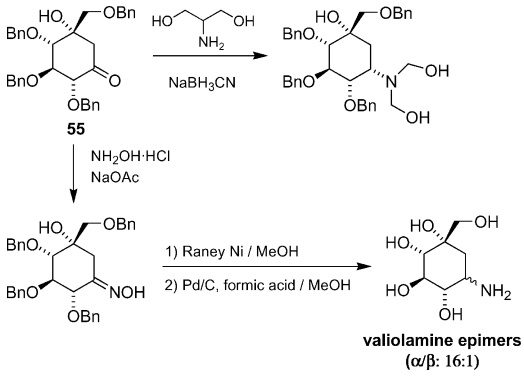
An interesting approach to aminocyclitol derivatives is based on the Pd-catalyzed desymmetrization of conduritol A dicarbonate **53**, as described by Trost et al.[32] (Scheme 38). The use of Pd catalysts bearing C_2-symmetric ligands allows discrimination between the two prochiral centers present in the starting *meso* compound. The enantiodiscriminating step of the process relies on the ability of the Pd catalyst to react with one of the two enantiotopic allylic esters, depending on the chirality of the ligand. Treatment of dicarbonate **53** with azide under these conditions, followed by alkaline hydrolysis of the crude reaction mixture with simultaneous [3,3] sigmatropic rearrangement of the initially formed allylic azide, led to azido cyclitol **54** in 70% yield and 93% *ee* (Scheme 38).



Scheme 38. Pd-catalyzed desymmetrization of conduritol A dicarbonate.

5.3. Reductive Amination

Reductive amination of cyclohexanones represents a classical approach to aminocyclohexanes. In the field of aminocyclitol chemistry, there are some classical precedents of this useful synthetic transformation. Thus, in one of the synthesis of valiolamine and several *N*-substituted derivatives,[92] reductive amination of a functionalized cyclohexanone derivative **55** in the presence of $NaBH_3CN$ allowed the introduction of an alkylamino side chain with total stereocontrol through attack of the reducing agent on the less hindered side of the intermediate Schiff's base. However, ketoxime formation from the above cyclohexanone, followed by catalytic hydrogenation, led to a mixture of epimeric aminocyclitols in an α/β ratio of 16:1 (Scheme 39).

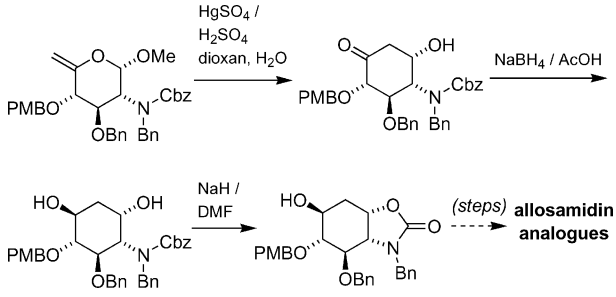


Scheme 39. Aminocyclitols by reductive amination of cyclohexenones and ketoxime reduction.

Reductive aminations leading to C6, C7, and C8 aminocyclitols in the search for new glycosidase inhibitors have also been reported in the literature.[83,101,102] In this case, reductive amination of the starting cycloalkanones was carried out under Mattson conditions[103] with $Ti(OiPr)_4$ as Lewis acid, followed by in situ reduction of the intermediate imine with $NaBH_3CN$ in MeOH. The diastereoselectivity of the processes ranged between 60:40 and 80:20, and in some cases the resulting epimeric aminocyclitols could be isolated by chromatography.

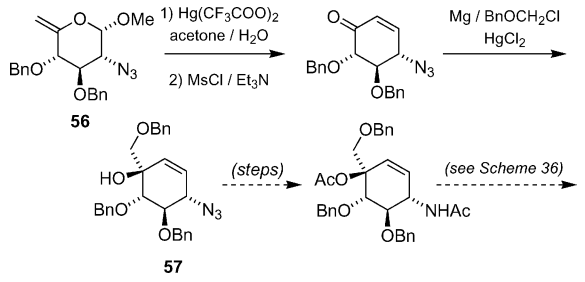
6. Rearrangements

Some rearrangement reactions have been successfully applied to aminocyclitol chemistry. As mentioned above, carbohydrates have been widely used as starting materials for conversion into functionalized carbocycles.[30,104] In this context, the Ferrier rearrangement is now considered a classical approach.[24] When applied to suitably protected amino sugars, this transformation gives access to versatile aminocyclohexenone precursors that have been used as starting materials for the synthesis of aminocyclitol derivatives. An example of this approach is to be found in the synthesis of pseudo-disaccharides related to allosamidin.[105] In this case, the β-hydroxy group of the initially formed β-hydroxycyclohexanone is used to elaborate the oxazoline moiety characteristic of natural products of this kind (Scheme 40).



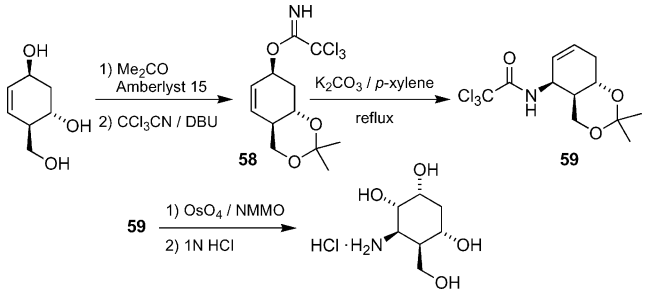
Scheme 40. Aminocyclitols through a Ferrier rearrangement of a glucosamine derivative.

A recent example of the use of the Ferrier rearrangement can be found in the synthesis of the 1-acetamido derivative of 6-epi-valienamine, an inhibitor of several β-*N*-acetylglucosaminidases.[100] Although the rearrangement reaction proceeded smoothly from the 2-acetamido precursor, problems associated with the reactivity of the resulting acetamidocyclohexenone with the Grignard reagent required for the introduction of the benzyloxymethyl side chain, led the authors to use the corresponding 2-azido precursor **56**, which also proved to be a suitable substrate for the rearrangement step (Scheme 41). The advanced intermediate **57** was used as starting material for the synthesis of a precursor of 1-acetamido-6-epi-valienamine (see also Scheme 36).



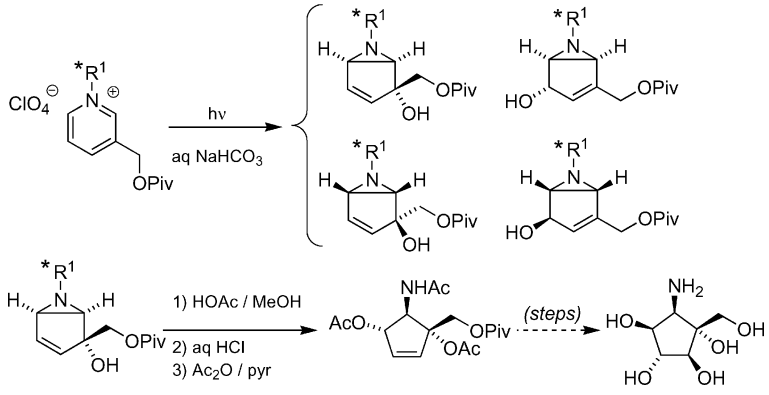
Scheme 41. Example of a Ferrier rearrangement in the synthesis of a valienamine analogue.

The sigmatropic rearrangement of allylic imidates, classically known as the aza-Claisen or Claisen-imidate rearrangement and nowadays also called the Overman rearrangement,[106] has also been used to provide access to aminocyclitol systems from suitable precursors. The process can be carried out either thermally or in the presence of Hg^{II} or Pd^{II} catalysts. Mehta et al. have used this rearrangement to convert trichloroacetimidate **58** into trichloroacetamide **59** under thermal conditions en route to aminocarbasugar analogues (Scheme 42).[85]



Scheme 42. Aminocyclitols through sigmatropic rearrangements of allylic imidates.

Finally, a strategy for the concise synthesis of trehazolamine, the aminocyclitol core of the potent trehalase inhibitor trehazolin, has been developed.[107] The methodology takes advantage of the photocyclization reaction of 1-(methoxyethoxymethyl)-3-(pivaloxymethyl)pyridinium perchlorate to generate a mixture of isomeric bicyclic aziridines (Scheme 43). Interestingly, this strategy has been used in an



Scheme 43. Enantioselective synthesis of aminocyclitols through photocyclization reactions of pyridinium perchlorate derivatives bearing chiral auxiliaries (*R^1).

enantiodivergent way with the help of a sugar-derived chiral auxiliary at the pyridinium nitrogen atom. In this way, enantiomerically pure aminocyclopentitol precursors can be obtained independently for further functional group manipulation.

7. Conclusions and Outlook

Over the last few years, the chemistry of aminocyclitols has become a very active field of research, in the areas both of natural product chemistry and of medicinal chemistry. Consistently with this assessment, the distribution by years of the total number of references extracted from "SciFinder Scholar" on the topic "synthesis of aminocyclitols or aminocarbasugars" is illustrative. At the time this review was written, around one-fourth of the total of papers on this topic had been published in the period 2000–2008. Since aminocyclitols are amino-carbasugars, their chemistry has greatly benefited from knowledge acquired on the synthesis of carbohydrates and carbocyclic-derived compounds. Thus, as pointed out in the above sections, many of the currently available methodologies for aminocyclitols are inspired by, or are adaptations of, some of the well established protocols taken from the above fields. However, applications of new synthetic strategies to the chemistry of aminocyclitols are starting to emerge. This is the case with biocatalysis, which despite being widely used in several areas of synthetic organic chemistry[108,109] still has scarce application to the total synthesis of aminocyclitols. A significant incorporation of biocatalytic approaches to the repertoire of available methodologies for the synthesis of aminocyclitols would be desirable in the years to come.

In summary, the chemistry of aminocyclitols is a solid area of organic synthesis that provides the contemporary chemist with a wide variety of synthetic methods to fulfill most needs in the search for better and improved analogues for use in several areas of research.

Acknowledgments

The author very gratefully thanks all the RUBAM members for their support in the elaboration of this review. Partial financial support from the Spanish Ministerio de Ciencia y Tecnología (MCYT) (Project CTQ2005-00175/BQU), the Fondos Feder (EU), the Spanish Ministerio de Sanidad y Consumo (Project PIO40767), and the Generalitat de Catalunya (Grant 2005SGR05-01063) is acknowledged.

[1] R. J. Ferrier, R. Blattner, K. Clinch, R. H. Furneaux, J. M. Gardiner, P. C. Tyler, R. H. Wightman, N. R. Williams, *Carbohydr. Chem.* **1996**, *28*, 251–262.
[2] E. S. el Ashry, N. Rashed, A. H. Shobier, *Pharmazie* **2000**, *55*, 251–262.
[3] E. S. el Ashry, N. Rashed, A. H. Shobier, *Pharmazie* **2000**, *55*, 331–348.
[4] E. S. el Ashry, N. Rashed, A. H. Shobier, *Pharmazie* **2000**, *55*, 403–415.
[5] Y. Chapleur, *Carbohydrate Mimics – Concepts and Methods*, Wiley-VCH, Weinheim, **1998**.
[6] Aminocyclitols in which only one hydroxy group is replaced by an amino group are also known as inosamines. Cyclitols with less than three hydroxy groups on the cyclohexane skeleton are better named according to the general rules of IUPAC nomenclature. For recommendations on the nomenclature of cyclitols, see: http://www.chem.qmul.ac.uk/iupac/cyclitol.
[7] O. Arjona, A. M. Gomez, J. C. Lopez, J. Plumet, *Chem. Rev.* **2007**, *107*, 1919–2036.
[8] X. Chen, Y. Fan, Y. Zheng, Y. Shen, *Chem. Rev.* **2003**, *103*, 1955–1978.
[9] T. Mahmud, *Nat. Prod. Rep.* **2003**, *20*, 137–166.
[10] P. Veyssier, A. Bryskier, *Antimicrob. Agents Chemother.* **2005**, 453–469.
[11] V. H. Lillelund, H. H. Jensen, X. Liang, M. Bols, *Chem. Rev.* **2002**, *102*, 515–553.
[12] A. Berecibar, C. Grandjean, A. Siriwardena, *Chem. Rev.* **1999**, *99*, 779–844.
[13] A. Delgado, J. Casas, A. Llebaria, J. L. Abad, G. Fabrias, *ChemMedChem* **2007**, *2*, 580–606.
[14] Z. Yu, A. R. Sawkar, J. W. Kelly, *FEBS Lett.* **2007**, *274*, 4944–4950.
[15] J. H. Clarke, *Curr. Biol.* **2003**, *13*, R815–817.
[16] B. J. Paul, J. Willis, T. A. Martinot, I. Ghiviriga, K. A. Abboud, T. Hudlicky, *J. Am. Chem. Soc.* **2002**, *124*, 10416–10426.
[17] V. N. Azev, M. D'Alarcao, *J. Org. Chem.* **2004**, *69*, 4839–4842.
[18] A. Ouadi, A. Loussouarn, L. Morandeau, P. Remaud, A. Faivre-Chauvet, J. Webb, J.-F. Gestin, *Eur. J. Med. Chem.* **2004**, *39*, 467–472.
[19] T. Hudlicky, X. Tian, K. Konigsberger, R. Maurya, J. Rouden, B. Fan, *J. Am. Chem. Soc.* **1996**, *118*, 10752–10765.
[20] T. Shing, L. Wan, *J. Org. Chem.* **1996**, *61*, 8468–8479.
[21] M. Carballido, L. Castedo, C. Gonzalez-Bello, *Eur. J. Org. Chem.* **2004**, 3663–3668.
[22] S. Ogawa, Y. Ohishi, M. Asada, A. Tomoda, A. Takahashi, Y. Ooki, M. Mori, M. Itoh, T. Korenaga, *Org. Biomol. Chem.* **2004**, *2*, 884–889.
[23] S. Ogawa, Y. Miyamoto, T. Nose, *J. Chem. Soc. Perkin Trans. 1* **1988**, 2675–2680.
[24] R. J. Ferrier, S. Middleton, *Chem. Rev.* **1993**, *93*, 2779–2831.
[25] G. Rassu, L. Auzzas, L. Battistini, G. Casiraghi, *Mini-Rev. Org. Chem.* **2004**, *1*, 343–357.
[26] J. Marco-Contelles, C. Alhambra, A. Martinez-Grau, *Synlett* **1998**, 693–699.
[27] J. Marco-Contelles, C. Pozuelo, E. de Opazo, *Carbohydr. Res.* **2001**, *332*, 341–349.
[28] A. M. Gomez, E. Moreno, C. Uriel, S. Jarosz, S. Valverde, J. C. Lopez, *Tetrahedron-Asymmetry* **2005**, *16*, 2401–2407.
[29] S. E. Denmark, M. Juhl, *Helv. Chim. Acta* **2002**, *85*, 3712–3736.
[30] R. Madsen, *Eur. J. Org. Chem.* **2007**, 399–415, and references therein.
[31] B. M. Trost, D. E. Patterson, E. J. Hembre, *Chem. Eur. J.* **2001**, *7*, 3768–3775.
[32] B. M. Trost, J. Dudash Jr, E. J. Hembre, *Chem. Eur. J.* **2001**, *7*, 1619–1629.
[33] T. Hudlicky, D. Gonzalez, D. T. Gibson, *Aldrichimica Acta* **1999**, *32*, 35–62.
[34] M. A. Podeschwa, O. Plettenburg, H. J. Altenbach, *Org. Biomol. Chem.* **2003**, *1*, 1919–1929.
[35] S. Kobayashi, K. Kamiyama, M. Ohno, *J. Org. Chem.* **1990**, *55*, 1169–1177.
[36] R. Chenevert, F. Jacques, *Tetrahedron: Asymmetry* **2006**, *17*, 1017–1021.
[37] L. El Blidi, M. Ahbala, J. Bolte, M. Lemaire, *Tetrahedron: Asymmetry* **2006**, *17*, 2684–2688.
[38] Y.-L. Chen, R. Leguijt, H. Redlich, *Synthesis* **2006**, 2242–2250.
[39] Y.-L. Chen, H. Redlich, K. Bergander, R. Fröhlich, *Org. Biomol. Chem.* **2007**, *5*, 3330–3339.
[40] J. Marco-Contelles, P. Gallego, M. Rodriguez-Fernandez, N. Khiar, C. Destabel, M. Bernabe, A. Martinez-Grau, J. L. Chiara, *J. Org. Chem.* **1997**, *62*, 7397–7412.
[41] H. Miyabe, A. Nishiki, T. Naito, *Chem. Pharm. Bull.* **2003**, *51*, 100–103.

[42] J. L. Chiara, I. Storch de Gracia, A. Bastida, *Chem. Commun.* **2003**, 1874–1875.
[43] T. K. M. Shing, W. F. Wong, H. M. Cheng, W. S. Kwok, K. H. So, *Org. Lett.* **2007**, *9*, 753–756 and references cited therein.
[44] K. Liu, B. R. Shelton, R. K. Howe, *J. Org. Chem.* **1980**, *45*, 3916–3918.
[45] M. Kleban, P. Hilgers, J. N. Greul, R. D. Kugler, J. Li, S. Picasso, P. Vogel, V. Jager, *ChemBioChem* **2001**, *2*, 365–368.
[46] J. K. Gallos, A. E. Koumbis, V. P. Xiraphaki, C. C. Dellios, E. Coutouli-Argyropoulou, *Tetrahedron* **1999**, *55*, 15167–15180.
[47] a) S. M. Jachak, N. P. Karche, D. D. Dhavale, *Tetrahedron Lett.* **2001**, *42*, 4925–4928; b) C. Chakraborty, V. P. Vyavahare, D. D. Dhavale, *Tetrahedron* **2007**, *63*, 11984–11990.
[48] G. Rassu, L. Auzzas, V. Zambrano, P. Burreddu, L. Pinna, L. Battistini, F. Zanardi, G. Casiraghi, *J. Org. Chem.* **2004**, *69*, 1625–1628.
[49] F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915–945.
[50] F. A. Luzzio, R. W. Fitch, *J. Org. Chem.* **1999**, *64*, 5485–5493.
[51] P. Magnus, J. Booth, L. Diorazio, T. Donohoe, V. Lynch, N. Magnus, J. Mendoza, P. Pye, J. Tarrant, *Tetrahedron* **1996**, *52*, 14103–14146.
[52] R. G. Soengas, J. C. Estevez, R. J. Estevez, M. A. Maestro, *Tetrahedron: Asymmetry* **2003**, *14*, 1653–1658.
[53] R. G. Soengas, J. C. Estevez, R. J. Estevez, *Org. Lett.* **2003**, *5*, 4457–4459.
[54] S. H. L. Verhelst, W. Wiedenhof, H. Ovaa, G. A. van der Marel, H. S. Overkleeft, C. A. A. van Boeckel, J. H. van Boom, *Tetrahedron Lett.* **2002**, *43*, 6451–6455.
[55] S. H. L. Verhelst, T. Wennekes, G. A. van der Marel, H. S. Overkleeft, C. A. A. van Boeckel, J. H. van Boom, *Tetrahedron* **2004**, *60*, 2813–2822.
[56] P. Garner, J. M. Park, *J. Org. Chem.* **1987**, *52*, 2361–2364.
[57] X. Cong, Q. J. Liao, Z. J. Yao, *J. Org. Chem.* **2004**, *69*, 5314–5321.
[58] C. Alegret, J. Benet-Buchholz, A. Riera, *Org. Lett.* **2006**, *8*, 3069–3072.
[59] S. Knapp, A. B. J. Naughton, T. G. Murali Dhar, *Tetrahedron Lett.* **1992**, *33*, 1025–1028.
[60] M. T. Crimmins, E. A. Tabet, *J. Org. Chem.* **2001**, *66*, 4012–4018.
[61] B. M. Trost, L. S. Chupak, T. Lubbers, *J. Am. Chem. Soc.* **1998**, *120*, 1732–1740.
[62] A. Arcelli, V. Cere, F. Peri, S. Pollicino, A. Ricci, *Tetrahedron* **2001**, *57*, 3439–3444.
[63] V. Cere, G. Mantovani, F. Peri, S. Pollicino, A. Ricci, *Tetrahedron* **2000**, *56*, 1225–1231.
[64] V. Cere, M. Minzoni, S. Pollicino, A. Ricci, F. Gasparrini, A. Ciogli, I. D′Acquarica, *J. Comb. Chem.* **2006**, *8*, 74–78.
[65] J. Marco-Contelles, M. T. Molina, S. Anjum, *Chem. Rev.* **2004**, *104*, 2857–2899.
[66] A. Furst, P. A. Plattner, *Helv. Chim. Acta* **1949**, *32*, 275–283.
[67] F. Calvani, P. Crotti, C. Gardelli, M. Pineschi, *Tetrahedron* **1994**, *50*, 12999–13022, and references therein.
[68] P. Serrano, A. Llebaria, A. Delgado, *J. Org. Chem.* **2002**, *67*, 7165–7167.
[69] P. Serrano, A. Llebaria, J. Vazquez, J. de Pablo, J. M. Anglada, A. Delgado, *Chem. Eur. J.* **2005**, *11*, 4465–4472.
[70] P. Serrano, A. Llebaria, A. Delgado, *J. Org. Chem.* **2005**, *70*, 7829–7840.
[71] P. Gonzalez-Bulnes, J. Casas, A. Delgado, A. Llebaria, *Carbohydr. Res.* **2007**, *342*, 1947–1952.
[72] P. Serrano, J. Casas, M. Zucco, G. Emeric, M. Egido-Gabas, A. Llebaria, A. Delgado, *J. Comb. Chem.* **2007**, *9*, 43–52.
[73] S. Ogawa, M. Mori, G. Takeuchi, F. Doi, M. Watanabe, Y. Sakata, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2811–2814.
[74] S. Ogawa, S. Fujieda, Y. Sakata, M. Ishizaki, S. Hisamatsu, K. Okazaki, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3461–3463.
[75] T. Zhan, H. Lou, *Carbohydr. Res.* **2007**, *342*, 865–869.
[76] M. Akiyama, T. Awamura, K. Kimura, Y. Hosomi, A. Kobayashi, K. Tsuji, A. Kuboki, S. Ohira, *Tetrahedron Lett.* **2004**, *45*, 7133–7136.
[77] T. K. Park, S. J. Danishefsky, *Tetrahedron Lett.* **1994**, *35*, 2667–2670.
[78] B. J. Paul, E. Hobbs, P. Buccino, T. Hudlicky, *Tetrahedron Lett.* **2001**, *42*, 6433–6435.
[79] Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539.
[80] B. B. Lohray, *Synthesis* **1992**, 1035–1052.
[81] T. K. M. Shing, T. Y. Li, S. H. L. Kok, *J. Org. Chem.* **1999**, *64*, 1941–1946.
[82] T. K. M. Shing, V. W. Tai, *J. Org. Chem.* **1995**, *60*, 5332–5334.
[83] O. Andriuzzi, C. Gravier-Pelletier, G. Bertho, T. Prange, Y. Le Merrer, *Beilstein J. Org. Chem.* **2005**, *1*, 12.
[84] P. Guedat, B. Spiess, G. Schlewer, *Tetrahedron Lett.* **1994**, *35*, 7375–7378.
[85] G. Mehta, S. Lakshminath, P. Talukdar, *Tetrahedron Lett.* **2002**, *43*, 335–338.
[86] M. V. De Almeida, E. T. Da Silva, M. Le Hyaric, A. S. Machado, M. V. N. De Souza, R. M. Santiago, *J. Carbohydr. Chem.* **2003**, *22*, 733–742.
[87] K. M. Sureshan, K. Ikeda, N. Asano, Y. Watanabe, *Tetrahedron Lett.* **2004**, *45*, 8367–8370.
[88] K. Arakawa, S. G. Bowers, B. Michels, V. Trin, T. Mahmud, *Carbohydr. Res.* **2003**, *338*, 2075–2082.
[89] S. Ogawa, Y. Shibata, T. Nose, T. Suami, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3387–3388.
[90] S. Ogawa, Y. Sakata, N. Ito, M. Watanabe, K. Kabayama, M. Itoh, T. Korenaga, *Bioorg. Med. Chem.* **2004**, *12*, 995–1002.
[91] S. Ogawa, M. Kanto, *J. Nat. Prod.* **2007**, *70*, 493–497.
[92] H. Fukase, S. Horii, *J. Org. Chem.* **1992**, *57*, 3651–3658.
[93] K. Tatsuta, H. Mukai, M. Takahashi, *J. Antibiot.* **2000**, *53*, 430–435.
[94] A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, E. J. J. Grabowski, *J. Org. Chem.* **1993**, *58*, 5886–5888.
[95] Y. K. Chang, B. Y. Lee, D. J. Kim, G. S. Lee, H. B. Jeon, K. S. Kim, *J. Org. Chem.* **2005**, *70*, 3299–3302.
[96] M. Li, A. Wu, *Synlett* **2006**, 2985–2988.
[97] M. Yoshikawa, N. Murakami, Y. Yokokawa, Y. Inoue, Y. Kuroda, I. Kitagawa, *Tetrahedron* **1994**, *50*, 9619–9628.
[98] J. Tsuji, in *Palladium reagents and catalysts; Innovations in Organic Synthesis*, 2nd ed., Wiley, Chichester, **1995**.
[99] S. Kok, C. C. Lee, T. K. M. Shing, *J. Org. Chem.* **2001**, *66*, 7184–7190.
[100] A. Scaffidi, K. A. Stubbs, R. J. Dennis, E. J. Taylor, G. J. Davies, D. J. Vocadlo, R. V. Stick, *Org. Biomol. Chem.* **2007**, *5*, 3013–3019.
[101] C. Gravier-Pelletier, Y. Le Merrer, *Curr. Org. Synth.* **2007**, *4*, 1–13 and references cited therein.
[102] O. Andriuzzi, C. Gravier-Pelletier, P. Vogel, Y. Le Merrer, *Tetrahedron* **2005**, *61*, 7094–7104.
[103] R. J. Mattson, K. M. Pham, D. J. Leuck, K. A. Cowen, *J. Org. Chem.* **1990**, *55*, 2552–2554.
[104] J. Marco-Contelles, M. Rodriguez-Fernandez, *Comp. Rendus Acad. Sci. Ser. II C* **2001**, *4*, 443–452.
[105] D. F. Corbett, D. K. Dean, S. R. Robinson, *Tetrahedron Lett.* **1994**, *35*, 459–462.
[106] L. E. Overman, N. E. Carpenter, *Org. React.* **2005**, *66*, 1–107.
[107] X. Feng, E. N. Duesler, P. S. Mariano, *J. Org. Chem.* **2005**, *70*, 5618–5623.
[108] E. Garcia-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2005**, *105*, 313–354.
[109] K. M. Koeller, C.-H. Wong, *Nature* **2001**, *409*, 232–240.

Received: March 3, 2008
Published Online: May 30, 2008

