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Synthesis of Cyclopentitols by Ring-Closing Approaches

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Contents

1. Introduction

Considerable effort has been devoted in the past decades to the development of new methods for the construction of five-membered carbocycles, since they play a fundamental role in synthetic organic chemistry, as both targets and intermediates. Cyclopentitols, hydroxylated cyclopentane derivatives of varying nature and complexity, exist as subunits in many products of biological importance. The prostanoids[1,2] are a family of biologically active lipids derived from the action of cyclooxygenases or prostaglandin synthases upon the 20-carbon essential fatty acids or eicosanoids,[3−5] which can be subdivided into three main groups, prostaglandins, prostacyclins, and thromboxanes. Prostaglandins,[6−11] one of the classical examples of lipid mediators acting as local hormones, and their botanical analogues, phytoprostanes,[12,13] have shown high potency and a diversity of biological activities in a variety of mammalian tissues. Prostacyclins are among the strongest pulmonary vasodilators with potent aggregation-inhibitory, anti-inflammatory, and antiproliferative properties.[8,14−16] Thromboxanes represent prostacyclin antagonists, which possess potent vasoconstrictor properties due to their capacity to produce platelet aggregation.[17−19] Rethrolones are the alcohol component of the pyrethrins, a group of natural insecticides, which are biodegradable and of low mammalian toxicity.[20−25] Terpenes, isoprene-based hydrocarbons with 5*n* carbon molecules, subdivided in monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), etc., constitute one of the largest and most diverse classes of natural products exhibiting a broad variety of medicinal properties or biological activities.[26−28]

Vanya B. Kurteva, born in Sofia (Bulgaria) in 1960, is an Associate Professor at the Institute of Organic Chemistry with Centre of Phytochemistry of the Bulgarian Academy of Sciences (IOCCP-BAS). She received her master degree in Organic and Analytical Chemistry in 1983 from the University of Sofia and her Ph.D. in 1991 in synthetic organic chemistry from IOCCP-BAS under the supervision of Prof. I. G. Pojarlieff and Assoc. Prof. M. J. Lyapova. She worked as a postdoctoral fellow in the laboratory of Prof. Carlos A. M. Afonso (Lisbon, Portugal, 2001−2004). Her current research interests are focused on the asymmetric synthesis of carba- and heterocycles with potential activity as chemotherapeutics and catalysts.

In recent years, the synthesis of carbocyclic nucleoside analogues has been the subject of great interest, due to their wide range of biological activity profiles.[29−40] Furthermore, these compounds are chemically and enzymatically more stable than the corresponding nucleosides, because of the absence of a typical glucoside bond in their molecules.[41−45] The role of the methylene group in the carbocycle as a bioisostere of oxygen is justified by the observed antiviral and antitumor efficiencies of some natural carbocyclic nucleosides, such as aristeromycin[46] and neplanocin A,[47] as well as synthetic ones, such as carbovir[48−50] and abacavir

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Carlos A. M. Afonso graduated from University of Coimbra (1984), and he joined the New University of Lisbon as teaching assistant and received his Ph.D. in 1990 under the supervision of Professor C. D. Maycock where he became assistant professor. He worked for one year as a postdoctoral fellow at the Imperial College of Science Technology and Medicine under the supervision of Professor W. B. Motherwell (1990), and one more academic year of sabbatical leave (1997−1998) at the University of Bath, U.K. (Professor J. Williams) and at the University of Toronto (Professor R. Batey). In 2004, he moved to Instituto Superior Técnico of the Technical University of Lisbon as associate professor and in 2008 received his *Agregação*. His research focuses on the development of more sustainable methodologies in asymmetric organic transformations and the development and application of new ionic liquids.

(Figure 1).[51−54] The latter shows great anti-HIV activity, and therefore, it is used clinically to treat AIDS and AIDS-related complex.

The construction of five-membered carbocycles is a fundamental synthetic process, which has attracted widespread attention among synthetic chemists. Considerable diverse methodologies emerged and were summarized in a series of reviews, which can be divided in two general categories: procedures based on the sequential functionalization of cyclopentanoid precursors, such as cyclopentene, cyclopentadiene, and fulvene,[55−64] and ring-closing routes from acyclic molecules, some being applied as key steps in the restructuring of readily available chiral materials, such as carbohydrates, quinic acid, and microbially produced cyclohexadiene diols, into carbocycles.[65−71] The search for new, more efficient, and versatile antitumor, anticancer, antibacterial, antimicrobial, etc. agents is among the priorities of the worldwide science. In particular, a serious part of the efforts of the leading scientific and industrial chemical organizations nowadays is directed toward the synthesis of natural and biologically active products,[72−74] and the improvement of the routes for the preparation of cyclopentanoid moieties is still growing at a steady pace.

In this review, an overview of the most efficient and widely applied modern methods for the construction of these fascinating carbocycles is provided. The emphasis is given to the most powerful ring-closing approaches and their application in the synthesis of natural and biologically active products.

2. Ring-Closing Metathesis

Ring-closing metathesis (RCM) is a synthetically powerful transformation that has emerged over the past decades and was afterward approved as an efficient stage in the total synthesis of natural products[75−83] and fundamentally changed the outlook of nucleoside chemistry. The conversion of sugars, cheap and readily available chiral starting materials, into different hydroxylated cyclopentene derivatives via RCM is nowadays among the most widely exploited routes to generate the cyclopentanoid core of carbanucleosides.[84−86]

The transformation presents an intramolecular variant of the olefin metathesis that allows the formation of complex ring systems from simple acyclic precursors (Figure 2a).[87−98] The reaction between substrate and catalyst proceeds via a reversible formation of a metallacyclobutane intermediate. A significant evolution in the development of olefin metathesis catalysts involves the discovery of ruthenium-based Grubbs' and molybdenum-based Schrock's catalysts (Figure 2b), which enable the production of novel compounds and high-performance materials for the pharmaceutical and materials science markets.

On October 5, 2005, Robert H. Grubbs, Richard R. Schrock, and Yves Chauvin received the Nobel Prize in Chemistry in recognition of their contributions to the development of the metathesis method in organic synthesis.

There are two generations of Grubbs' catalysts,[99,100] which are extraordinarily versatile because they tolerate a variety of functional groups in the alkene and are compatible with a wide range of solvents.[101] However, both catalysts are generally not effective for producing trisubstituted double bonds.[102,103] These difficulties are overcome by using the Schrock catalyst, which is more active and is useful in the conversion of sterically demanding substrates.[104]

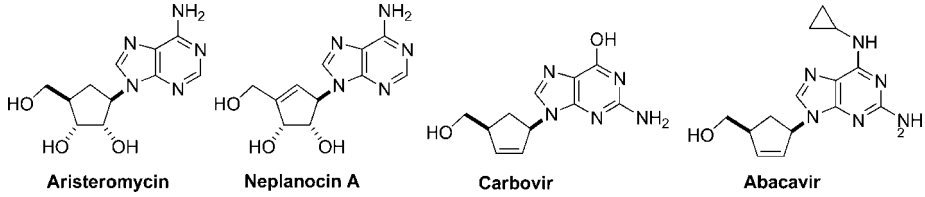
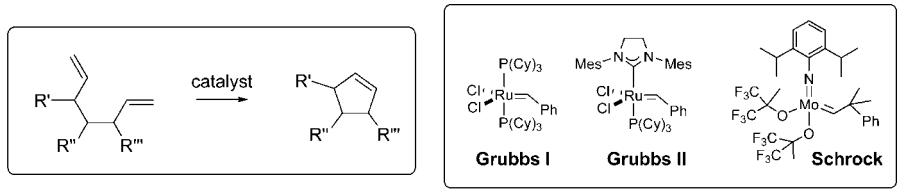


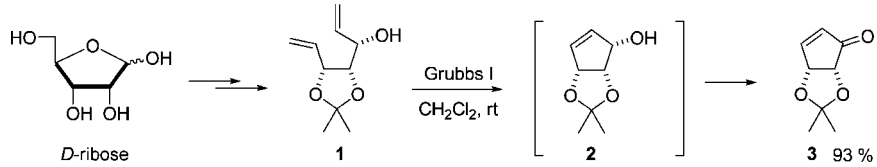
Figure 1. Some natural and synthetic carbocyclic nucleosides.



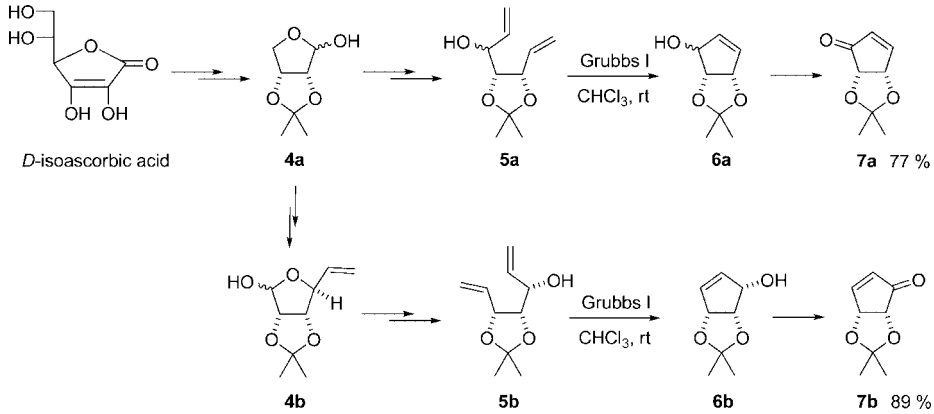
a) RCM reaction b) Most widely used RCM catalysts

Figure 2. Ring-closing metathesis (RCM) route and the most widely applied catalysts in cyclopentitol synthesis.

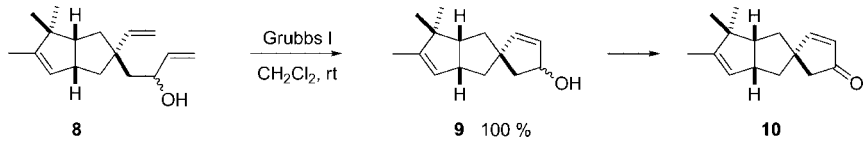
Scheme 1



Scheme 2



Scheme 3



Research in the past decade has yielded the development of a series of structurally well-defined metathesis catalysts that are used to synthesize an array of molecules with unprecedented efficiency.[105−109] *N*-Heterocyclic carbene ligands, introduced as analogues to phosphines, are recently getting wide attention in the design of diverse homogeneous catalytic systems.[110−113] Among them, Hoveyda−Grubbs catalysts are extremely robust and demonstrated improved activity toward electron-deficient alkenes.[114−126] Ease of handling, stability to air and moisture, and the possibility for immobilization and catalyst reuse conferred additional advantages. Other phosphine-free catalysts of the Hoveyda-type have been prepared by introducing different substitution patterns on the chelating benzylidene ether ligand. Thus, sterically hindered Blechert complexes bearing binaphthyl or biphenyl chelating ligands[127−129] and Grela's catalysts disclosing benzylidene ether moieties with electron-withdrawing substituents, such as nitro group, in the position para to the alkoxy group[130−133] have been developed. Both of these steric and electronic alterations of the original ligand have resulted in faster-initiating catalysts than the parent Hoveyda complex. Piers' catalysts are 4-coordinate ruthenium complexes possessing an open coordination site *trans* to a phosphine or an *N*-heterocyclic carbene ligand, which directly mimic the active 14-electron olefin-metathesis catalytic species and negate any prior ligand dissociation step that is necessary with the original 5-coordinate Grubbs- and Hoveyda-type catalysts.[134,135] These catalysts are more active than the Grubbs catalysts for the metathesis of terminal olefins but slower for metathesis reactions involving only internal olefins. They are highly functional-group tolerant and are active at low temperature, which makes them particularly useful in inhibiting double-bond migrations.

However, the examples of the efficiency of these precious modern catalysts for the formation of cyclopentanones in the literature are quite limited, and therefore, we will concentrate in this review on the application of the initial metathesis catalysts, Grubbs and Schrock.

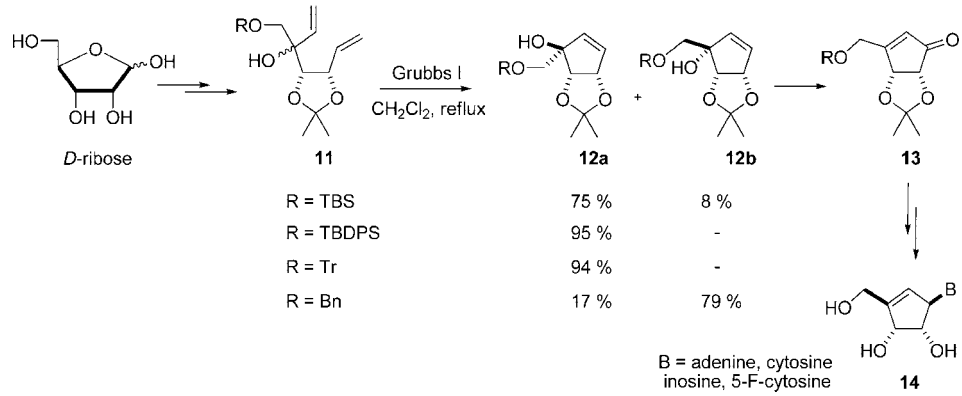
2.1. First Generation Grubbs Catalyst

The first generation Grubbs catalyst is easily accessible via a one-pot protocol.[136] It is moderately stable in solid form compared with other catalysts but is sensitive to oxygen and moisture in solution. The latter prevents its wide use on a large scale for the production of useful, high-value olefins from ordinary olefin feedstock in industry. However, the catalyst is applied to achieve ring-closing metathesis to cyclopentenes with a variety of substitution patterns.

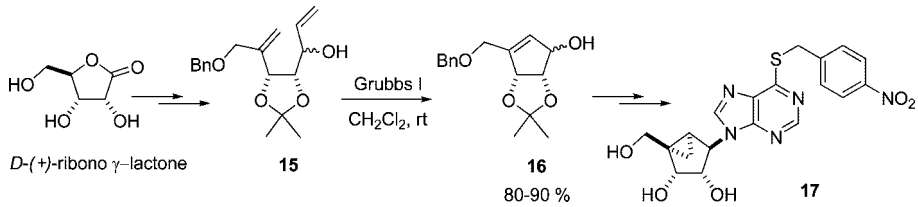
Carbohydrates are among the most frequently used starting materials. An efficient and practical scheme for conversion of D-ribose to the key cyclopentenone intermediate **3** has been developed, and the target product was isolated in good overall yield.[137] The conditions of the metathesis cyclization of diene **1** have been optimized, and it was found that 1% of the catalyst in dry dichloromethane at room temperature provided the best results to obtain cyclopentenol **2**, which was oxidized without isolation to cyclopentenone **3** in excellent yield (Scheme 1).

Both D- and L-isomers of the same cyclopentenone derivative **7** have been obtained from the cheap and commercially available D-ascorbic acid.[138] Grubbs I-catalyzed RCM of dienes **5** to the highly hydroxylated cyclopentenes **6** has been successfully achieved in chloroform at room temperature (Scheme 2).

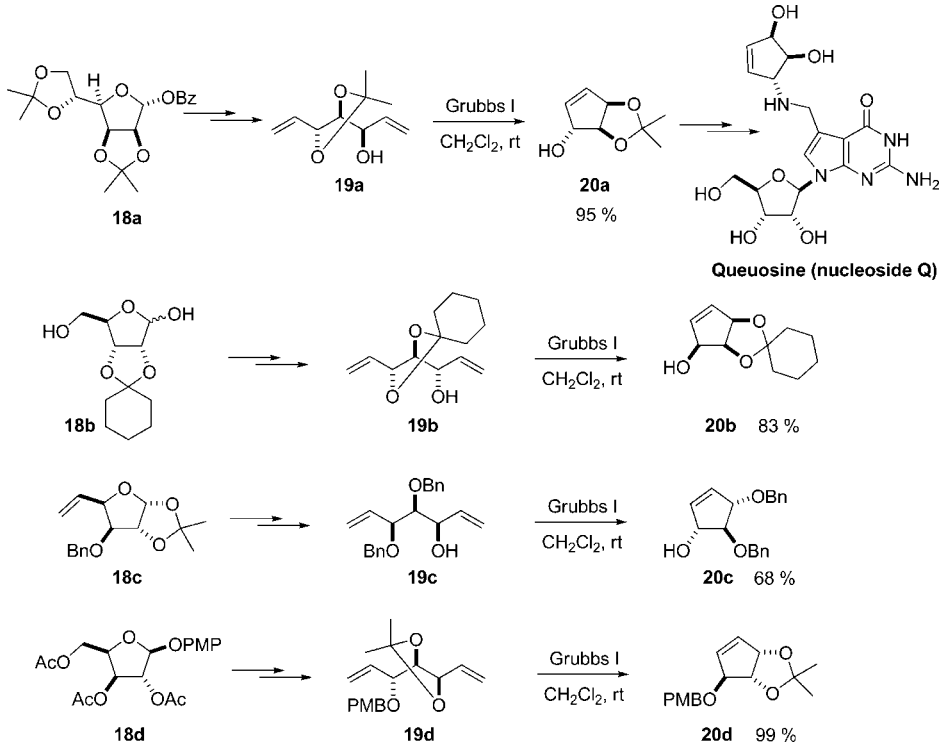
Scheme 4



Scheme 5



Scheme 6



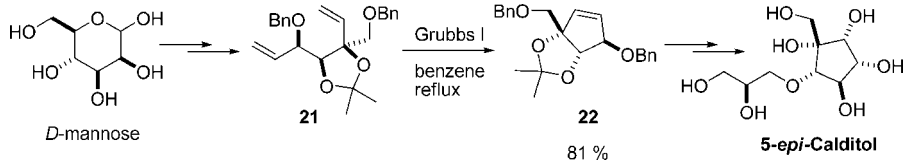
It has been observed that the cyclization proceeded smoothly to afford the cyclopentenols **6** in very good yields. The protocol has been further improved and the same optically active cyclopentenones **7** were obtained via RCM from D-ribose in a shorter sequence.[139] The conversion of **5b** to **6b** and afterward to **7b** has been achieved in 90% overall yield as a step in a modified practical synthesis of (−)-aristeromycin from D-ribose.[140]

Similarly, the spiroannulated cyclopentane derivative **9** has been obtained quantitatively from diene **8** as a step for the enantiospecific synthesis of a komarovispirane diterpene **10** (Scheme 3).[141]

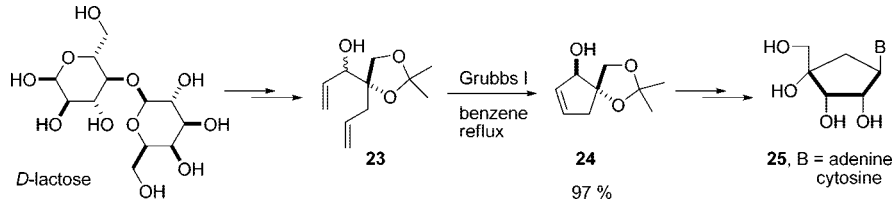
An improved method for the synthesis of enantiomerically pure unsaturated cyclopentyl nucleosides **14** from D-ribose has been accomplished in eight steps,[142] and their activity against orthopox viruses have been evaluated.[143] The key 3,4,5,5-tetrasubstituted cyclopentene intermediate **12** has been prepared in high yield by RCM of mono-TBS-protected diene **11** in refluxing dichloromethane (Scheme 4). It was found that the reaction evolved selectively and a ratio of 10:1 was determined for the corresponding α- and *β*-cyclopentenols **12a** and **12b**.

The selectivity of the reaction has been studied and enhanced by varying the bulk of the protective group.[144] It

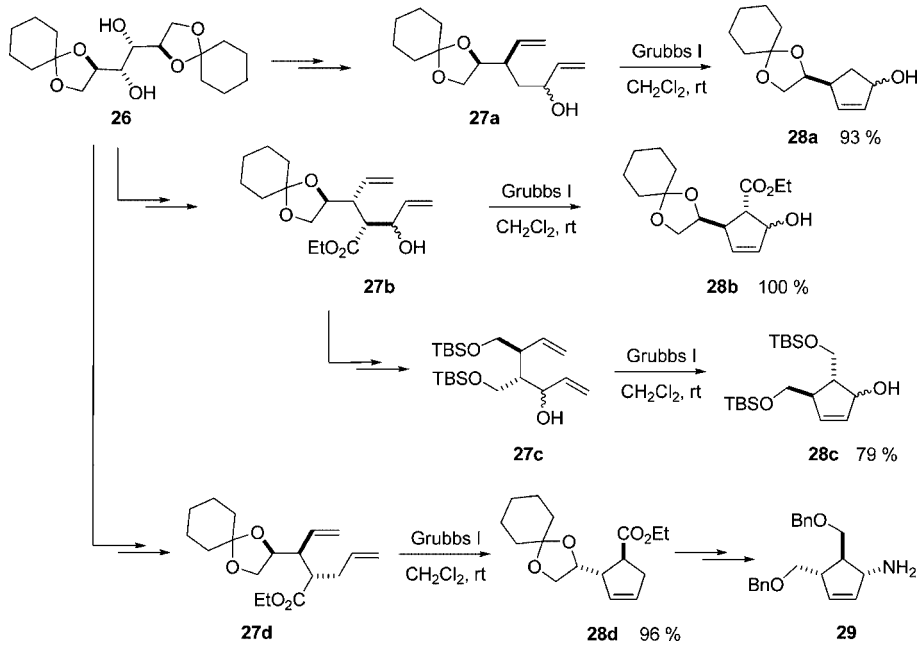
Scheme 7



Scheme 8



Scheme 9



was found that the bulkier *tert*-butyldimethylsilyl group and *tert*-butyldiphenylsilyl and trityl ethers have led to a clean **12a** formation, while **12b** was isolated as a main product with benzyl protection. Because **12a** is the only reactive isomer in the next step, the protocol presents a short, efficient, and preparative route to convert D-ribose into cyclopentenone **13**, a key molecule in the synthesis of carbocyclic nucleosides.

The (*N*)-methanocarba nucleoside **17** has been obtained from D-(+)-ribono γ-lactone, and the effect on nucleoside transport has been studied.[145] The crucial metathesis reaction was accomplished in high yield by exposure of a dichloromethane solution of diene **15** to 0.2 equiv of Grubbs catalyst, resulting in a diastereoisomeric mixture of 2,3,4,5-cyclopentenetetraols **16** (Scheme 5).

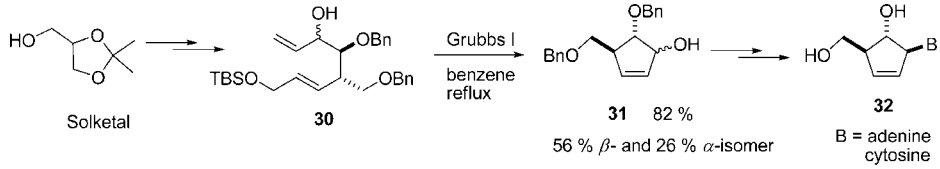
The 2,3,4-trihydroxylated cyclopentene product **20a** has been obtained as a step in an efficient stereoselective route to the side chain moiety of the hypermodified nucleoside queuosine from D-mannofuranose derivative **18a** (Scheme 6).[146] The synthetic scheme involved Grubbs I-catalyzed RCM of diene **19a** to cyclopentene **20a** in excellent yield and selectivity.

Similarly, four partially protected stereoisomeric cyclopentenetriols **20a**−**20d** have been obtained by RCM of carbohydrate-derived 1,6-dienes **19** (Scheme 6).[147] The products **20** are useful chiral building blocks due to the presence of a differentiated allylic hydroxyl group, which allows a variety of synthetic transformations to be performed. The latter has been demonstrated by the conversion of **20a** into highly versatile structural entities, such as the side-chain modified nucleoside Q and carbaxylofuranose derivatives.

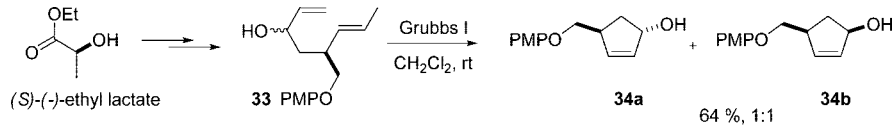
RCM in refluxing benzene has been successfully achieved during the synthesis of differently protected cyclopentitols from D-mannose.[148] Thus, the 2,2,3,4-substituted cyclopentene derivative **22** has been obtained stereoselectively from diene **21** and was further converted to 5-*epi*-calditol, the enantiomer of the natural cell wall component calditol (Scheme 7).

An efficient synthetic route for various types of carbocyclic nucleosides **25** from the carbohydrate chiral template D-lactose has been reported.[149] The required stereochemistry of the target nucleosides has been successfully controlled by Grubbs' cyclization of the diene intermediate **23** to the trihydroxycyclopentene **24** (Scheme 8). The latter transformation has been performed in refluxing benzene, and the product was isolated in excellent yield.

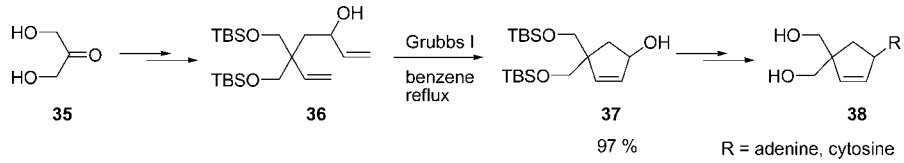
Scheme 10



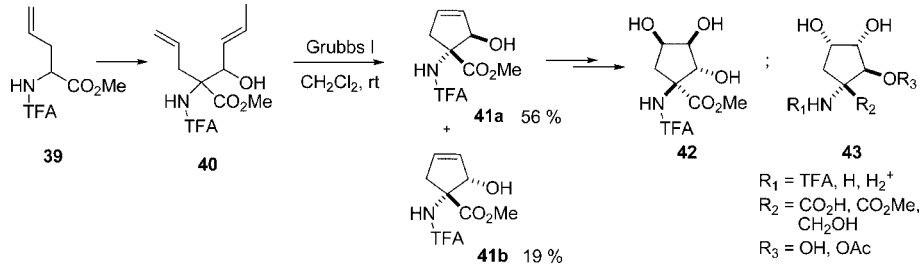
Scheme 11



Scheme 12



Scheme 13



The synthesis of highly functionalized cyclopentenol derivatives, versatile building blocks for a vast array of biologically active compounds, from D-mannitol derivative **26** has been reported.[150,151] The ring-closing metathesis of the dienes **27** has been achieved as a key step, and the corresponding *trans*-disubstituted cyclopentenes **28** were isolated in excellent yields (Scheme 9). It has been observed that the alkoxy groups at the C-5 allylic position of 1,6-dienes accelerated significantly the RCM reactions.

The cyclopentenol **28d** later has been converted to an amino cyclopentene **29**, the carbocyclic core of the nucleoside (−)-bis(hydroxymethyl)cyclopentenyl adenine (BCA), a potent inhibitor of HIV reverse transcriptase.[151]

The cheap and commercially available triol solketal has been used as a starting compound in a stereocontrolled synthesis of hydroxyl carbovir analogues **32**.[152] For the crucial step, Grubbs I-catalyzed metathesis of diene **30** has been achieved in high yield in refluxing benzene to provide the cyclopentene derivative **31** as a separable mixture of stereoisomers (Scheme 10).

Enantioselective construction of the protected carbocycle moiety of the anti-HIV drug carbovir has been achieved in 11 steps from (*S*)-(−)-ethyl lactate.[153] The key ruthenium-catalyzed ring-closing metathesis of the diene **33** has been carried out at room temperature, leading to 4-(4-methoxyphenoxymethyl)-cyclopent-2-enol **34** as an easily separable isomeric mixture (Scheme 11). The product **34a** possesses the correct chirality to mimic the ribose moiety of natural nucleosides.

4′α-*C*-hydroxymethyl branched carbocyclic nucleosides **38** have been efficiently obtained from a simple acyclic precursor 1,3-dihydroxy acetone **35**.[154] The required stereochemistry of the carbocyclic core **37** has been successfully elaborated by Grubbs I-catalyzed RCM of diene **36** in refluxing benzene with excellent yield (Scheme 12).

A series of polyhydroxylated aminocyclopentanes **42** and **43** have been obtained as potential glycosidase inhibitors.[155] The cyclopentene ring has been constructed by ruthenium-catalyzed metathesis of diene **40** as an easily separable mixture of isomers **41a** and **41b** (Scheme 13).

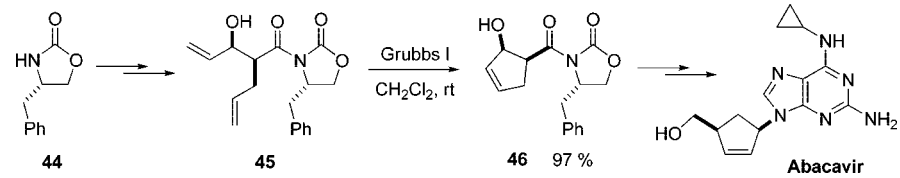
An efficient asymmetric synthesis of abacavir, a highly potent inhibitor of HIV reverse transcriptase, has been reported.[156] The critical RCM of diene **45** to cyclopentenol derivative **46** has been accomplished in high yield and selectivity under mild conditions (Scheme 14).

The protocol has been further applied to a general asymmetric approach to carbovir, abacavir, and their 2′-methyl derivatives as well as to hexenopyranosyl nucleoside analogues.[157]

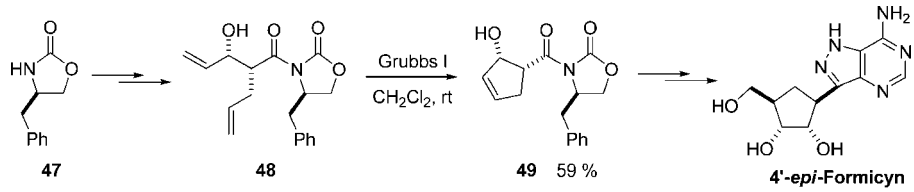
The same procedure has been applied to prepare the stereoisomeric cyclopentenol **49** as a step in the synthesis of the carbocyclic nucleoside 4′-*epi*-formicyn (Scheme 15).[158] The absence of antiviral activity of the latter has been explained as a consequence of its failure to undergo conversion to the 5′-nucleoside derivative.

A similar asymmetric aldol-RCM strategy has been completed in a formal total 18 steps synthesis of the aminocyclopentitol pseudosugar (+)-trehazolin, specific and potent inhibitor of trehalase used as an insecticide, with control of both the relative and absolute stereochemistry (Scheme 16).[159]

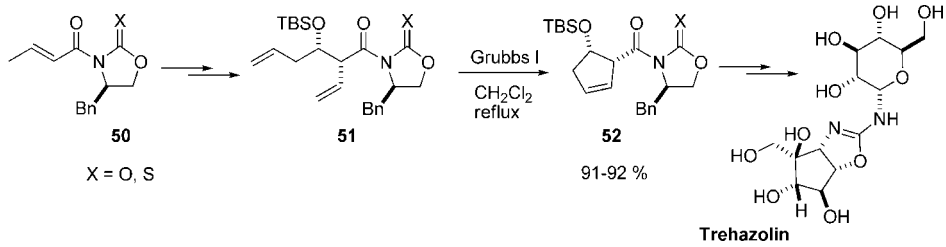
Scheme 14



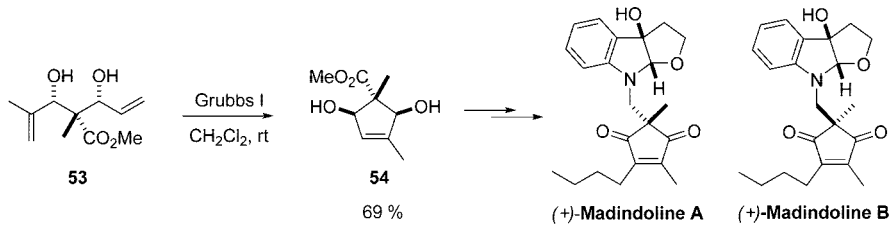
Scheme 15



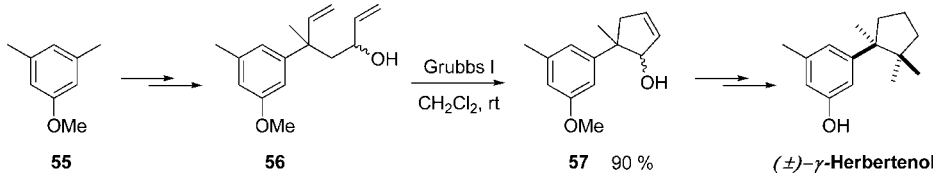
Scheme 16



Scheme 17



Scheme 18



An efficient and convergent total synthesis of (+)-madindoline A and (−)-madindoline B, rare natural products possessing antibiotic activity, has been achieved.[160] The five-membered carbocycle unit has been constructed by RCM of diene **53** to the cyclopentene derivative **54** by using the Grubbs I catalyst in 0.2 mol % (Scheme 17). The final products have been obtained in 19 linear steps in 8% overall yield, and their relative and absolute configuration were assigned.

The ruthenium-catalyzed RCM has been applied as a step in the total synthesis of the aromatic sesquiterpene (±)-γ-herbertenol, the first herbertane isolated from nonherbertus source (Scheme 18).[161] The cyclopentenol **57** has been isolated in high yield as a diastereoisomeric mixture and was further converted to the target sesquiterpene in an attempt to confirm the structure of the natural product.

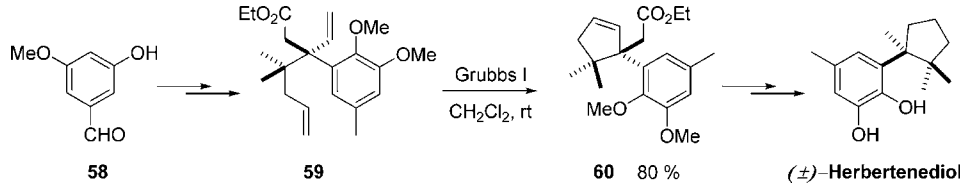
A similar protocol has been applied to the preparation of **60** from **59** as a step in a total synthesis of a natural sesquiterpene (±)-herbertenediol from vanillin **58** (Scheme 19).[162]

The fungal metabolite (+)-puraquinonic acid has been obtained from phenolic aldehyde **61** by applying a ring-closing metathesis as a key step (Scheme 20).[163] Therefore, the diene **62** has been converted to bicyclic product **63** in high yield by using Grubbs I catalyst.

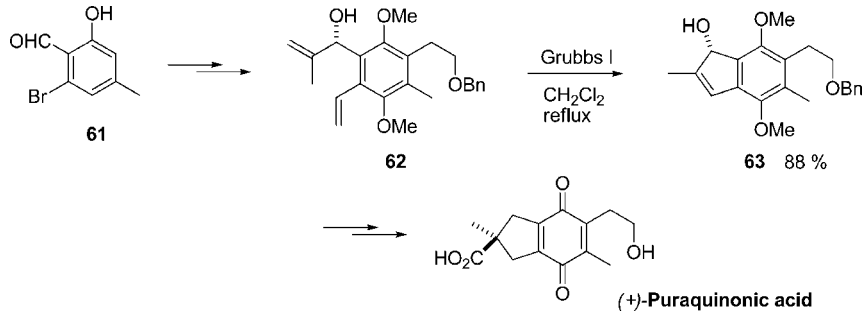
Tandem ring-opening/ring-closing metathesis reactions of functionalized cyclohexenoids **64** derived from (−)-α-pinene have been achieved in an attempt to construct the AB ring of taxoids (Scheme 21).[164] The compound **65** was obtained as a major product along with small amount of **66** as detected by TLC and NMR. Compound **65** was converted into **66** during the chromatography purification, providing **66** as the sole isolated product. The formation of the latter was explained by allylic rearrangement on the silica gel surface.

The authors have suggested that **65** was generated from **64** via the initial formation of the Ru-carbene intermediate at one of the terminal olefins followed by six-membered ring-opening metathesis, RCM to new Ru-carbene center, and finally a reaction of the latter with the remaining terminal double bond.

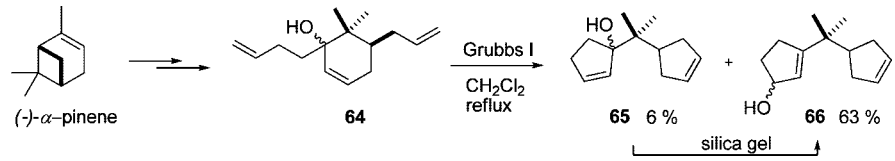
Scheme 19



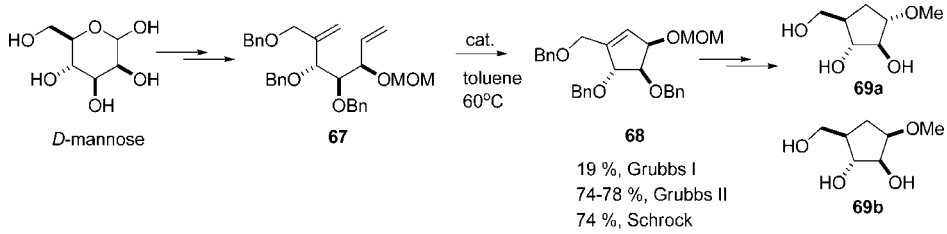
Scheme 20



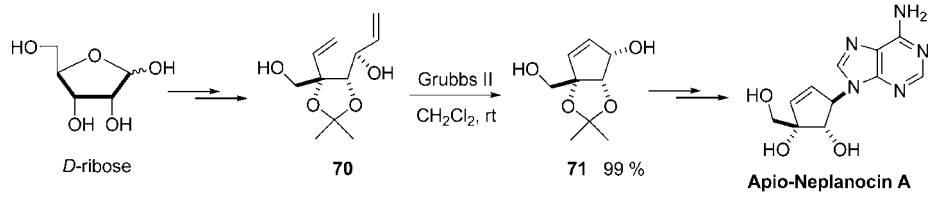
Scheme 21



Scheme 22



Scheme 23



2.2. Second Generation Grubbs Catalyst

The second generation Grubbs catalyst is a more active analogue of the first one and has the same uses in organic synthesis. It presents an *N*-heterocyclic carbene, where ruthenium is coordinated to two carbene groups. This catalyst is even more versatile and air stable and is easily accessible from Grubbs I and alkoxy-protected 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene.[165]

Carba-arabinofuranosides **69** have been obtained starting from D-mannose.[166] The olefin metathesis of diene **67** has been achieved in good yield by using Grubbs II or Schrock catalysts, while very low conversion was observed by Grubbs I (Scheme 22). The conformational preferences in **69a** and **69b** have been investigated by NMR techniques, and it was found that the favored position about the C_1-O_1 bond is similar to that in the glycosides.

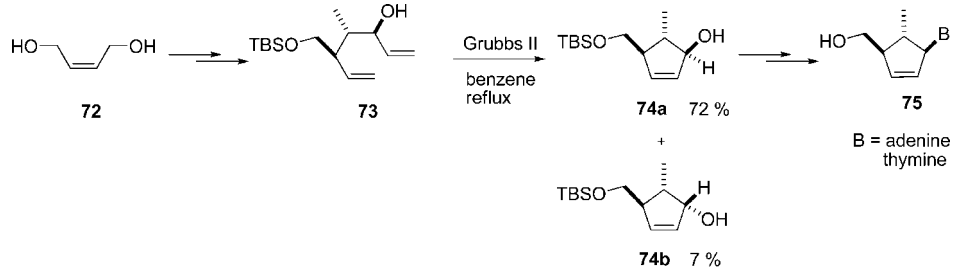
A total synthesis of apio-neplanocin A, which combines the properties of apio nucleoside and neplanocin A, has been accomplished starting from D-ribose.[167] The Grubbs II catalyzed metathesis of diene **70** has been used as a step, and the polyhydroxylated cyclopentene derivative **71** has been obtained quantitatively and with the desired stereochemistry (Scheme 23).

A stereoselective synthesis of 6′-branched carbovir analogues **75** has been accomplished starting from dihydroxy butene **72** (Scheme 24).[168] The cyclopentenol **74** has been obtained in good yield by RCM of diene **73** as an easily separable isomeric mixture.

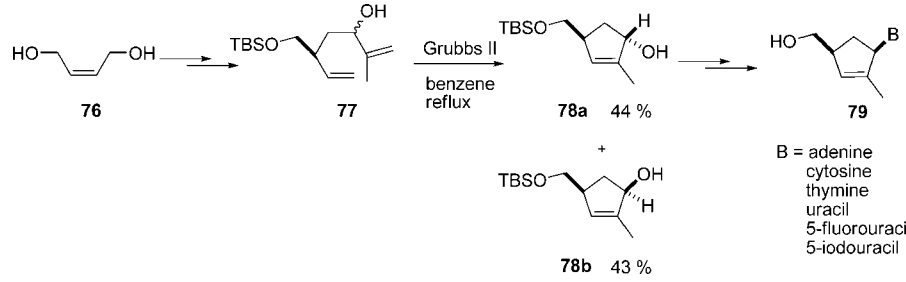
The same starting material has been used for the preparation of a series of 2′-branched carbovir analogues **79** via the metathesis product **78a** (Scheme 25).[169]

A concise method for the synthesis of 1′,4′-dimethyl[170] and 1′-methyl-4′-phenyl[171] doubly branched carbocyclic

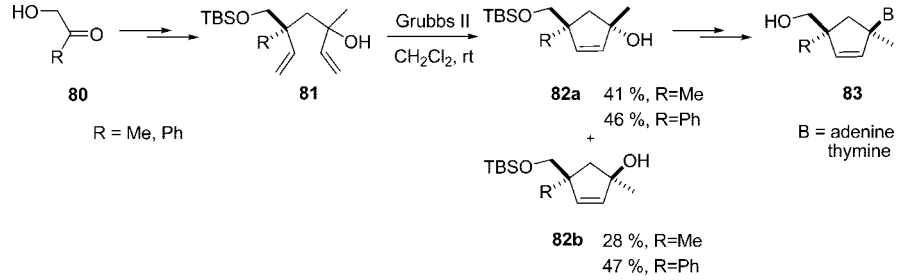
Scheme 24



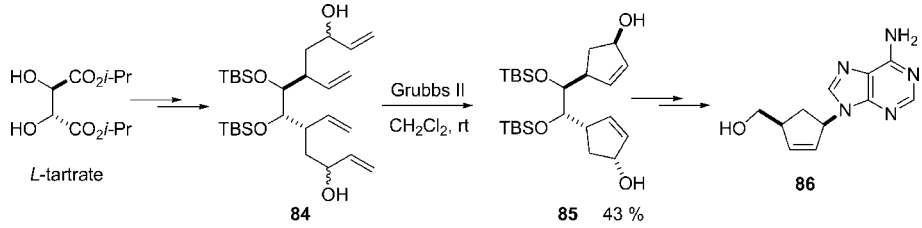
Scheme 25



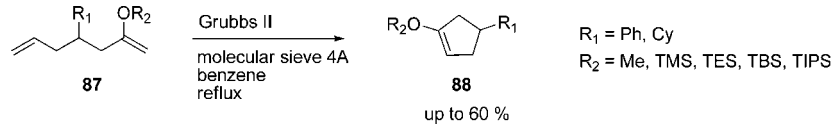
Scheme 26



Scheme 27



Scheme 28

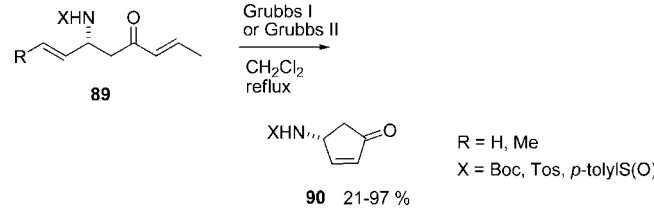


nucleosides **83** from α-hydroxy ketones **80** has been developed. As a step, the dienes **81** have been converted into cyclopentene derivatives **82** by applying Grubbs II-catalyzed metathesis (Scheme 26). The required β-configuration of the nucleosides **83** has been successfully controlled by the α-configuration of compound **82a**.

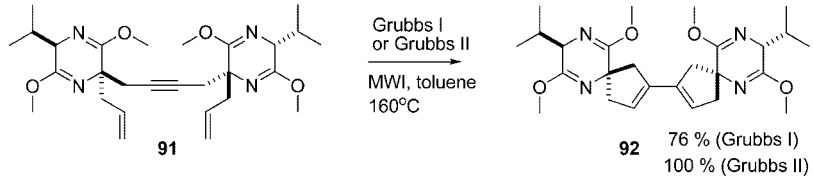
A dissymmetric synthetic route to nucleoside **86** has been achieved starting from the C_2-symmetric chiral starting material L-tartrate.[172] A double ring-closing metathesis strategy has been used as a step, and the dissymmetric construction of a cyclopentene system **85** from **84** was accomplished in moderate yield in mild conditions (Scheme 27).

A series of carbocyclic enol ethers **88** has been synthesized regiospecifically by RCM in the presence of molecular sieves.[173] The metathesis of diene **87** has been achieved in moderate yield by using second generation Grubbs catalyst, while no conversion was detected with Grubbs I (Scheme

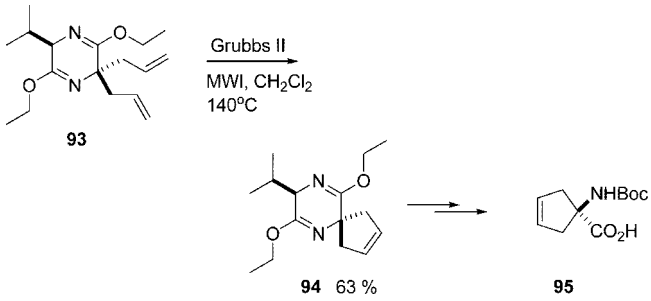
Scheme 29



Scheme 30



Scheme 31



28). Several silyl enol ethers have been studied, and it has been shown that for substrates with a high propensity for cyclization trimethylsilyl enol ethers could be employed but for general substrates the bulky *tert*-butyldimethylsilyl enol ethers were more desirable.

RCM of amino ketodienes **89** has been employed for the asymmetric synthesis of (*R*)-(+)-aminocyclopentenone **90**, a valuable chiral building block for the synthesis of antiviral and anticancer carbocyclic nucleosides (Scheme 29).[174] The conditions have been optimized, and it was found that, with an exception, both Grubbs I and Grubbs II catalysts gave good to excellent yields of **90** when R = H, while only the second catalyzed the transformation if R = Me.

Ruthenium-catalyzed domino RCM of diene **91** to the complex spiro-compound **92** has been achieved under microwave irradiation (Scheme 30).[175]

It has been found that microwaves significantly accelerate the transformation. High to complete conversions were observed both with Grubbs I and Grubbs II within 45 and 10 min, respectively, while the second catalyst was efficient only after prolonged reaction in refluxing toluene. It has been shown that the short times required avoided the catalyst decomposition that is observed under conventional heating.

The same approach has been used in the preparation of spirane **94**, which was further converted into the Boc-protected spiro-amino acid **95** (Scheme 31).[176]

2.3. Schrock Catalyst

Schrock's catalyst is a molybdenum−carbene complex possessing bulky substituents on the imido and alkoxide ligands (Figure 2b).[177] It is quite oxygen and moisture sensitive and must be handled in rigorously dried solvents using Schlenck techniques. However, the catalyst's superb reactivity, which is especially useful for the conversion of sterically hindered olefins, compensates this inconvenience and renders its wide applicability in metathesis reactions.

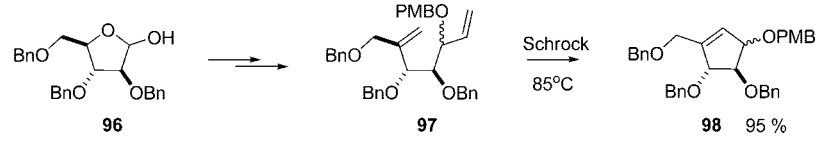
The key cyclopentene analog of carba-D-arabinofuranose has been prepared in five steps from 2,3,5-tri-*O*-benzyl-D-arabinofuranose **96** (Scheme 32).[178] Molybdenum-catalyzed RCM has been accomplished, and the product **98** was isolated in high yield as a separable diastereoisomeric mixture.

RCM of sterically hindered 1,6-dienes **100** has been achieved by using Schrock's catalyst, while the experiments with Grubbs I have led to very slow conversion (Scheme 33).[179] The densely substituted cyclopentene derivative **101** has been further transformed into five-membered branched cyclitols.

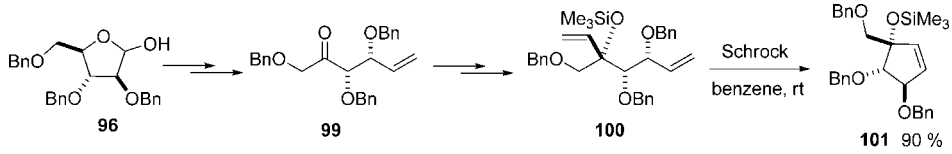
A total synthesis of carba-D-fructofuranose **104** from the same D-arabinofuranose derivative **96** has been accomplished via an 11 step sequence in excellent overall yield of 45% (Scheme 34).[180] As a key step, Schrock's catalyst has been employed on the unique substituted diene synthon **102** to furnish the pentahydroxylated cyclopentene **103**.

A total enantioselective synthesis of a cyclopentitol **108** from tetra-*O*-benzyl-D-galactopyranose **105** has been reported (Scheme 35).[181] The cyclopentene ring construction has been

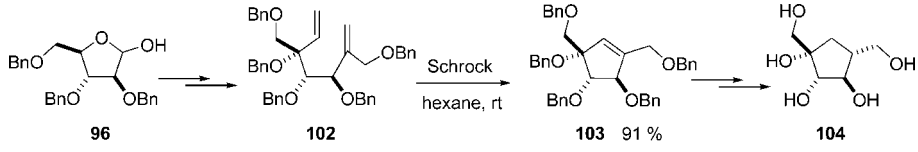
Scheme 32



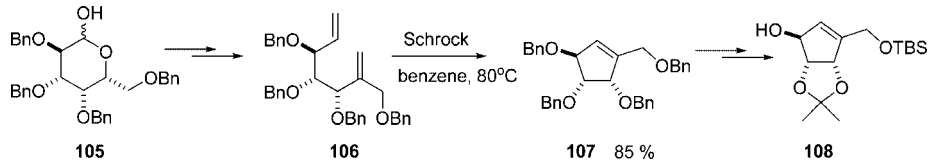
Scheme 33



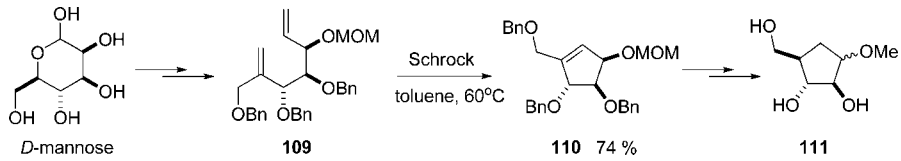
Scheme 34



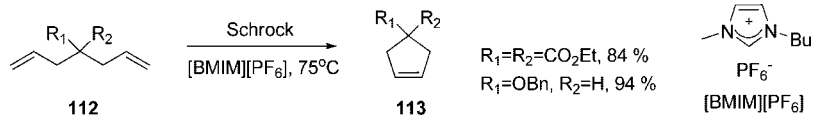
Scheme 35



Scheme 36



Scheme 37



accomplished via a molybdenum-catalyzed metathesis of the diene **106** to provide the cyclopentene derivative **107**, a versatile intermediate for the synthesis of L-cyclopentenyl carbocyclic nucleosides.

Schrock-catalyzed RCM has been applied as a key transformation in a total synthesis of methyl 4a-carba-D-arabinofuranosides **111** from D-mannose (Scheme 36).[182] The method has allowed control of the stereochemistry at the pseudo-anomeric position leading to either α or β glycoside mimetics being obtained. It provides the possibility to access the entire family of pentocarbafuranoses on the basis of the hexopyranose.

A room-temperature ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) has been used as a solvent for RCM of dienes **112** with Schrock's catalyst (Scheme 37).[183] The products **113**, containing a variety of functional groups, have been obtained quantitatively, thus making the protocol comparable to that in convenient solvents.

The method is general and applicable even on small scales for a broad variety of substrates, only the most polar excepted. Additionally, the authors have developed a new method to extract the products from the ionic liquid by carrying out a Soxhlet extraction using polydimethylsiloxane thimbles.

3. Pauson−Khand Reaction

The Pauson−Khand reaction (PKR) is one of the most convergent methods for the preparation of cyclopentenones, convenient cyclopentitol precursors.[184] It was discovered in the early 1970s[185,186] as a cobalt-mediated formal [2 + 2 + 1] cycloaddition involving an alkene, an alkyne, and a carbon monoxide source, which proceeds via alkyne hexacarbonylcobalt complex (Figure 3).

The Pauson−Khand annulation has received great attention during the last decades due to its wide applicability in the synthesis of complex molecules. It is tolerant of a broad variety of functional groups, such as alcohols, ethers, thioethers, esters, nitriles, amines, amides, and sulfonamides. The transformation is well-known as both intermolecular and intramolecular versions, the latter being more widely exploited after its introduction in the early 1980s.[187] Several metal carbonyls have been applied as carbon monoxide source instead of dicobalt octacarbonyl, such as molybdenum,[188−194] titanium,[195−203] zirconium,[197,204,205] ferrium,[206] nickel,[207,208] iridium,[209−212] rhodium,[213−220] and ruthenium[213,221−224] carbonyls. More recently, it has been found that $PdCl_2$ coordinated to a thiourea ligand could also catalyze an intramolecular reaction.[225−227] The classical version of PKR involved a stoichiometric quantity of cobalt carbonyl, while the recent catalytic variants require substoichiometric amounts of cobalt or other transition metals. In order to circumvent the high temperatures and long reaction times necessary to effect the PK cycloaddition, different promoters of the reaction have been widely applied, such as *N*-methylmorpholine *N*-oxide,[228] trimethylamine *N*-oxide,[229] phosphine oxides,[230] alkyl sulphides,[231] thioureas,[232,233] and hard Lewis bases,[234] and it has been found that the selectivity of the reaction depends both on the substrate structure and on the nature of the metal carbonyl/promoter.[235]

The cyclization has been also performed as environmentally friendly green protocols, such as in dry-state adsorption conditions,[236] under microwave irradiation,[237,238] in ionic liquids,[239,240] in water,[241,242] and in supercritical ethylene.[243,244]

The asymmetric approach to the Pauson−Khand reaction has been efficiently achieved, based on chiral auxiliary-directed π-face discrimination in acetylenic−cobalt carbonyl complexes.[245−247] It has also been found that vinyl sulfoxides

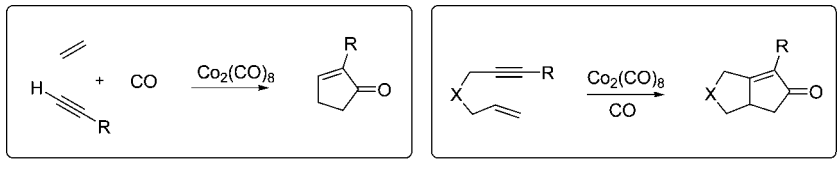
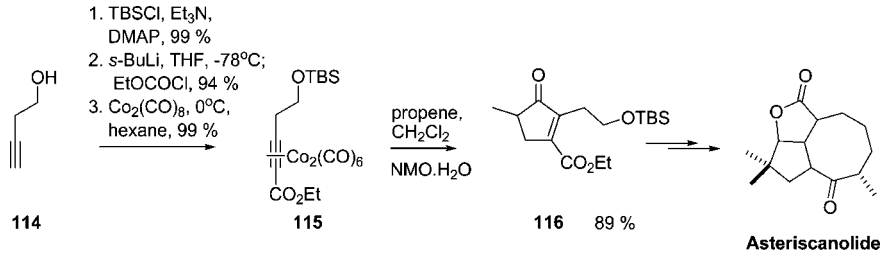
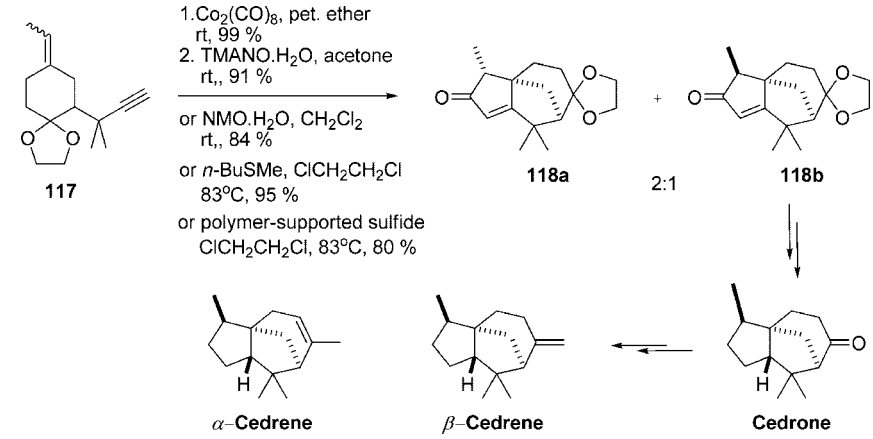


Figure 3. General Pauson−Khand reactions (PKR).

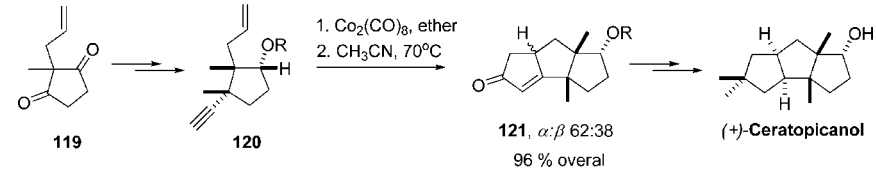
Scheme 38



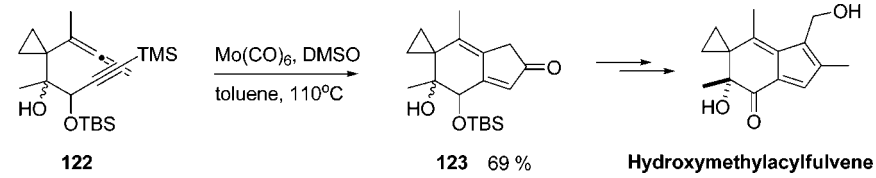
Scheme 39



Scheme 40



Scheme 41



reacted with a wide variety of alkyne−-cobalt complexes with exceptionally high levels of regio- and stereocontrol.[248−250] More recently, the stereoselectivity of the PK products was controlled by applying a broad variety of chiral promoters in metalcarbonyl complexes, such as phosphines,[251−258] phosphites,[259−262] phosphoramidites,[263] brucine *N*-oxide,[264] and camphor-derived thiols.[265]

Most of the synthetic PK schemes have been summarized in a series of reviews,[266−281] and therefore, we will focus only on the application of the transformation in the synthesis of some natural and biologically active products.

The intermolecular reaction leading to cyclopentenone **116** represents the key starting point in the total synthesis of (±)-asteriscanolide, a natural cyclooctane sesquiterpene lactone (Scheme 38).[282]

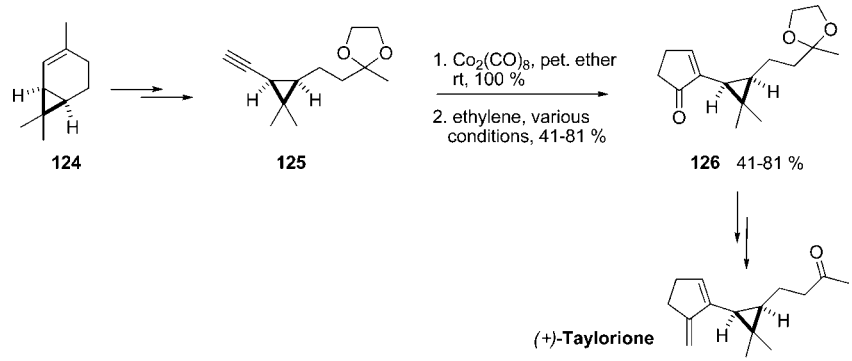
The authors have overcome the difficulties with alkylation of des-methyl cyclooctane by generating the cyclopentene unit prior to eight-membered ring formation.

The ketone **118b**, possessing the carbon skeleton of the tricyclic sesquiterpenes α- and β-cedrene, has been directly and efficiently assembled from a simple monocyclic precursor **117** by the strategic use of a high-yielding intramolecular PKR (Scheme 39).[283] Further transformations have given cedrone, thus constituting a concise formal total synthesis of cedrenes. Different techniques have been applied for the key PK cyclization, and the best results (95%) were obtained by using soluble *n*-butyl methyl sulfide in refluxing dichloroethane. The annulation proceeded smoothly to provide enones **118a** and **118b** as a 2:1 isomeric mixture.

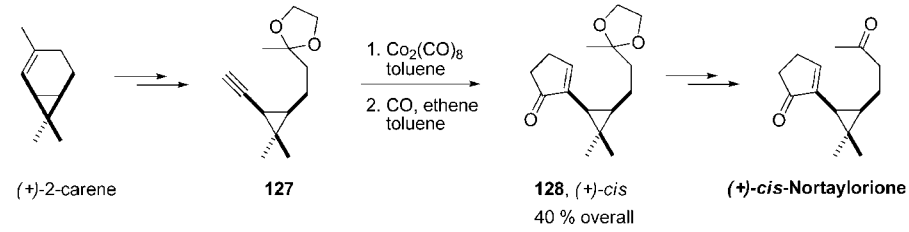
The total synthesis of a triquinane sesquiterpene ceratopicanol has been achieved from commercially available dione **119** (Scheme 40).[284] The enone **121** has been prepared in high yield by PK cyclization in various conditions albeit with constantly low stereoselectivity in all cases.

Molybdenum-mediated intramolecular PKR has been applied as a step for the synthesis of sesquiterpene hydroxymethylacylfulvene (Scheme 41).[285] The latter has been proven effective against breast, lung, and colon tumors in animal models, exhibiting dramatically reduced toxicity with respect to the naturally occurring analogues. The cyclopentenone intermediate **123** has been constructed within 10 min from allene **122** under standard conditions.

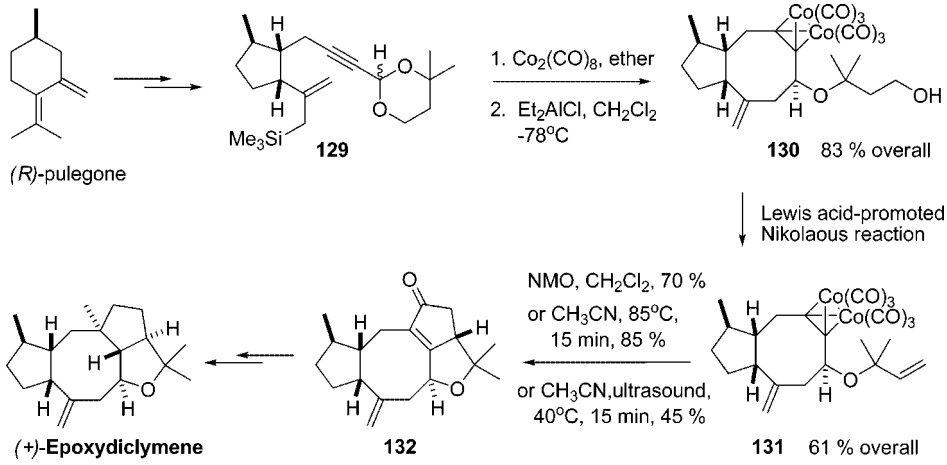
Scheme 42



Scheme 43



Scheme 44



Two complementary Pauson−Khand annulation protocols, using a gaseous alkene (ethylene), have been utilized as the key transformations in the total synthesis of the sesquiterpene (+)-taylorione. The PKR product **126** has been obtained in a good overall yield from readily available (+)-2-carene **124** (Scheme 42).[286] It has been shown that these *N*-oxide promoted reactions proceeded both under mild autoclave conditions and, more conveniently, at atmospheric pressure.

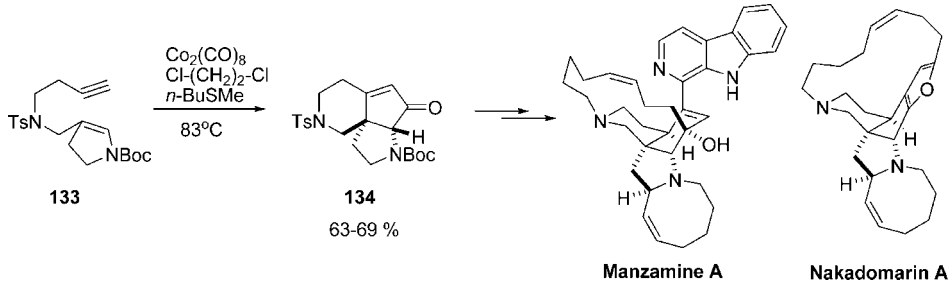
Similar nor-sesquiterpene nortaylorione has been isolated among the minor components of hybrid plants essential oil. Its asymmetric synthesis has been achieved starting from (+)-carene by applying PK reaction as a key step (Scheme 43).[287] Thus, the intermediate **127** has been converted into **128** as a *cis*/*trans* racemic mixture, which gave directly the target natural product after simple hydrolysis. The desired (+)-*cis*-isomer has been isolated by high-performance flash chromatography.

Similarly, cobalt-mediated intramolecular ring closing of **129** to **132** has been achieved as a step in an asymmetric synthesis of the diterpene (+)-epoxydictymene from (*R*)-pulegone (Scheme 44).[288] The final product, which is one of the four natural terpenes containing the strained *trans*-fused 5-5 ring system, was obtained in its natural configuration for all five asymmetric centers.

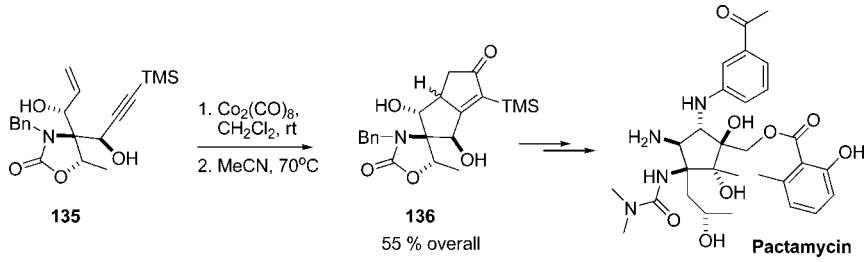
The alkaloids manzamine A and nakadomarin A have been isolated from sponges and have inhibited the growth of P388 mouse leukemia cells and demonstrated cytotoxicity against murine lymphoma L1210 cells, respectively. The second product was shown to have antimicrobial activity against a fungus and a Gram-positive bacterium as well. The tricyclic core of both compounds has been synthesized stereoselectively via PK ring closing of **133** (Scheme 45).[289] The authors have obtained the product **134** in the presence of sulfide, while either no reaction or decomposition to complex mixtures has been observed without a promoter.

The naturally occurring potent antitumor and antimicrobial antibiotic pactomycin has been isolated from a fermentation broth. Cobalt-mediated PKR has been achieved as a key step during its synthesis from D-glucose-derived enyne **135**, leading to the tricyclic compound **136** as an inseparable mixture of isomers (Scheme 46).[290] The product possessed all the carbon atoms of the cyclopentane core of pactomycin and suitable structure for installation of the remaining functionalities.

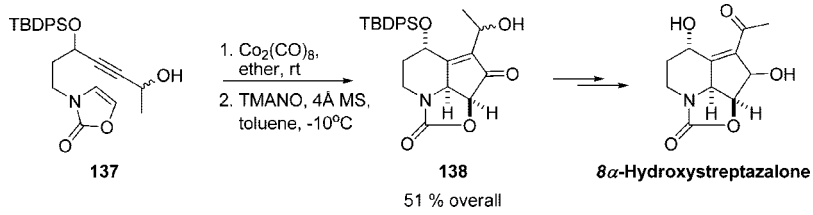
Scheme 45



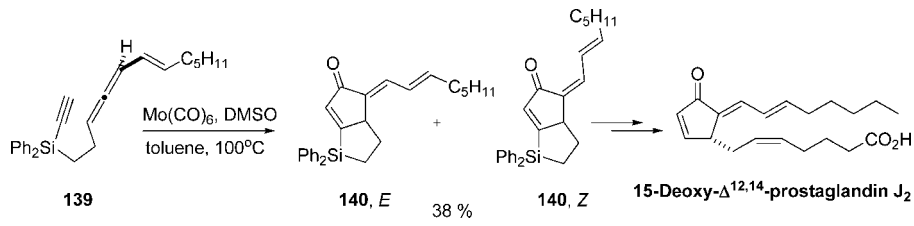
Scheme 46



Scheme 47



Scheme 48



8α-Hydroxystreptazalone belongs to the group of the oxidized streptazolin-related natural products, which have unique structural features and a promising biological activity profile, such as antibiotic and antifungal activity. Its tricyclic skeleton **138** has been directly constructed by the intramolecular PKR of the 2-oxazolone derivative **137** as a key intermediate in the total synthesis of the product (Scheme 47).[291]

Cyclopentenone prostaglandins have shown antineoplastic, anti-inflammatory, and antiviral activities and have elicited biological response by interacting with cellular targets. The bicyclic intermediate **140** of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 has been formed via molybdenum-mediated intramolecular PKR of **139** (Scheme 48).[292] Despite the relatively low yield of the annulation, the product **140** contains nearly all of the functionality necessary to assemble the target structure.

A general solution to the synthesis of biologically important stable prostacyclin PGI_2 analogues has been achieved via stereoselective intramolecular PKR.[293] Among them treprostinil (UT-15) has proven effective in the treatment of pulmonary hypertension, a debilitating and often fatal lung disease. The key tricyclic enone **142** has been obtained by cobalt-mediated closure in high yield and almost 100% chiral induction (Scheme 49).

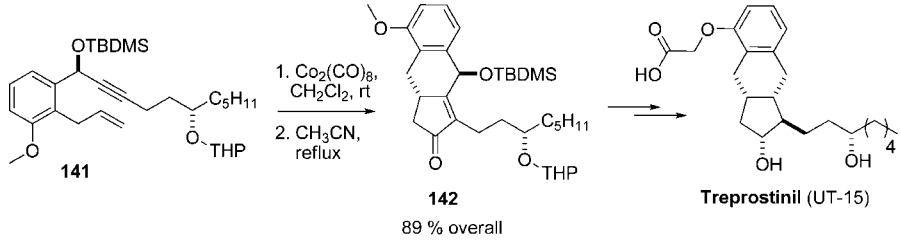
The transformation was performed in both its stoichiometric and its catalytic version, and the same conversions and stereoselectivities were observed. The authors have suggested that the results must be mechanistically controlled with steric effects being determinant.

4. Radical Cyclization

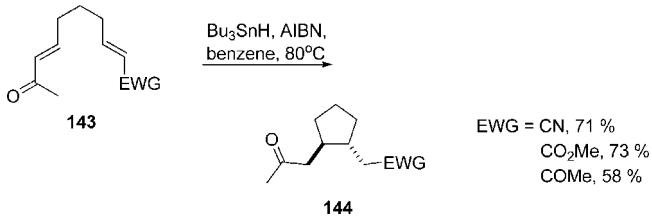
Radical chemistry has advanced tremendously since Moses Gomberg's discovery of the triphenylmethyl radical in 1900.[294] However, it was only in the mid-1980s that the synthetic potential of radicals emerged as a useful tool thanks to a few pioneer works.[295−298]

Nowadays, free radical cyclization has become an important tool for the construction of various types of cyclic compounds, including complicated biologically active natural products and medicines, and has solved various fundamental problems associated with ionic reactions. The methodology has possessed great synthetic potential in terms of predictability, generality, variability, the possibility of performing unique rearrangements, and high stereoselectivity.[299−311]

Scheme 49



Scheme 50



Most organic radical reactions occur through a cascade of two or more individual steps.[312,313] In synthesis, both the generation of the initial radical of the cascade and the removal of the final radical are crucial events. The radicals can be prepared, either photochemically or thermally by the reaction of a radical source with a promoter, peroxide or azo-compound. Among the variety of radical sources, tributyltin hydride and samarium diiodide are the most widely applied in cyclopentitol preparation.

4.1. Tributyltin Hydride-Mediated Reactions

Tributyltin hydride is among the most popular reagents to conduct free-radical reactions. It is mild and selective, so carbonyl groups and alcohols do not need to be initially protected.

The tributyltin hydride-induced intramolecular cyclization reaction of unsaturated ketones with electronically deficient olefins **143** to functionalized cyclopentanes **144**, bearing two synthetically useful carbon appendages, has been investigated (Scheme 50).[314] It has been shown that the reaction was initiated by an *O*-stannyl ketyl formed by the addition of a tributyltin radical to a carbonyl, which has both anionic and radical characters, and that an activating or electron-withdrawing function on the alkene was essential to the cyclization.

A dilution study has revealed that excellent *anti*-stereoselectivities (>50:l) could be achieved, which was attributed to a reversible cyclization. Additionally, the radical reactivity has been separated from the anionic reactivity of the *O*-stannyl ketyl by the participation of labile functional groups and external electrophiles. It was shown that the anionic character of the ketyl could be utilized in the form of a tin enolate, which was demonstrated by the presence of minor biscyclopentane products and enolate-trapping studies.

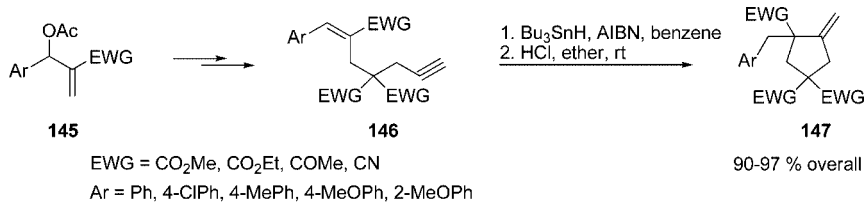
An efficient synthesis of highly substituted cyclopentane derivatives **147** has been achieved by radical cyclization of modified Baylis−Hillman adducts **146** (Scheme 51).[315] Tributyltin hydride-mediated radical step has been performed in benzene in the presence of AIBN, and the products **147** were obtained selectively via the 5-*exo*−*trig* mode in excellent yields.

A facile general synthetic route to tricyclo[4.3.*n*.$0^{1,5}$]alkane skeletons **149** from conjugated cyclic enones **148** has been developed through a tandem free radical cyclization reaction sequence, involving the cyclopropylmethyl radical mediated rearrangement (Scheme 52).[316] The scope and limitation of the reaction has been investigated, and it was clearly demonstrated that the reaction pathway could be different to form the tricyclic compounds depending on the presence and the stereochemistry of the substituents in the tether.

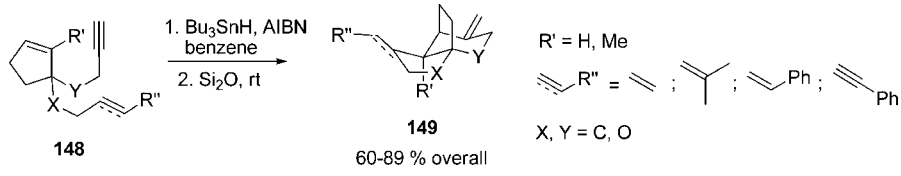
A series of aminocyclopentitols **152**, which possess the carbocyclic core of cyclopentane-type glycosidase inhibitors, has been obtained.[317] The free radical cyclization of enantiomerically pure carbohydrate-derived alkyne-tethered oxime ethers **151** has been achieved by using triphenyltin hydride or tributyltin hydride and triethylborane (Scheme 53). It has been shown that the presence of borane is absolutely necessary for the success of the process and that the correct selection of the radical precursor is crucial to obtain very high diastereoselection, independent of the type of the substituents borne at the propargylic position.

An enantioselective construction of the cyclopentane moiety of clavulactone from D-glucose has been reported.[318] As a key step, the radical-mediated cyclization of thioesters

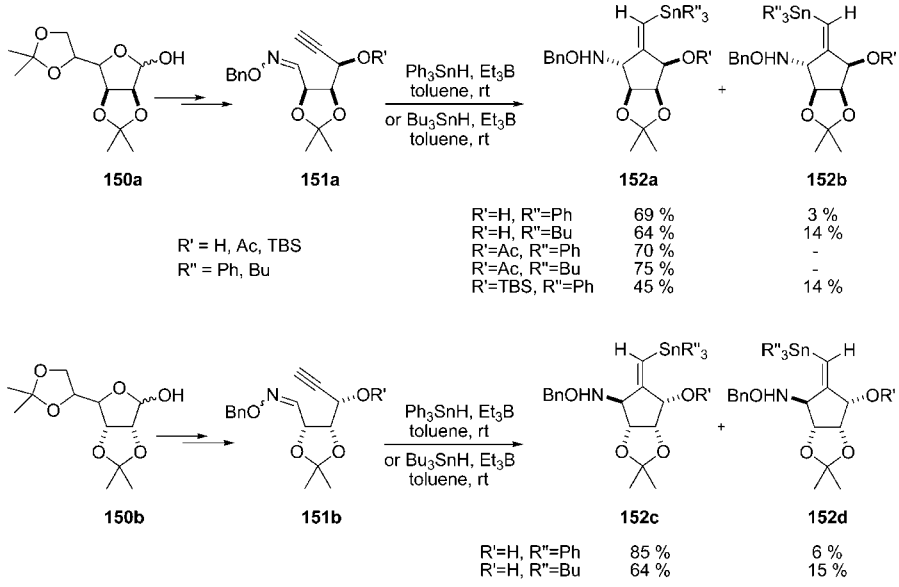
Scheme 51



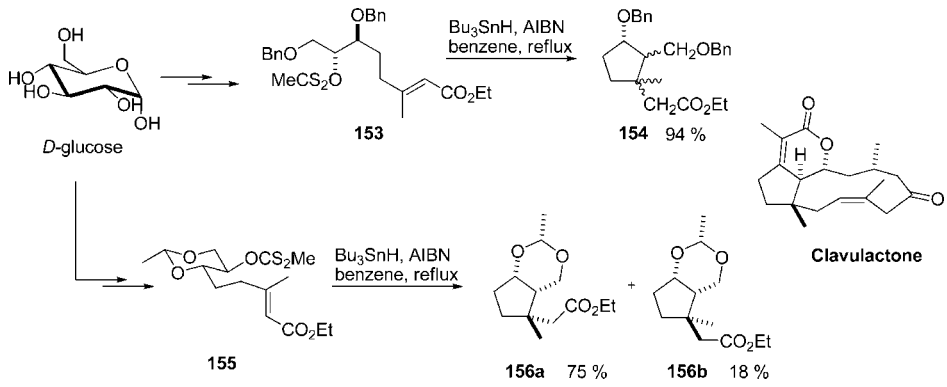
Scheme 52



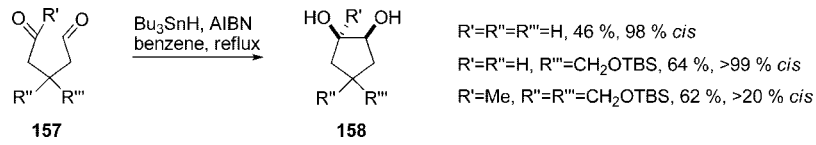
Scheme 53



Scheme 54



Scheme 55



has been achieved in high yield by tributyltin/AIBN (Scheme 54). The cyclopentane **154** was obtained from **153** as a mixture of isomers, while starting from derivative **155** with cyclic acetal-protected 1,3-dihydroxyl functionality, the product **156** was isolated with high selectivity. The results have been explained by the conformational advantage of the more rigid cyclic acetal transition state with respect to that from the open-chain counterpart.

Intramolecular pinacol coupling of dicarbonyl compounds **157** has been achieved under radical conditions (Scheme 55).[319] The cyclopentane diols **158** have been obtained in good yields and excellent *cis*-selectivity. It has been demonstrated that group 14 metal hydrides were effective for this transformation; however, tributyltin was the most effective.

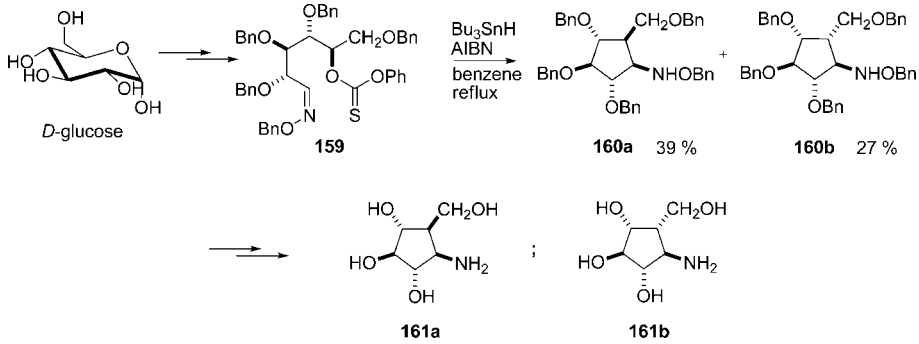
Aminocyclopentitol inhibitors of β-glucosidases **161** have been prepared from D-glucose by applying tin-promoted cyclization of oxime **159** as a key step (Scheme 56).[320] The products **160** have been obtained as an easily separable isomeric mixture and were further converted into desired unprotected compounds. The authors observed that both isomeric cyclopentitols **161** were potent inhibitors of β-glucosidases and that **161b** exhibited cross-reactivity with α-mannosidase. It has been shown that the presence of a basic amino group and the relative configuration of the substituents were essential for both inhibition potency and selectivity.

Similarly, the oxime ethers **162**, derived from D-glucose, D-galactose, and D-xylose, have been converted into isomeric mixtures of aminocyclitols **163** (Scheme 57), which were separated by chromatography and further effectively transformed into two types of glycosidase inhibitors.[321]

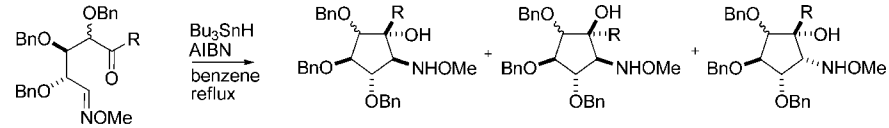
Stereocontrol in the cyclization of nitrates **165**, obtained from tartrate derivative **164**, has been investigated,[322] and it was found that the dioxanyl radicals gave rise to *cis*-fused bicyclic dioxolanes **166** (Scheme 58). Stereochemical induction at the third center was also observed, and it was shown that its magnitude was sensitive to the nature of the substrate, the best selectivity achieved with nitrate ester, **165** when R = CO_2Et.

The tetrole **170**, a biosynthetic precursor of aristeromycin and neplanocin A, has been synthesized from a derivative

Scheme 56

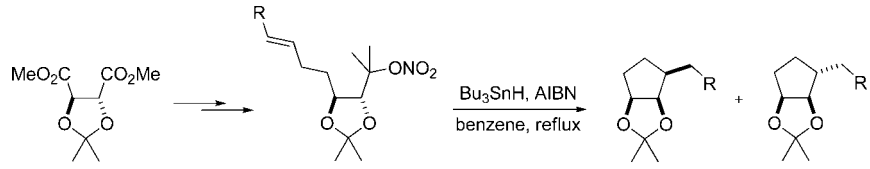


Scheme 57



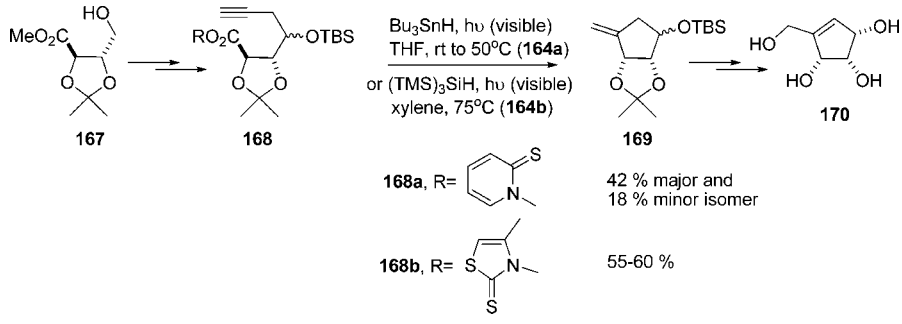
R = CH_2OBn, 4βH	28	40	-
R = CH_2OBn, 4αH	44	8	23
R = H, 4βH	27	23	-

Scheme 58



R = CO_2Et	84	8
R = CN	59	12
R = C(O)Ph	46	11
R = C_5H_{11}	54	21

Scheme 59



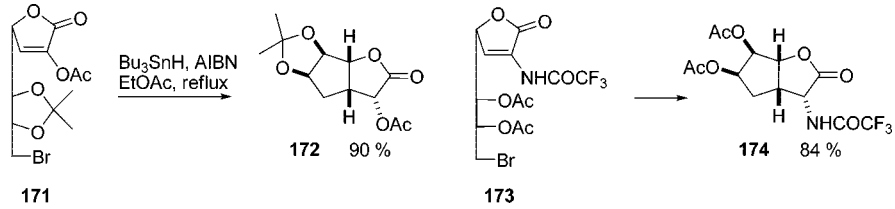
of L-tartaric acid **167** (Scheme 59).[323] The key step, conversion of the thiohydroxamate esters **168** into methylene cyclopentane **169**, has been achieved by visible light photolysis in the presence of tributyltin hydride in the case of **168a** and by trimethylsilyl silane from **168b**. The authors have shown that both schemes were suitable for the formation of **169**; however, the former is the method of choice for large scale experiments.

Carbaaldohexofuranoses have been prepared by using a 5-*exo*−*trig* radical cyclization of C-2 substituted unsaturated bromolactones **171** and **173** as the key step (Scheme 60).[324] During the cyclization step, two stereogenic centers have been formed with high stereoselectivity, and the bicyclic lactones have been isolated in high yields as single **172** or main **174** isomer; only 6% of the corresponding stereoisomer of **174** was formed.

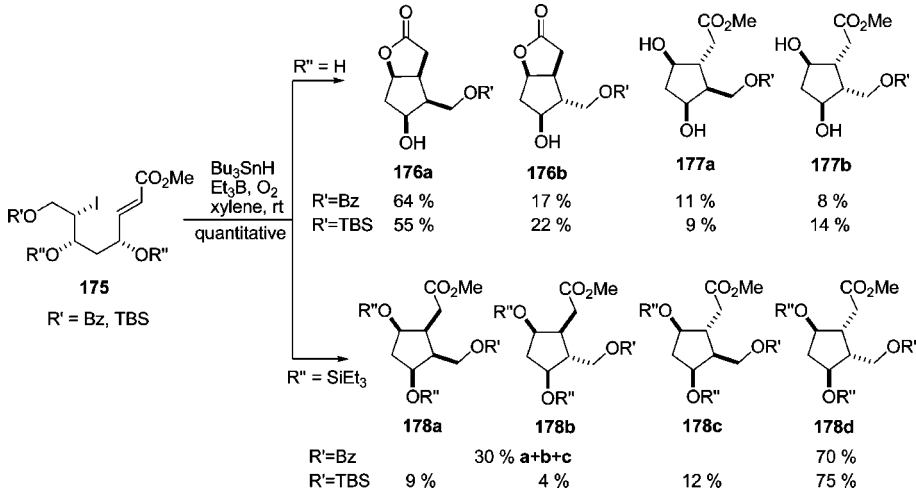
Polysubstituted cyclopentane rings have been synthesized with good to high stereocontrol by radical cyclization using tributyltin hydride and triethylborane−O_2 as a radical initiator (Scheme 61).[325] It has been demonstrated that the nature (protected or unprotected) of the hydroxy functions in positions 2 and 4 were responsible for the stereochemical cyclization outcome of acyclic compounds **175**. The presence of a 2,4-diol has led to the all-*syn* precursor of isoprostanes **176a**, while the diprotected diols afforded the diastereoisomer *syn*−*anti*−*syn* precursor **178d**.

A sequential radical cyclization of acyclic polyenes, having a vinyliodide moiety **179** that can act both as a radical donor

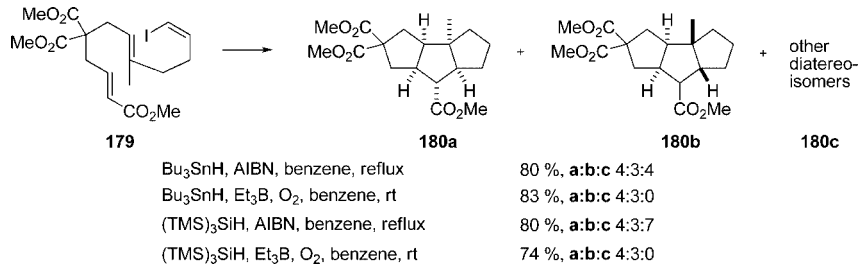
Scheme 60



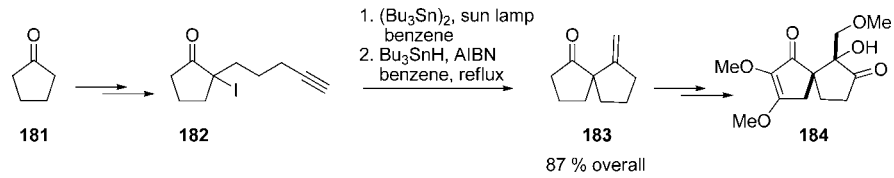
Scheme 61



Scheme 62



Scheme 63



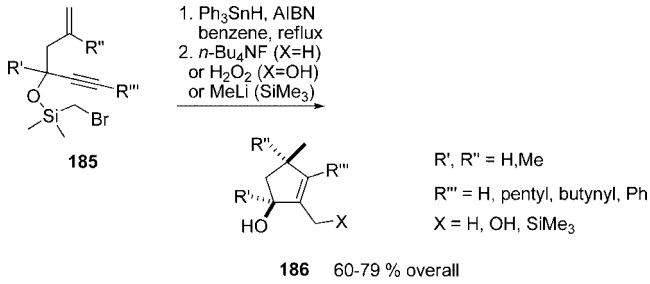
and an acceptor during the same reaction, has been reported (Scheme 62).[326] The radical reaction of iodo trienoate **179** has been performed under different conditions. The cascade reaction with tributyltin hydride−AIBN in refluxing benzene afforded linear triquinane framework **180** in high yield as a mixture of more than four isomers. The selectivity has been improved by performing the transformation at room temperature in the presence of Et_3B, and only two isomers were formed. The tris(trimethylsilyl)silane method has led to similar results.

The total synthesis of dimethyl gloiosiphone A **184**, a red marine algae compound with profound antimicrobial activity against several *Staphylococcus* species, from cyclopentanone **181** has been reported.[327] As a key step, iodo ketone **182** was converted into the spirocyclic product **183** via an α-carbonyl radical cyclization (Scheme 63). The authors have achieved the transformation in high yield by adopting an atom transfer radical reaction, irradiation of a benzene solution of ketone **182** at reflux with a sun lamp in the presence of $(Bu_3Sn)_2$ followed by reduction of the resulting vinyl iodide with Bu_3SnH using AIBN as initiator, while the product was isolated in lower yield (50%) under standard conditions with Bu_3SnH.

A radical cyclization of bromomethyl dimethylsilyl propargyl ethers **185** has been accomplished with excellent regio-, chemo-, and stereoselectivity (Scheme 64).[328] It has been found that when R′ and R‴ were H or alkyl, the triphenyltin hydride mediated *5-exo* ring closure leading to **186** was 90−100% regioselective, while in the case of R‴ = Ph, an almost equal mixture of five- and six-membered products was obtained.

Similarly, a one-pot transangular radical cyclization and Tamao oxidation of cycloundecadienyol **188** has been achieved as a key step in a biomimetic diastereoselective total synthesis of fungal sesquiterpene metabolite *epi*-illidol from isoprene oxide **187** (Scheme 65).[329] Tributyltin hydride

Scheme 64



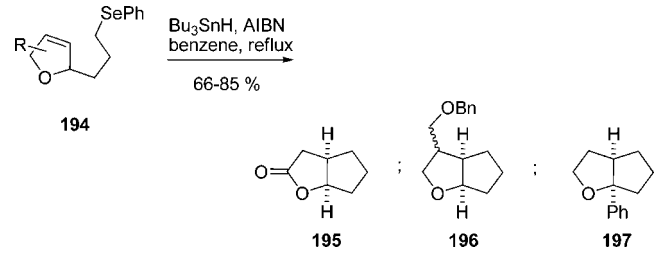
has been used as a radical source and the tricyclic framework **189** was obtained as a single diastereoisomer in good yield. The approach presents an unprecedented pathway for the synthesis of different products of the protoilludene family.

The synthetic power of radical cascades has been illustrated by a highly diastereoselective preparation of functionalized linear triquinane frameworks from acyclic precursors **190** (Scheme 66).[330] The unprotected compound has furnished the product **191** as a single diastereoisomer but in poor yield, while the silyl-protected derivative has led to a mixture of two adducts, **192** and **193**, in much higher combined yield.

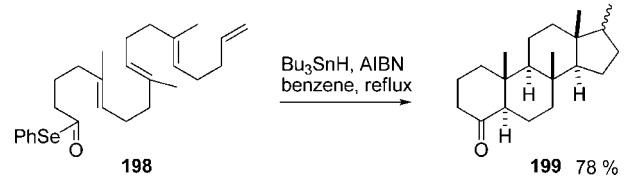
Phenyl selenides play a prominent role in the development of radical cyclization. A special feature of the group as a source of carbon radicals is that it is able to withstand a very wide range of conditions and can even tolerate the presence of strong bases. The bicyclic products **195**−**197** have been obtained by a sequential application of two powerful bond-forming processes, ring-closing metathesis and radical cyclization.[331] The radical step (Scheme 67) has been performed under standard conditions with phenyl selenides **194**, and it was established that the PhSe group served as a very convenient radical source, which could be introduced at an early stage in synthetic routes.

The angular fused-ring polycycle **199** has been obtained via consecutive 6-*endo*−*trig* modes of cyclization by treatment of a polyene acyl radical intermediate, the Se-phenyl

Scheme 67



Scheme 68

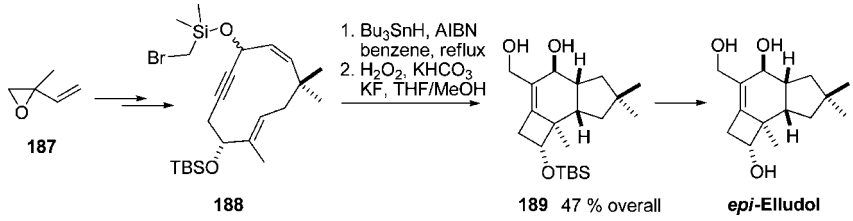


tetraeneselenoate **198**, with Bu_3SnH−AIBN (Scheme 68).[332] The all-*trans* isomer of the tetracyclic ketone **199** was isolated as a mixture of ring D methyl epimers, which structures and stereochemistries were determined by NMR experiments. The transformation has been applied as a step in the estrone total synthesis.[333]

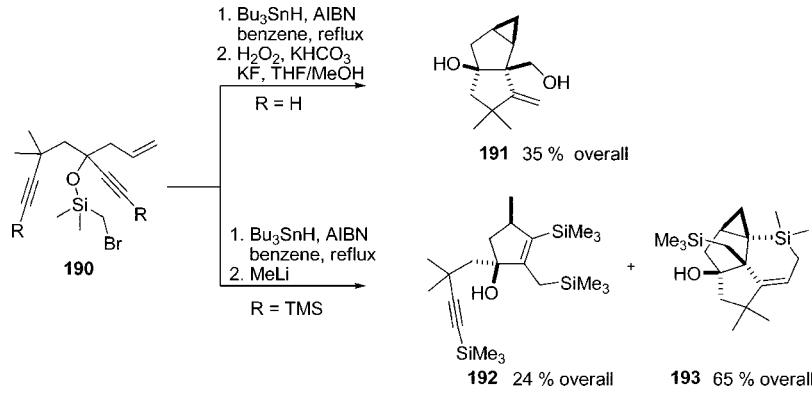
Similarly, a sequential cascade 6-*endo*−*trig* cyclization/macrocyclization/transannulation reaction approach to steroid ring construction has been achieved and exemplified in the synthesis of the *cis*,*anti*,*cis*,*anti*,*cis* tetracycle **201** from polyene selenyl ester **200** (Scheme 69).[334] The authors have extended the scope of the radical cascade cyclization strategy toward the steroid ring construction and uncovered a route to the unusual all *cis*-stereochemistry for the steroid ring system. The latter has been confirmed by X-ray analysis of the crystalline carbinol **202**, obtained from **201** by selective reduction.

The *N*-aziridinyl imino group has been utilized as a radical precursor as well as a radical acceptor in radical cyclization

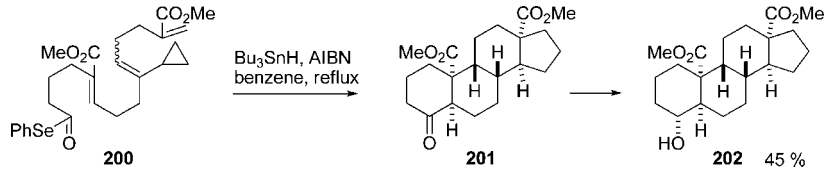
Scheme 65



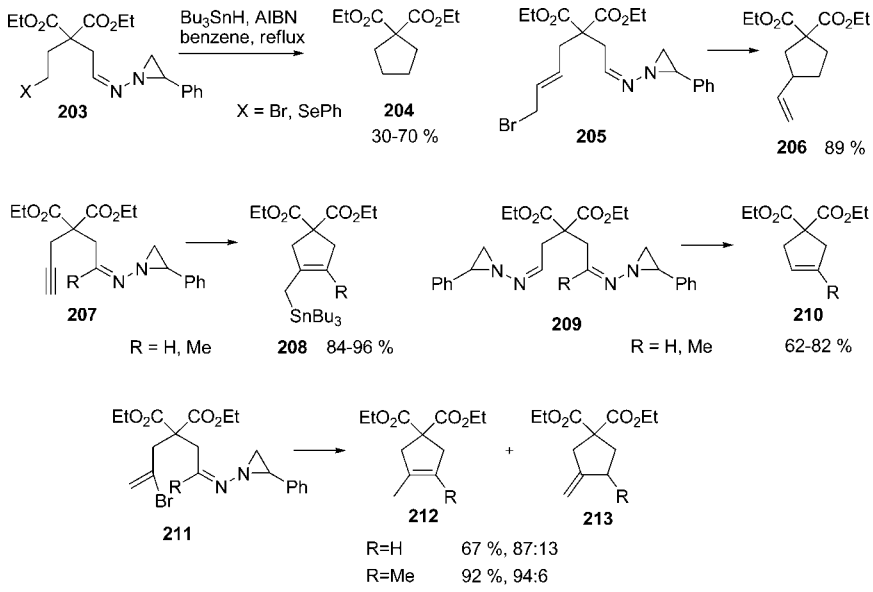
Scheme 66



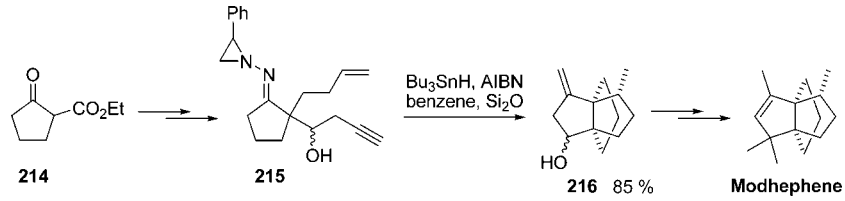
Scheme 69



Scheme 70



Scheme 71



(Scheme 70).[335] The approach is based on three factors along with the original Eschenmoser reaction: alkyl radicals are known to add to oxime ethers; β-fragmentation of three-membered rings is a facile process due to the relief of ring strain; consecutive β-fragmentations via ejection of styrene and nitrogen were expected to be fast processes. The possibility of using the aziridinyl imines as radical precursors has been briefly studied, and the approach relied on intermolecular addition of Bu_3Sn radical to an aziridinyl imino group to generate the α-Bu_3Sn-substituted carbon-centered radical.

Similarly, the radical cyclization of the *N*-aziridinylamine **215** has been applied as a key step in a facile synthesis of *dl*-modhephene from the ketoester **214** (Scheme 71).[336] The transformation has been achieved in standard conditions and the propellane **216** was obtained with complete stereocontrol.

4.2. Samarium Diiodide Promoted Transformations

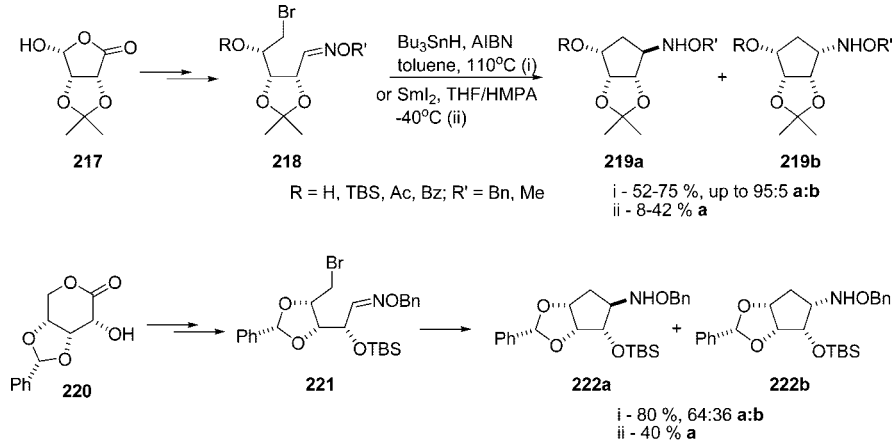
Samarium diiodide is a powerful single electron transfer agent, which is extensively used for C−C bond formation reactions.[337]

The intramolecular reductive coupling of a series of highly functionalized carbohydrate-derived oxime ethers promoted by tributyltin hydride or samarium diiodide has been reported.[338] It has shown that the reactions proceed under mild conditions, in good chemical yield, and with high stereoselectivity, thus providing a selective entry to enantiomerically pure aminocyclitols of varying regio- and stereochemistry. When studying the δ-bromo-functionalized oximes **218** and **221**, the authors observed that tributyltin hydride led to diastereoisomeric mixtures, while single isomers **219a** and **222a** were isolated when the coupling was performed with samarium diiodide albeit in low yields due to side reactions (Scheme 72).

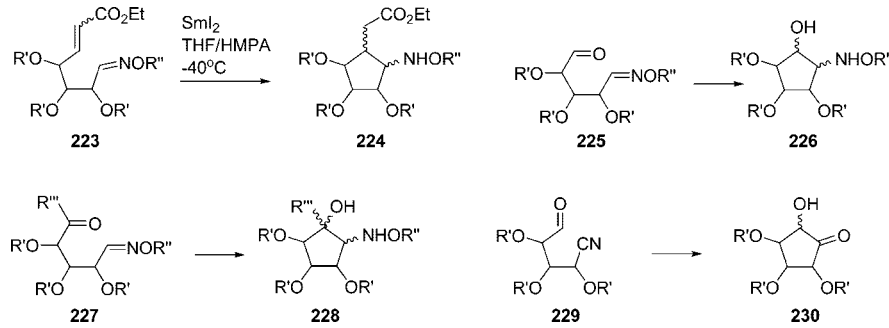
The samarium diiodide cyclization has been further expanded to oximes possessing ester, ether, carbonyl, or nitrile functionality (Scheme 73). It has been found that the coupling of α,β-unsaturated esters **223** with an oxime ether proceeded with good diastereoselection in moderate yield in the presence of HMPA, while the reaction with carbonyl-tethered oxime ethers **227** led to the target cyclopentane derivatives in both good chemical yield and stereoselectivity under very mild conditions in the absence of HMPA.

Densely functionalized cyclitols have been prepared during the synthesis of trehazolamine, the aglycon of the potent carbocyclic glycosidase inhibitor trehazolin, and its unnatural analogue **236** (Scheme 74).[339] The key transformation, samarium diiodide-promoted reductive carbocyclization of the *in situ* generated ketoaldehyde **232**, has been achieved

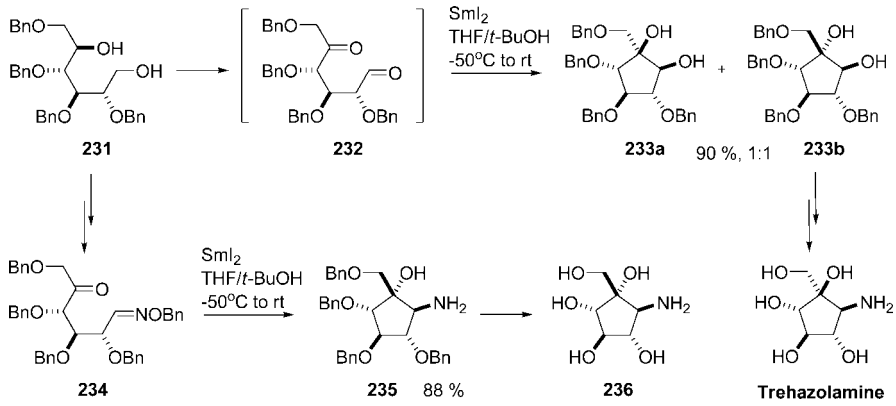
Scheme 72



Scheme 73



Scheme 74



as a high-yielding two-step one-pot sequence from D-glucose-derived diol **231**. Finally, trehazolamine was obtained in 39% yield over nine steps, while its diastereoisomer **236** has been synthesized in a shorter and more direct four step approach in 57% overall yield.

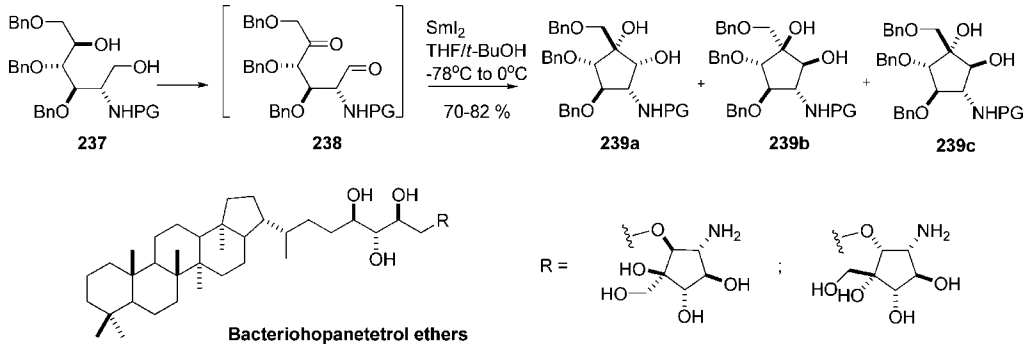
Similarly, the conversion of D-glucosamine-derived diol **237** into a stereoisomeric mixture of aminocyclopentitols **239** has been achieved (Scheme 75).[340] The protocol presents the first synthesis of the cyclopentitol units in bacterial hopanoids, triterpenoids of the hopane family.

Stereoisomeric hexahydroxylated cyclopentanes **243a** and **243b** have been obtained in good yield as a conveniently separable mixture in an attempt to determine the structure and absolute configuration of calditol isolated from the archaeon *Sulfolobus acidocaldarius* (Scheme 76).[341] After several transformations, four isomeric all acetyl-protected compounds have been isolated, and it was shown that one of them was fully identical to the natural product, thus ascertaining its structure and stereochemistry.

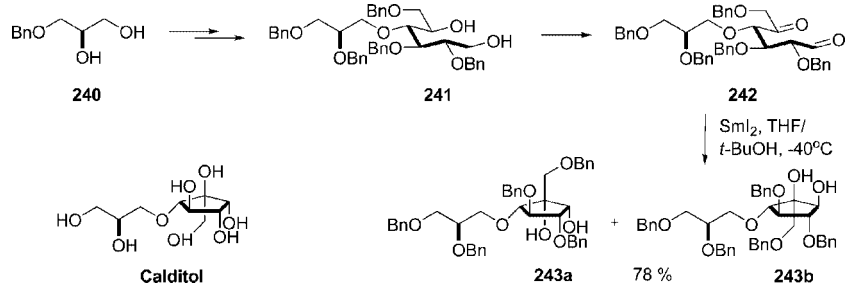
Cyclopentane-based congeners of the second messenger 1D-*myo*-inositol 1,4,5-trisphosphate and its enigmatic metabolite 1D-*myo*-inositol 1,3,4,5-tetrakisphosphate, cyclopentanepentaol triphosphate **247** and tetrakisphosphate **248**, respectively, have been obtained starting from D-xylose.[342] The key step, a five-membered ring construction, has been achieved by one-pot Swern oxidation−samarium diiodide-mediated pinacol coupling, and the pentasubstituted cyclopentanes **246** were isolated in good overall yield as a separable mixture of diastereoisomers (Scheme 77). The identity of the major product **246b** has been established by chemical correlation with known compounds.

The *cis*-diol **251a** has been obtained from the readily available deoxyiditol **249** via a ketoaldehyde **250** by samarium-mediated cyclization as a step in the synthesis of the natural carbocyclic monosaccharide caryose (Scheme 78).[343] The product has been prepared in good yield and stereoselectivity, only traces of the isomeric diol **251b** were

Scheme 75



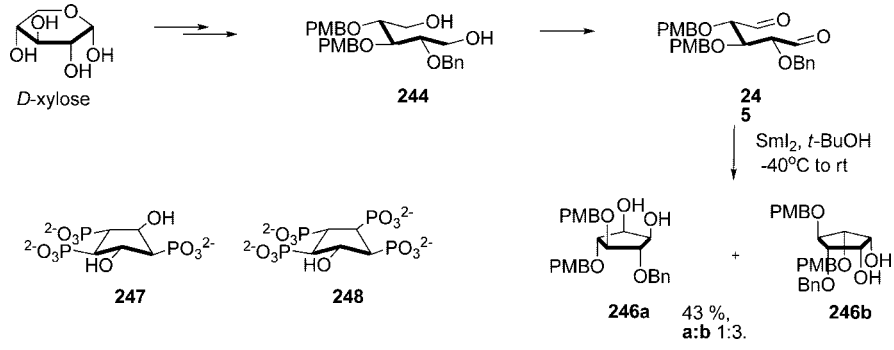
Scheme 76



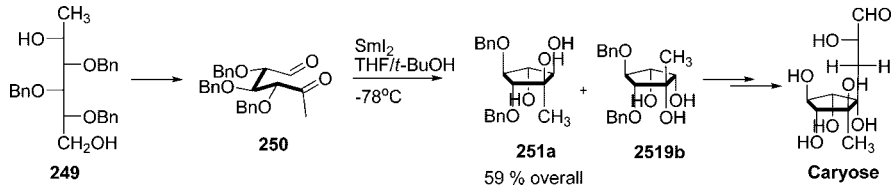
isolated, and it was further converted to caryose, thus confirming the structure and configuration of the natural product.

A short and concise synthesis of the cyclopentane segment of jatrophane diterpene kansuinine A from commercially available chiral hydroxyester **252** has been reported (Scheme 79).[344] As a key construction method, a SmI_2-mediated cyclization of δ-iodoester **253** has been achieved, and the fully functionalized cyclopentane framework **254** was obtained with excellent stereocontrol. Several additives have been tested in an attempt to increase the reduction potential of the samarium species and $Fe(acac)_3$ was found to be the most effective.

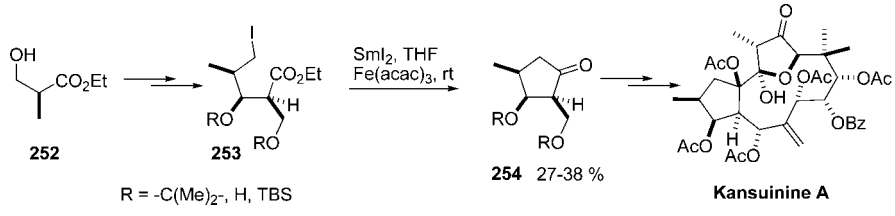
Scheme 77



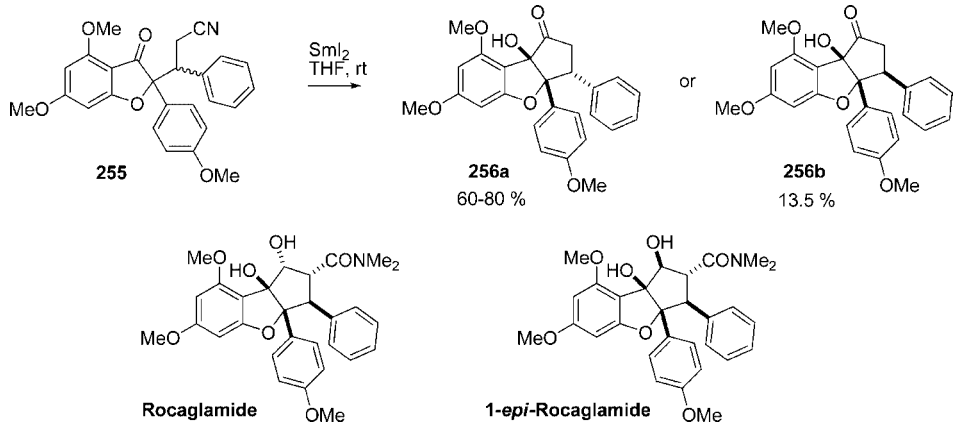
Scheme 78



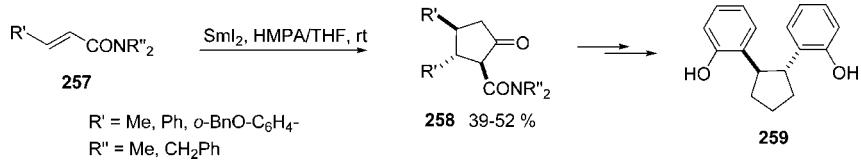
Scheme 79



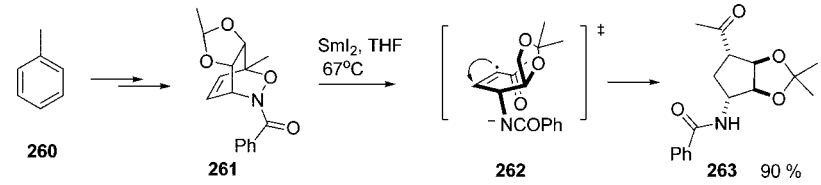
Scheme 80



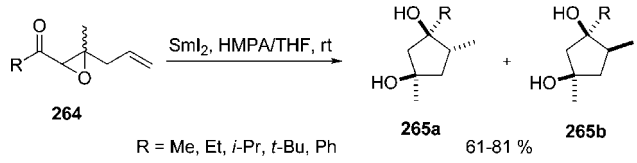
Scheme 81



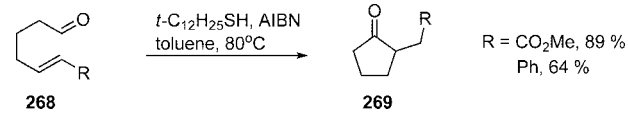
Scheme 82



Scheme 83



Scheme 85



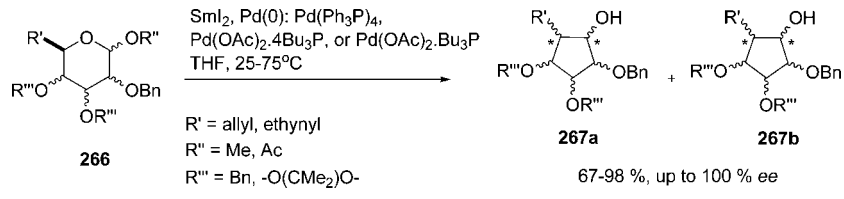
The antileukemic natural product rocaglamide has been synthesized in racemic form in a multistep sequence starting from phloroglucinol (Scheme 80).[345] Samarium diiodide pinacol coupling of keto nitriles **255** has been achieved as a step, and it was found that good yields of ketone **256a** were obtained from nitrile with α-phenyl, whereas the *β*-phenyl nitrile led to much lower yield of the required coupled product **256b**. The total synthesis of 1-*epi*-rocaglamide was also described.

A series of 1,2-*trans*-2,3-*trans* stereoisomers of 5-oxocyclopentanecarboxamides **258** has been obtained from α,*β*-unsaturated amides **257** via a highly *dl*-selective reductive coupling/Dieckmann condensation sequence with samarium diiiodide/HMPA (Scheme 81).[346] The 2,3-dimethyl derivative with *o*-benzyloxyphenyl substituents on the amide function has been readily transformed into a new biphenol ligand **259**.

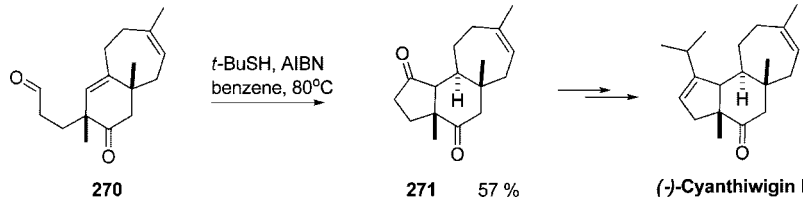
An unusual samarium diiodide-mediated reductive ring contraction of a tricyclic oxazine **261**, obtained in four steps from toluene, to a highly functionalized cyclopentane **263** with a high degree of stereochemical control has been reported (Scheme 82).[347] It has been found that the type of the products were temperature dependent; while the cyclopentane derivative **263** has been obtained in high yield at 67 °C, the corresponding cyclobutane or cyclohexane products were isolated at 25 °C and at −78 °C, respectively. The authors have proposed that the cyclopentane construction was a result of a 5-*endo*−*trig* ring closing of the intermediately formed radical **262**.

A series of *cis*-1,3-cyclopentanediols **265** has been prepared by samarium diiodide-promoted epoxide ring-opening/ketyl olefin cyclization sequence from α,*β*-epoxy ketones **264** (Scheme 83).[348] It has been shown that the relative stereochemistry could be controlled at three stereocenters in

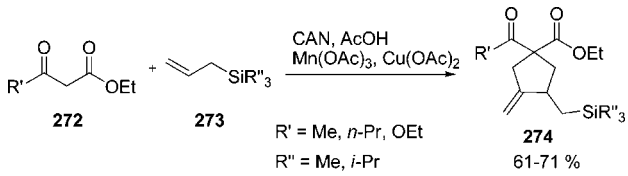
Scheme 84



Scheme 86



Scheme 87



the cyclization product. In all cases, complete selectivity for *cis*-1,3-diols has been achieved, while the diastereoselectivity at the second newly formed stereocenter was found to be substrate dependent.

A variety of vinyl- or alkynyl-substituted polyhydroxylated cyclopentanes **267** have been prepared in enantiomerically pure form from appropriate carbohydrate precursors **266** in a direct one-step ring-contraction procedure promoted by samarium diiodide and a catalytic amount of Pd(0) (Scheme 84).[349]

It has been proposed that the reaction proceed through intermediate ring-opened allyl- or allenylsamarium complexes and subsequent ring closure by intramolecular carbonyl addition. A predominant *trans* relationship has been found between vinyl (or alkynyl) and hydroxyl groups at the two newly created stereogenic centers, with good to excellent levels of stereoselectivity being observed in the formation of homopropargyl cyclopentanol products. Under appropriate conditions, preparatively useful yields were obtained for stereoisomers not directly available using alternative methodology.

4.3. Others

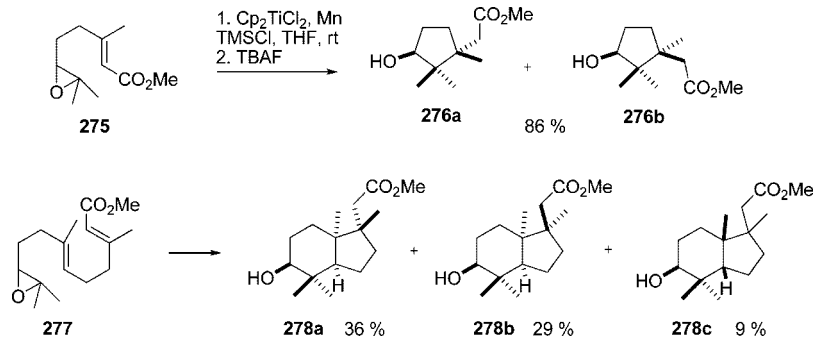
Thiol-catalyzed direct generation of acyl radicals and their intramolecular addition to the olefinic bond of unsaturated alkenals **268** have been investigated (Scheme 85).[350] It has been found that the combination of odorless *tert*-dodecanthiol and AIBN was the initiator of choice among surveyed radical generators for the cyclization of alkenals. The desired 2-substituted cyclopentanones **269** have been obtained in reasonably good yields, and it was shown that aldehydes having electron-deficient olefins cyclized more easily than those having unactivated olefins. It was suggested that the thermal decomposition of AIBN initiated the reaction by the formation of cyanoalkyl radical, which abstracted hydrogen from thiol to give thiyl radical. It was demonstrated that the stability of cyclized radical intermediate strongly influenced the yields of the products.

The same approach has been applied as a step in the total synthesis of the sea sponge diterpenoid (−)-cyanthiwigin F exhibiting cytotoxic activity against human primary tumor cells (Scheme 86).[351] The completion of the carbocyclic core **271** was achieved in good yield by *t*-BuSH/AIBN cyclization of the bicyclic intermediate **270**.

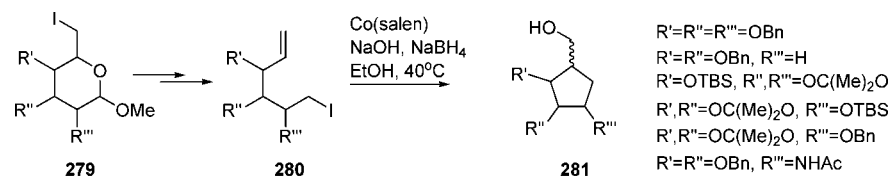
A one-pot sequential process, involving allylation, free-radical cyclization, and elimination for the preparation of multifunctional carbocycles possessing *exo* methylene unit, has been developed.[352] Accordingly, β-ketoesters **272** have been converted into silicon-containing cyclopentanes **274** by using ceric ammonium nitrate (CAN)/$Mn(OAc)_3$/$Cu(OAc)_2$ evolving via carbocationic and carboradical intermediates, of which formation and chemical activities were controlled by a β-silyl group (Scheme 87).

The Ti(III)-catalyzed radical cyclizations of epoxypolyprenes have been reported.[353] It has been found that the presence of an α,β-unsaturated ester caused a change in the regioselectivity on the closing of the second cycle. Thus, the isomeric 5-*exo*−*trig* cyclization products **276** have been

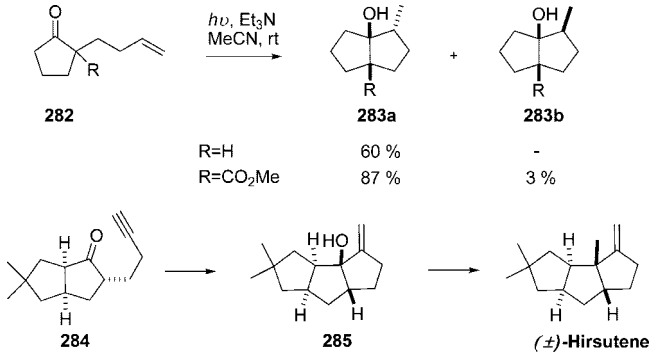
Scheme 88



Scheme 89



Scheme 90



obtained from epoxyalkene **275** in the presence Cp_2TiCl_2 as an easily separable mixture since **276b** was quantitatively transformed into a bicyclic derivative during the chromatography separation on silica gel (Scheme 88). The exposure of **277** to the same experimental conditions used for **275** has led to compounds **278** as a result of tandem 6-*endo*−*trig* and 5-*exo*−*trig* cyclizations.

A series of carbapentofuranoses **281** have been synthesized from hexopyranosides **279** via a cobalt-catalyzed radical cyclization/oxygenation sequence of iodoenitols **280** (Scheme 89).[354] The reaction has proceeded under very mild conditions, and only products of 5-*exo*−*trig* cyclization were obtained in moderate to good yields with an exception for R‴ = NHAc where no conversion was detected.

Cyclization of unsaturated ketyl radical anions, photochemically induced by electron transfer from triethylamine to unsaturated ketones, has been reported.[355] The cyclization reaction has been regio-, stereo-, and chemoselective and cyclopentanols **283** have been obtained in high yields as single (R = H) or mainly (R = CO_2Me) **283a** isomer (Scheme 90). Furthermore, the protocol has been applied for the preparation of the tricyclic skeleton system **285** from δ,ε-unsaturated ketone **284** as a key step to a short synthesis of (±)-hirsutene.

5. Aldol Condensation

The aldol reaction is one of the most powerful methods for carbon−carbon bond formation.[356−365] It represents a nucleophilic addition of an enolate equivalent to a carbonyl compound to form β-hydroxy carbonyl product, which can undergo thermal or catalytic dehydration to the corresponding α,β-unsaturated carbonyl substance. The intramolecular

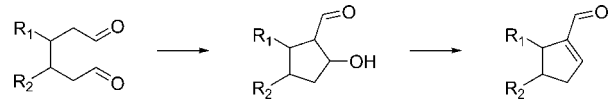


Figure 4. Intramolecular aldol cyclodehydration of 1,6-dialdehydes.

variant of the condensation is a crucial way to (tool in) the preparation of functionalized carbocycles, where both the aldol and the dehydrated products are of great importance because they exist as structural subunits in many natural products and pharmaceuticals.

The synthesis of enantiomerically pure or enriched compounds has emerged as one of the most important fields in organic synthesis during the past two decades. The asymmetric aldol condensation is among the most widely investigated reactions due to its strategic significance both in chemistry and in biology, where it presents a critical biological transformation in the context of metabolism. The classical version of the transformation is highly atom-economic; however, it evolves with very low selectivity. This problem is overridden by the catalytic asymmetric variant,[366−371] which is one of the most elegant and economically attractive ways to introduce chirality into a molecule.

5.1. Intramolecular Aldol Cyclodehydration of 1,6-Dialdehydes

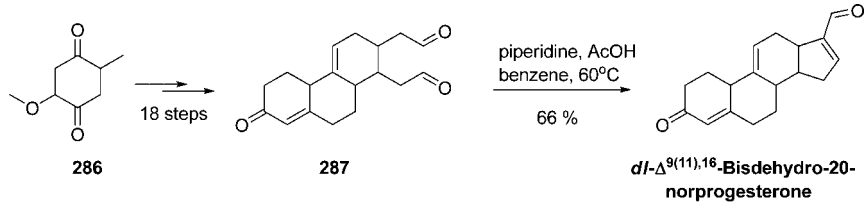
The direct intramolecular catalytic aldol cyclodehydration of 1,6-dialdehydes presents an aldol condensation to hydroxycyclopentane carbaldehydes followed by dehydration to the corresponding cyclopentene carbaldehydes (Figure 4), key cyclopentanoid precursors in the synthesis of a broad range of biologically active products.

The transformation is catalyzed by salts of a secondary amine and a carboxylic acid, leading to the dehydration product formation in general.

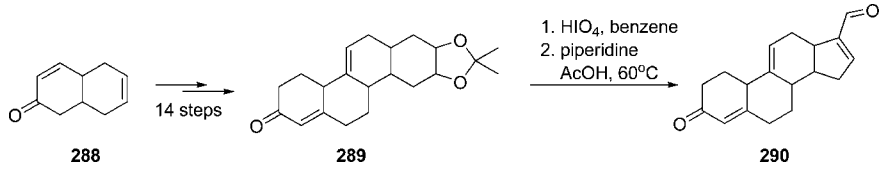
The intramolecular catalytic aldol cyclodehydration has been first reported as a step in Woodward's classical steroid synthesis,[372] the preparation of *dl*-$\Delta^{9(11),16}$-bisdehydro-20-norprogesterone (Scheme 91), the first totally synthetic nonaromatic steroid.

The relatively unstable dialdehyde **287**, obtained in 18 steps from quinone **286**, has been converted to the target carbaldehyde by using piperidinium acetate as a catalyst in good yield and regioselectivity; only slight impurity of the isomeric aldehyde was isolated. The same steroid **290** in

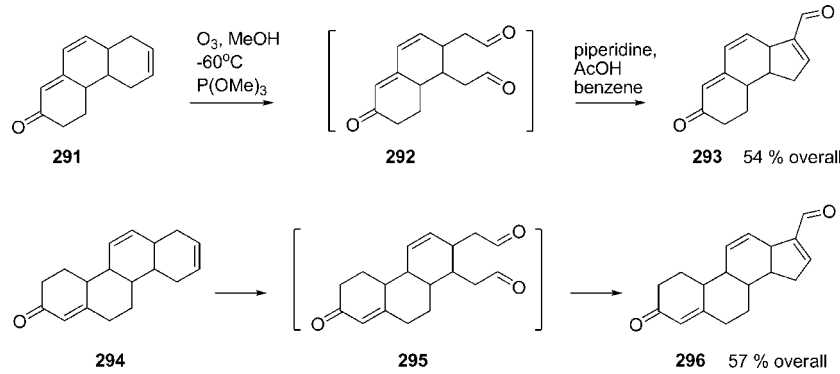
Scheme 91



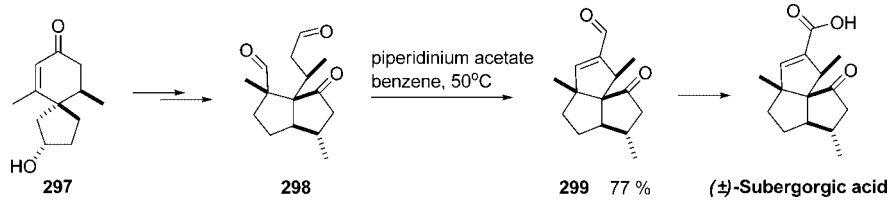
Scheme 92



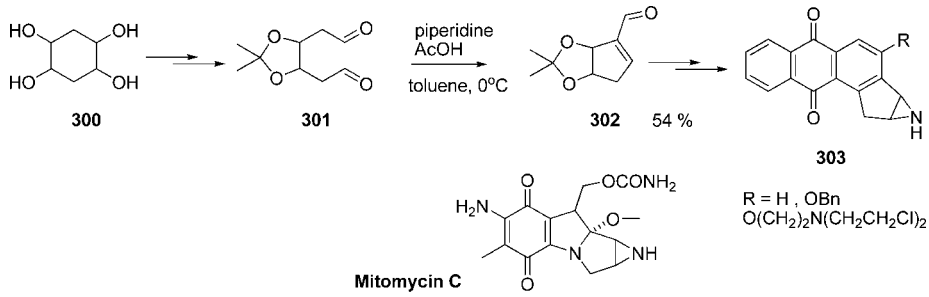
Scheme 93



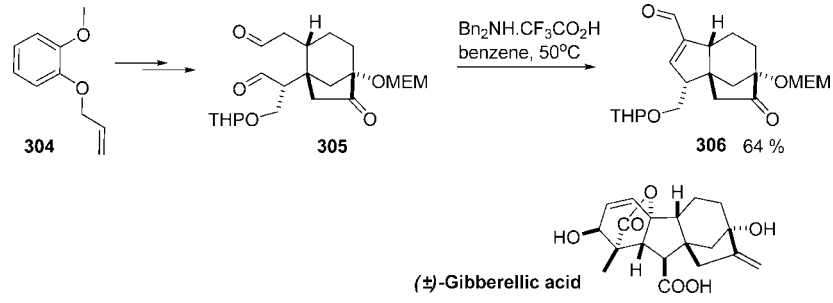
Scheme 94



Scheme 95



Scheme 96



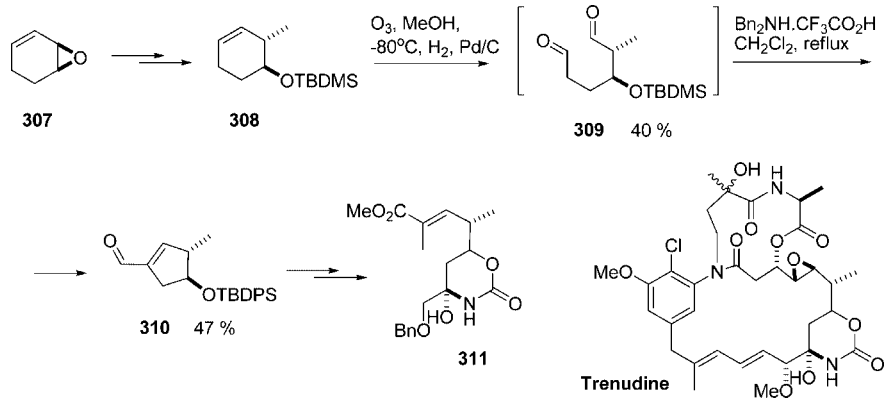
optically active form has been obtained by a slightly modified route from so-called Woodward bicyclic ketone **288** (Scheme 92).[373] The carbaldehyde **290** has been prepared from the acetonide **289** by applying the same procedure but as a one-pot protocol without isolation of the intermediately formed dialdehyde. Additionally, **290** was converted to the corresponding methyl carboxylate, methyl 3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate to establish the fact that the optically active product **290** has the same absolute configuration as the natural steroid.

The multistep and laborious conversion of the double bond into dialdehyde has been overridden by applying ozonolysis, followed by reductive workup, a rather rapid and convenient protocol.[374] Thus, the tricyclic and tetracyclic olefinic intermediates **291** and **294** have been converted during steroid synthesis into the corresponding carbaldehydes **293** and **296** via the dialdehydes **292** and **295** in good overall yields, 54% and 57%, respectively (Scheme 93).

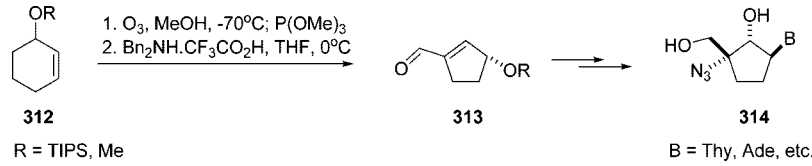
The intramolecular aldol cyclodehydration has been applied not only in steroid synthesis but also for the preparation of alkaloids, prostanoids, sesquiterpenes, pentomycin antibiotics, and many others. A stereoselective total synthesis of the angular triquinane sesquiterpene (±)-subergorgic acid possessing cardiotoxic activity has been achieved by starting from the chiral bicyclic hydroxyketone **297** (Scheme 94).[375] As a key step, the triquinane aldehyde **299** has been generated from the corresponding dialdehyde **298** in very good yield.

A series of analogues of the anticancer drug mitomycin C, possessing cyclopentanthraquinone skeleton, has been obtained.[376] The five-membered carbocycle of the target tetracyclic products **303** has been constructed by converting

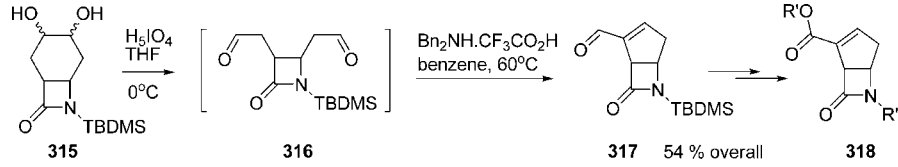
Scheme 97



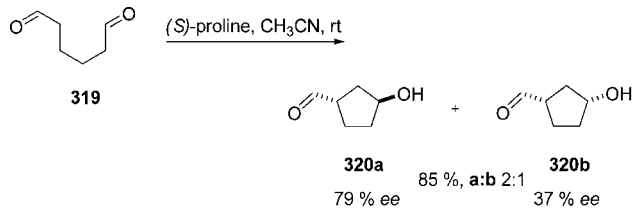
Scheme 98



Scheme 99



Scheme 100



the dialdehyde **301** to the carbaldehyde **302** (Scheme 95). It was found that both the aziridine function and the mustard side chain of the products played a significant role in the cytotoxicity against leukemic cell growth in culture.

Dibenzylammonium trifluoroacetate has also been found to be an efficient catalyst for the direct catalytic aldol cyclodehydration. The regioselectivity of the aldol product was fully controlled, providing high yields in many cases, where piperidinium acetate was not effective. The key tricyclic intermediate **306** in the total synthesis of the fungus alkaloid (±)-gibberellic acid (Scheme 96) has been obtained from 2-allyloxyanisole **304** via the dialdehyde **305** in good overall yield.[377] The reported structurally unambiguous and stereospecific scheme was the first total synthesis of gibberellic acid.

The cyclic carbamate **311** has been prepared as a key intermediate in the total synthesis of trenudine, a natural maytansinoid possessing exceedingly potent insect antifeedant activity (Scheme 97).[378] As a step, the alkene **308** has been converted into the carbaldehyde **310** in moderate yield via the corresponding dialdehyde **309**.

Racemic carbocyclic analogues **314** of anti-HIV active 4′-azido-2′-deoxy-nucleosides have been prepared in order to determine whether the substitution of a methylene group for the furanose oxygen would provide therapeutic advantages in the 4′-substituted series.[379] The cyclopentene derivative **313** has been obtained from cyclohexene **312** by subsequent ozonolysis at low temperature with reductive workup to a dialdehyde and aldol cyclodehydration to the carbaldehyde **313** in a one-step protocol (Scheme 98).

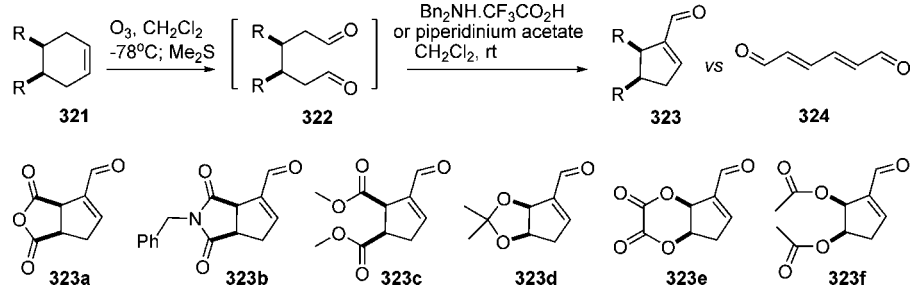
A series of azabicycloheptenes **318** has been synthesized and evaluated as antimicrobial agents and β-lactamase inhibitors (Scheme 99).[380] The key precursor, carbaldehyde **317**, has been obtained from the diol **315** by consecutive oxidation and aldol cyclodehydration.

The asymmetric (*S*)-proline-catalyzed aldolization of hexanedial **319** has been investigated (Scheme 100).[381] It has been found that the transformation was less stereoselective with respect to the six-membered ring formation and the aldol product **320** was obtained with only modest diastereo- and enantioselectivities.

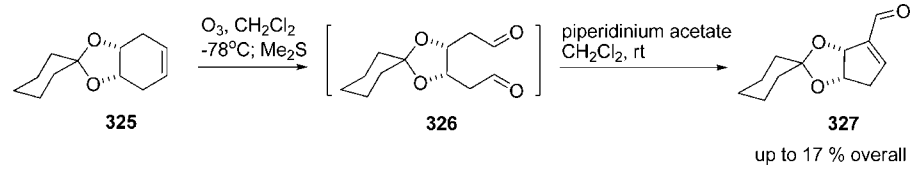
The intramolecular catalytic aldol cyclodehydration of different *meso*-3,4-disubstituted 1,6-dialdehydes **322** has been investigated, and it was found that both the type of the products and the catalyst efficiency were controlled by the cyclohexene substituents (Scheme 101).[382] Thus, the products **323a**, **323b**, and **323c** have been obtained by using both dibenzylammonium trifluoroacetate and piperidinium acetate; only the second catalyzed the formation of **323d**, while no **323e** and **323f** generation has been detected with both catalysts, and an open chain conjugated dialdehyde, 2,4-hexadienedial **324**, was isolated only.

It has been shown that a secondary amine catalyzed the transformation itself, leading to the same product formation, even in the cases where the corresponding ammonium salt was not effective as a catalyst. The asymmetric version of the transformation has been accomplished on the examples

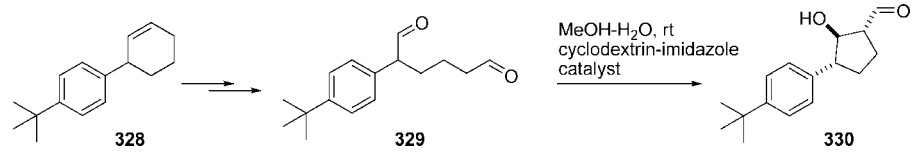
Scheme 101



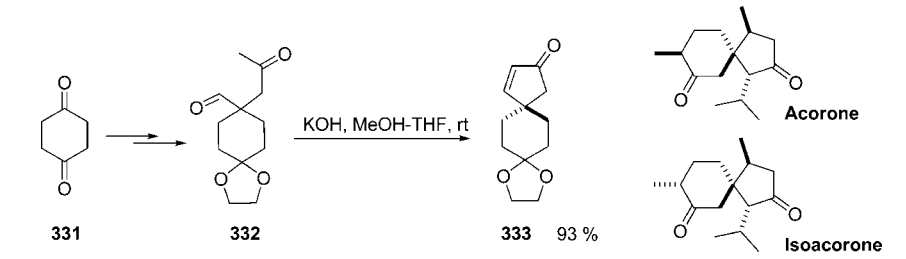
Scheme 102



Scheme 103



Scheme 104



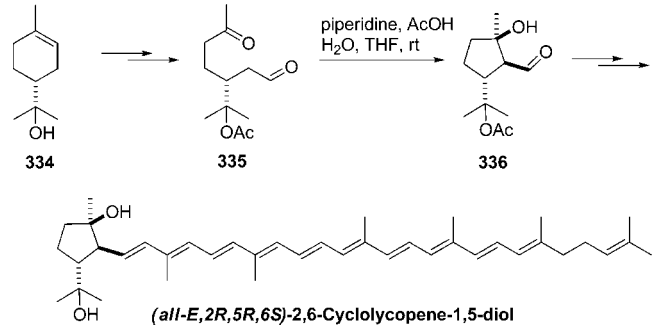
of **323b** and **323d** formation,[383] and it was found that the presence of a hydroxyl group in the catalyst's molecule seemed to be crucial to reach stereocontrol. Additionally, it has been observed that chiral phosphines and phosphites were highly effective catalysts for this cyclodehydration but without inducing stereocontrol.

The approach has since been extended toward an asymmetric synthesis of **327** in order to study its behavior in Claisen rearrangement (Scheme 102).[384] The required dialdehyde **326** has been obtained via a short synthetic sequence starting from benzene. After an array of racemic catalysts and asymmetric organocatalysts was screened, the product **327** was isolated in a disappointingly low yield by using piperidinium acetate. The authors have suggested that the latter was caused by decomposition of the precursor dialdehyde **326** by E1cB elimination of the acetal protecting group.

Cyclodextrine−imidazole enzyme mimics have been examined as catalysts in a selective intramolecular aldol condensation.[385] The dialdehyde **329**, prepared from alkene **328**, has been treated with a catalytic amount of β-cyclodextrin carrying imidazole groups and the aldol hydroxycarbaldehyde **330** was isolated instead of the corresponding dehydrated product (Scheme 103).

The carbaldehyde **330** has been obtained regioselectively (97%) when the reaction was catalyzed by the imidazole groups of a cyclodextrin-bis-imidazole enzyme mimic, while a mixture of regioisomers was isolated from the transformation performed in an imidazole buffer.

Scheme 105

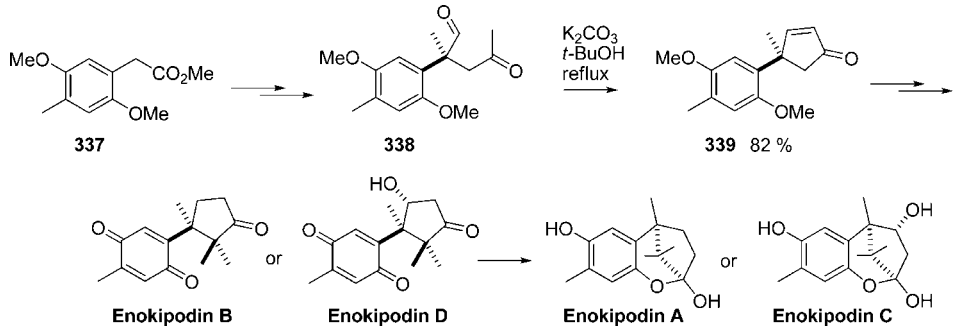


5.2. Aldol Condensation of Ketoaldehydes and Diketones

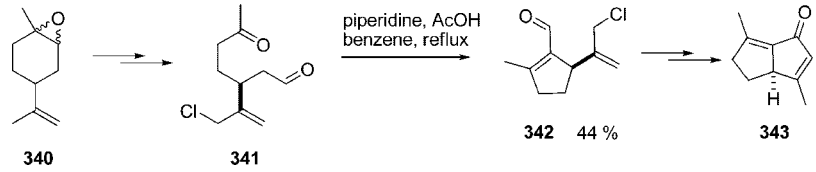
Ketoaldehydes and diketones are also widely exploited in the synthesis of five-membered carbocycles by intramolecular aldol cyclization. As in the case of dialdehydes, the transformation leads to the formation of aldol or dehydrated product, both being of great importance as cyclopentitol precursors.

The base-catalyzed intramolecular aldol cyclization of the ketoaldehyde **332** to the spirobicyclic ketone **333** has been

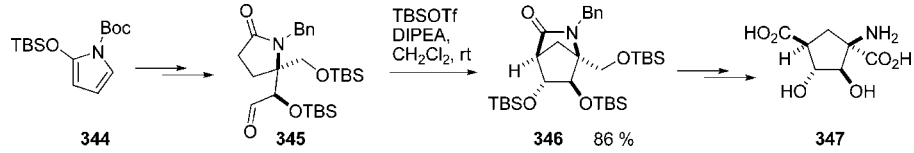
Scheme 106



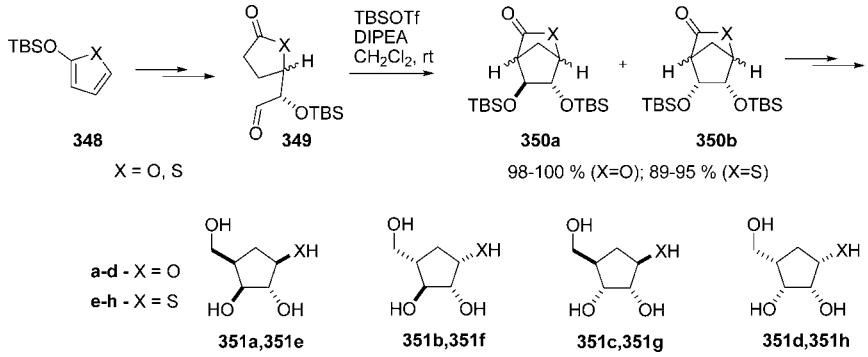
Scheme 107



Scheme 108



Scheme 109



achieved as a key step in the synthesis of epimeric natural sesquiterpenes acorone and isoacorone from a simple diketone **331** (Scheme 104).[386] The stereocontrolled construction of spirocyclic carbon skeleton was conceived by the authors as a test scheme in an attempt to develop a general methodology for spiroannulation of a five-membered ring to an existing cycle.

The total synthesis of the cyclopentane moiety of the optically active carotenoid (*all-E*,2*R*,5*R*,6*S*)-2,6-cyclolycopene-1,5-diol, which possessed anticancer activity against prostate cancer, has been achieved in four steps from (*R*)-α-terpineol **334** (Scheme 105).[387] The cyclic aldehyde **336** with the correct substitution pattern has been synthesized by aldol cyclization of ketoaldehyde **335** catalyzed by piperidinium acetate.

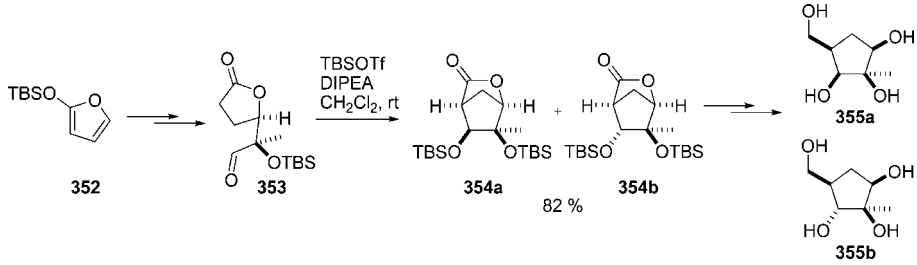
The aldol condensation of ketoaldehyde **338** has been applied as a key step to the first enantioselective total synthesis of enokipodins A−D, highly oxidized α-cuparenone-type sesquiterpenes possessing antimicrobial activity (Scheme 106).[388] The target products have been obtained in 11−13 steps with 8−28% overall yields from the ester **337** and confirmed the absolute configurations of the natural enokipodines.

The α,β-unsaturated enone **343**, a useful chiral building block in the preparation of a variety of compounds having a bicyclo[3.3.0]octane framework, has been synthesized from limonene oxide **340** (Scheme 107).[389] As a step, piperidinium acetate catalyzed cyclodehydration of ketoaldehyde **341** to carbaldehyde **342** has been achieved in moderate yield.

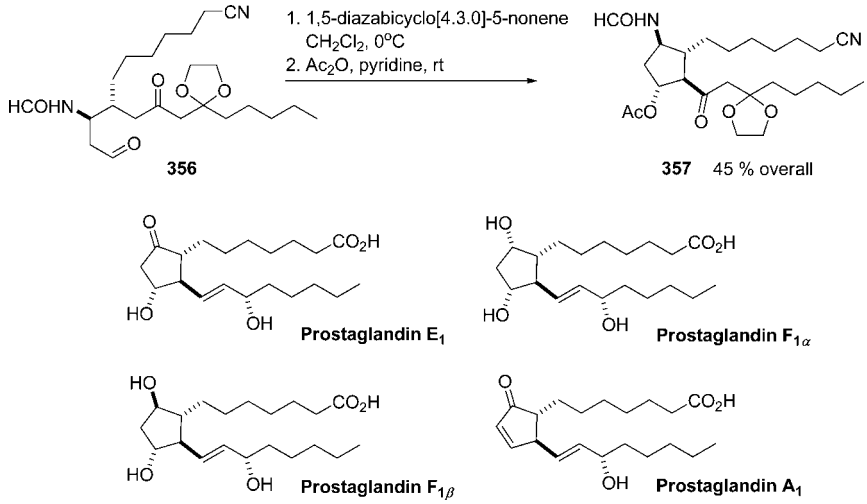
The intramolecular silylative aldolization of the ketoaldehyde **345** to the bicyclic product **346** has been achieved as the key step for the enantioselective total synthesis of cyclopentanedicarboxylic acid **347**, a rigid and functionalized L-glutamic acid analogue (Scheme 108).[390] The synthetic protocol, performed in 15 linear steps from silyloxypyrrole **344**, presents a full-aldol access to carbaketose derivatives.

A similar silylative cycloaldolization procedure has been applied in the synthesis of stereoisomeric carbafuranoses **351a**−**351d** and carbafuranosylthiols **351e**−**351h** (Scheme 109).[391] The cyclopentane ring construction has been achieved by intramolecular diisopropylethylamine/*tert*-butyldimethylsilyl triflate-assisted aldolization of ketoaldehyde **349** with

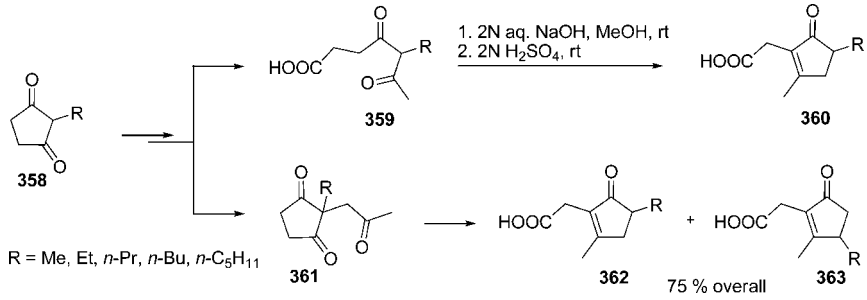
Scheme 110



Scheme 111



Scheme 112



subsequent silylation of the aldols formed. The reaction conditions have been varied on the example of the formation of *trans*-fused bicyclic products with X = O. It has been found that at low temperatures the cycloaldolization was reversible for the *trans* isomer **350a** and irreversible or at least slower to equilibrate for the *cis* counterpart **350b**, while at higher temperatures, there was a more comparable thermodynamic equilibration of both **350a** and **350b** resulting in the preferential formation of the more stable *trans* isomer **350a**.

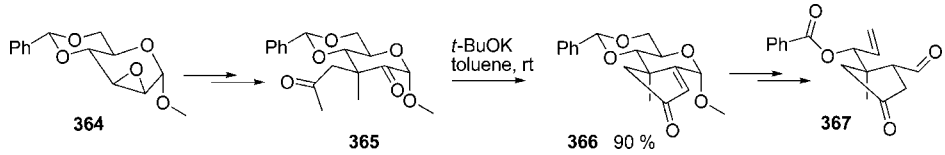
Finally, the cyclopentitols **351a**, **351b**, **351e**, and **351f** were obtained from the *trans*-configured bicycles **350a**, whereas *cis*-disposed **350b** served as the precursors for **351c**, **351d**, **351g**, and **351h**. It has been shown that the procedure tolerated a variety of precursors and was suitable for scaling-up. The protocol has been applied to the crucial construction of the cyclopentane frame of the C(2)-methyl branched carbafuranoses **355** (Scheme 110).[392]

Diazabicyclononane-catalyzed aldol cyclization of the ketoaldehyde **356** to the cyclopentane derivative **357** has been performed as a step in the total synthesis of a series of prostaglandins (Scheme 111).[393] The aldol product has been acetylated *in situ* to avoid the dehydration and was further transformed into the target prostaglandins.

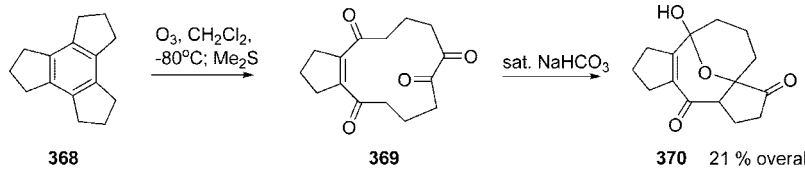
Cyclopentenones **360**, possessing a carboxylic moiety in the side chain, have been prepared from the cyclic diketone **358** by successive alkylation, ring cleavage, hydration, and base-catalyzed intramolecular aldolization of thus obtained diketones **359** (Scheme 112).[394] When carrying out the aldolization via triketones **361**, the authors have obtained the aldol products **362** along with the isomeric cyclopentenones **363** as byproducts. The proposed mechanism, involving deprotonation, nucleophilic attack with ring enlargement, alkali-promoted ring opening, and condensation to cyclopentenone, was confirmed by the isolation of the six-membered cyclic intermediate by acidification.

Cyclopentaannulation of the diketone **365** has been applied as a key step in a protocol for the stereoselective conversion of glucose into an enantiomerically pure cyclopentanone carbaldehyde **367** (Scheme 113).[395] The intramolecular aldol condensation of the diketone **365**, obtained from a readily available epoxide **364**, has been successfully achieved by using potassium *tert*-butoxide to afford the cyclopentenone **366** in high yield.

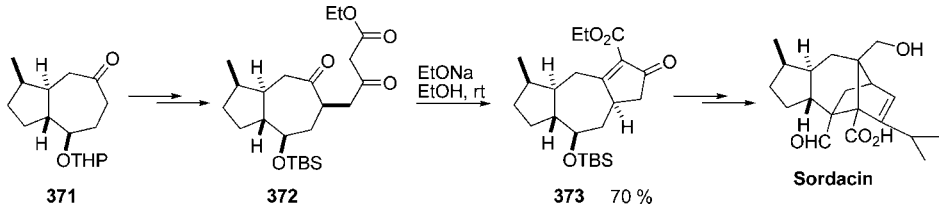
Scheme 113



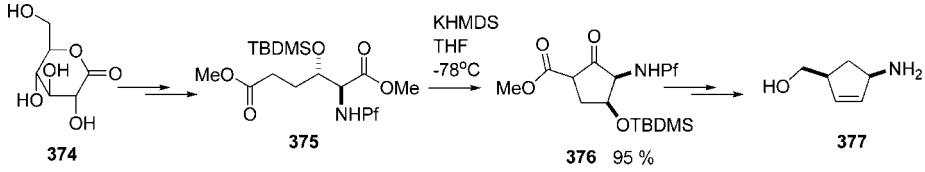
Scheme 114



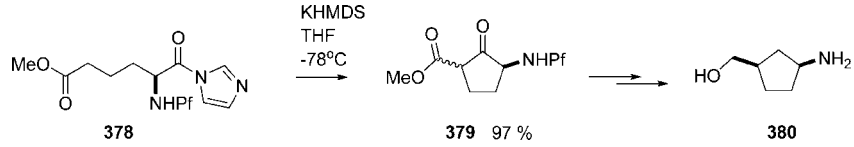
Scheme 115



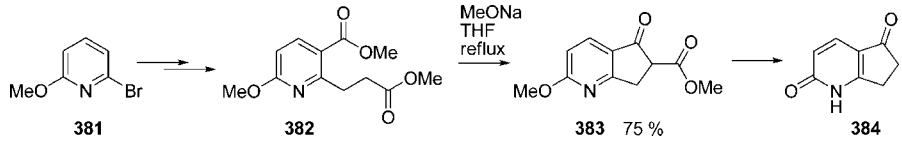
Scheme 116



Scheme 117



Scheme 118



The complex tetracyclic system **370** has been obtained from trindane **368** by ozonolysis and subsequent base-catalyzed aldol condensation of the intermediately formed tetraketone **369** (Scheme 114).[396] It was found that the milder ruthenium tetroxide led to oxidation products of all three π-bonds in **368**, while the ozonolysis resulted in the oxidative cleavage of two of the three endocyclic olefins. The product **370** presents a composite feature of several classes of natural products and has an overall profile comparable to that of taxols, dolastanes, isodancanediol, germacren, quainaolide, etc., which offers opportunities for synthesis of complex natural products from trindane **368**.

5.3. Miscellaneous Enolate Strategies

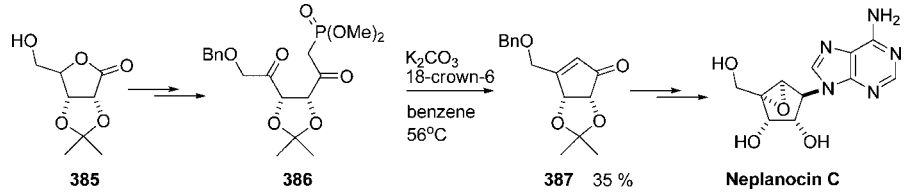
The Knoevenagel cyclization has been applied as a key step for the synthesis of (±)-sordaricin, a diterpene aglycon of antifungal sordarin. Thus, the diketoester **372**, obtained from bicyclodecanone derivative **371**, has been converted into the tricyclic cyclopentenone derivative **373** in the presence of a catalytic amount of sodium ethoxide (Scheme 115).[397]

The Dieckmann condensation of the diester **375** has been achieved in excellent yield with regio- and stereointegrity during the preparation of cyclopentene moiety **377** of carbocyclic nucleosides from D-glucono-δ-lacone **374** (Scheme 116).[398] It has been found that the regio- and stereoselectivities for the formation of **376** were strongly influenced by the sterically demanding 9-phenyl-9-fluorenyl protecting group on nitrogen.

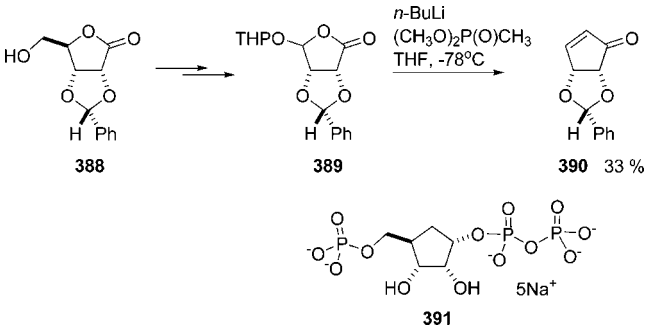
Similarly, imidazolide **378** has been converted into ketoester **379** as a step in a chirospecific synthesis of (1*S*,3*R*)-L-amino-3-(hydroxymethyl)cyclopentane **380** from aspartic acid (Scheme 117).[399] The condensation product **379** has been obtained in excellent yield as a 3:2 mixture of diastereomers, which was used directly in the next step since the separation led to decomposition.

A straightforward synthesis of a non-glycosidic cardiotonic agent cyclopenta[*b*]pyridine-2,5-dione **384** from commer-

Scheme 119



Scheme 120



cially available pyridine derivative **381** has been reported (Scheme 118).[400] The bicyclic ketoester **383** has been obtained in very good yield via Dieckmann condensation in the presence of sodium methoxide.

A Wittig-type aldol cyclodehydration has been applied in the first synthesis of the naturally occurring carbocyclic nucleoside neplanocin C, a minor component of the neplanocin family possessing antiviral and antitumor activities (Scheme 119).[401] The cyclopentenone **387** was obtained in moderate yield from the diketo derivative **386** in the presence of potassium carbonate and crown ether and was subsequently converted into the target natural product neplanocin C as a step in a convergent enantioselective 12 step sequence.

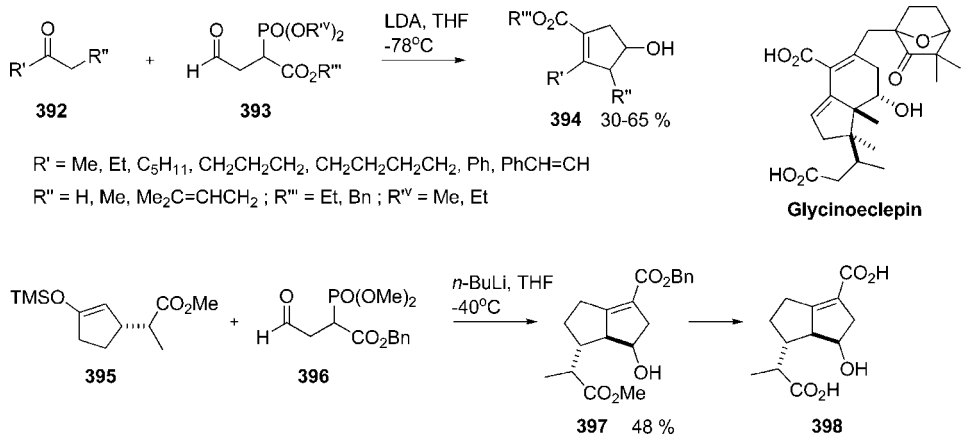
A similar bicyclic product **390** has been obtained via a one-pot protocol during the synthesis of an optically active carbocyclic analogue **391** of phosphoribosyl pyrophosphate (Scheme 120).[402] It has been observed that the carbocyclization reaction, leading from **389** to **390**, was very sensitive to temperature and that the best conditions involved generation of the lithium salt of dimethyl methylphosphonate followed by condensation with **389** at low temperature. The target structure provides a highly useful tool for the mechanistic and crystallographic investigations of the phosphoribosyltransferases due to the low reactivity of the carbocyclic analogue.

The hydroxycyclopentenoic esters **394** have been obtained in a one-pot procedure by annulation of ketone enolates **392** and phosphonate aldehydes **393** (Scheme 121).[403] It has been found that the reaction was limited by the size of R′ when it is branched and open-chain unsaturated ketoesters were isolated instead of the corresponding aldol products. The protocol has been applied to glycinoeclepin analogue synthesis. Additionally, the hydroxy diacid **398** has been prepared to ascertain the hypothesis that a hydroxy diacid was the minimum functionality for hatching stimulus activity for the soybean cyst nematode.

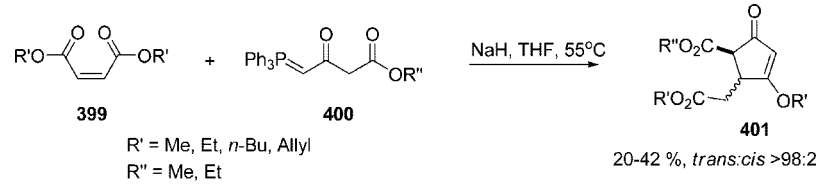
A regio- and diastereoselective formation of functionalized cyclopentenones **401**, useful building blocks in prostaglandin synthesis interval, has been achieved by the domino Michael−Ester−Wittig reaction of maleic diesters **399** with phosphoranes **400** (Scheme 122).[404] The products **401** have been obtained in moderate yields and high *trans* selectivity.

A base-catalyzed nitro-aldol condensation of nitroethane and the dialdehyde **403** has been achieved as the key step in the synthesis of a series of five stereoisomers of amino cyclopentanetetrols **405** in order to elucidate the essential core structure of potent α-mannosidase inhibitors. The aldol

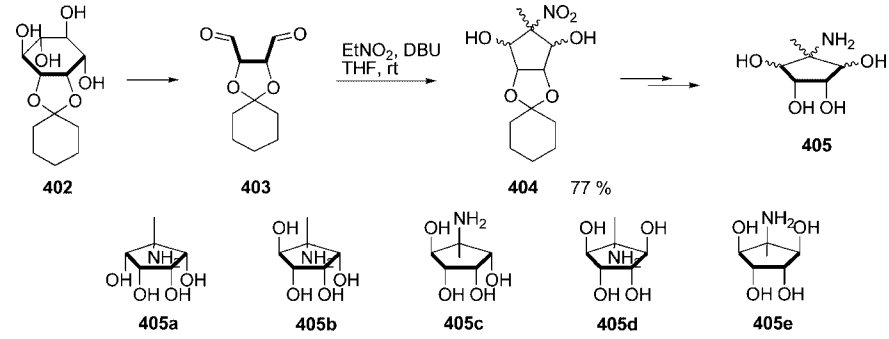
Scheme 121



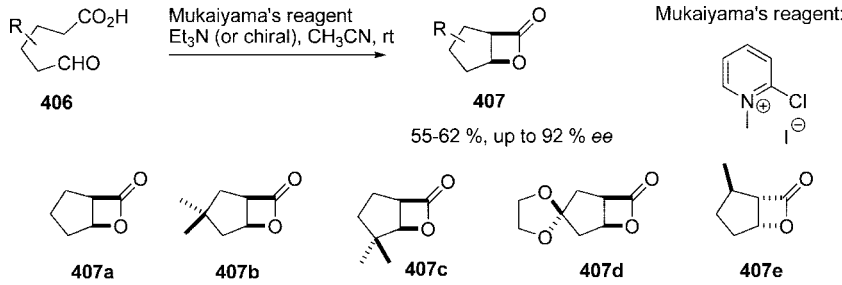
Scheme 122



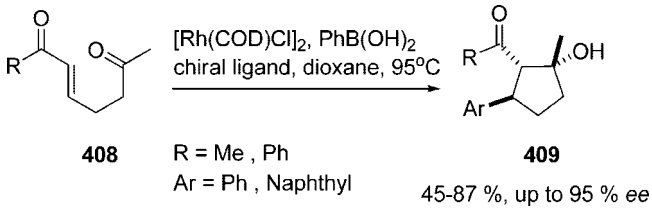
Scheme 123



Scheme 124



Scheme 125



meso-cyclopentitol **404** formed has shown a nitro group in position *cis* to the dioxolane ring (Scheme 123).[405] The inhibitory activity of the stereoisomers **405a**−**405e** against six glycosidases has been evaluated, and the results have suggested that the *all-cis* configuration of the amino and three hydroxyl groups on the cyclopentane ring is crucial to exhibit activity.

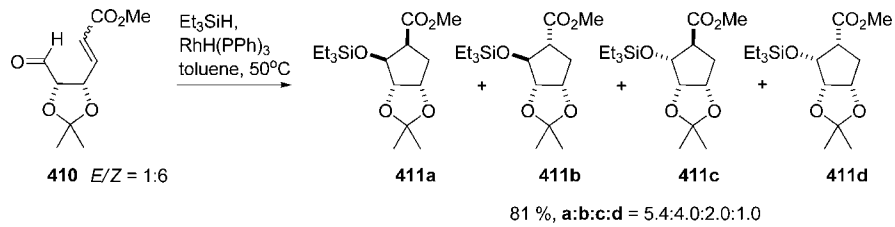
A series of bicyclic β-lactones **407**, a structural motif found in several natural products, has been obtained by intramolecular nucleophile-catalyzed aldol lactonization of aldehyde acids **406** (Scheme 124).[406] The transformation has been performed for the first time with unactivated aldehydes. By application of chiral amine catalysts, the reaction has been accomplished as an asymmetric catalytic version, and high selectivities were achieved, of up to 92% ee. The conversion has been additionally improved by using modified Mukaiyama's reagents, possessing triflate counteranions instead of iodide.[407] The products have been synthesized efficiently (70−82%) in shorter reaction times without erosion of enantioselectivity, 91−98% ee.

A simple and effective method for the diastereo- and enantioselective catalytic carbometallative aldol cycloreduction of aromatic and aliphatic monoenone monoketone precursors **408** to five-membered ring products **409** has been developed (Scheme 125).[408] The transformation has been described as a tandem rhodium-catalyzed conjugate addition of arylboronic acids and aldol cyclization, and its simplified mechanism has been proposed by the authors. A range of chiral ligands have been screened, and it was found that the Rh−BINAP system was among the most promising. An attractive feature of this methodology resides in the ability to create three contiguous stereogenic centers, including a quaternary center, in a single manipulation with high levels of relative and absolute stereochemical control.

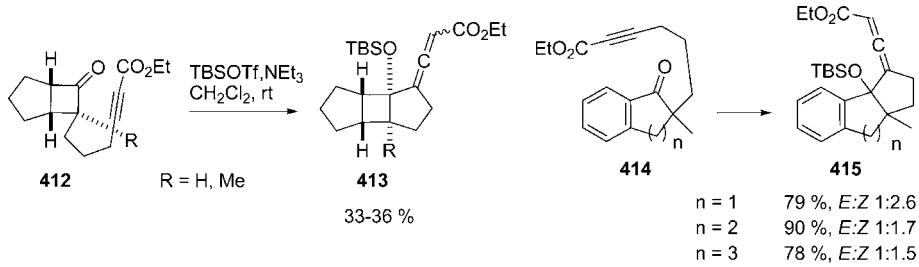
Rhodium-catalyzed tandem hydrosilylation−intramolecular aldol reaction of the oxohexanoate **410** has been achieved as a key step in the enantioselective synthesis of the highly potent anti-HIV carbocyclic nucleosides carbovir and abacavir from D-ribose (Scheme 126).[409] The cyclopentanoid **411** has been obtained stereoselectively, and after chromatography separation, **411a** was converted in several steps into (−)-carbovir and (−)-abacavir.

An intramolecular alkynylogous Mukaiyama aldol-type reaction of acetylenic esters **412** and **414** promoted by TBSOTf/Et_3N has been studied (Scheme 127).[410] The tricyclic α-allenic esters **413** have been isolated in moderate yields together with spiroketoesters, while **415** were obtained in high yields with *cis*-ring junction.

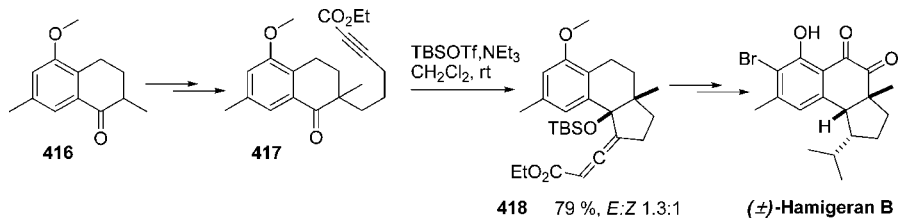
Scheme 126



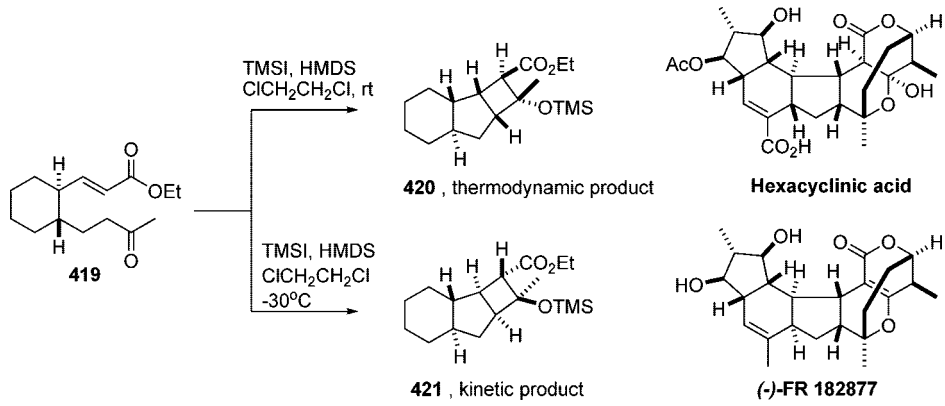
Scheme 127



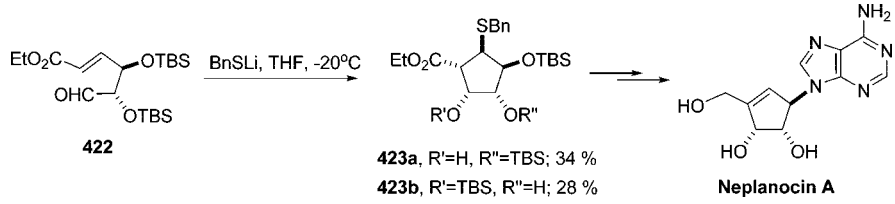
Scheme 128



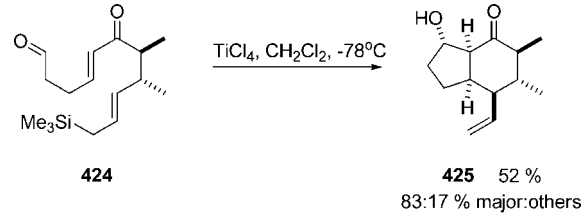
Scheme 129



Scheme 130



Scheme 131



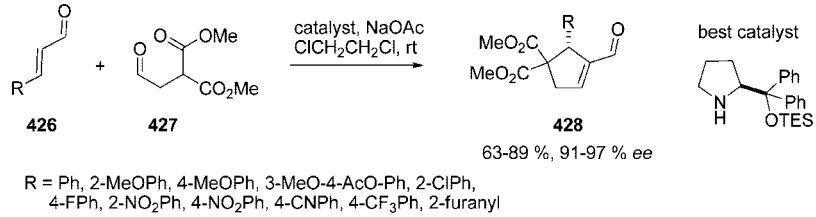
The transformation has been further extended toward the preparation of allenoate **418** from **417** as a step in the formal total synthesis of the marine sponge alkaloid (±)-hamigeran B, which showed complete virus inhibition against herpes and polio viruses (Scheme 128).[411]

A tandem intramolecular Michael−aldol reaction has been achieved as a tool for the construction of the C-ring of the cytotoxic active natural products hexacyclinic acid and (−)-FR 182877 (Scheme 129).[412] By change of the reaction conditions, either the kinetic product **421** or the thermodynamic product **420** has been obtained selectively.

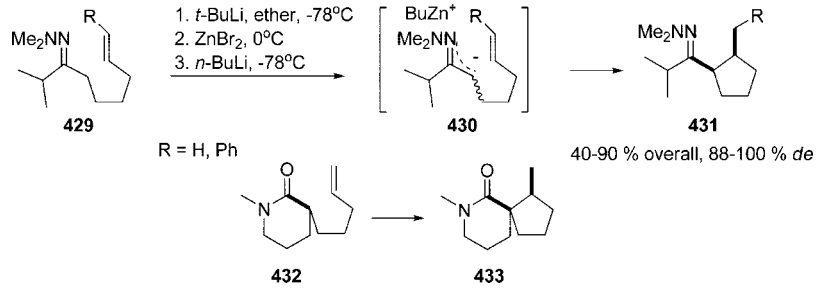
Lithium thiolate-initiated Michael−aldol tandem cyclization reaction has been applied as a step in the total synthesis of the natural carbanucleoside with *S*-adenosylhomocystein hydrolase inhibitory activity, (−)-neplanocin (Scheme 130).[413] The stereoselectivity observed for the preparation of the cyclic product **423** has been rationalized by the combination of a conformational control of the enolate by allylic strain and coordination of the aldehyde oxygen to lithium.

A tandem Sakurai−aldol reaction in a fully intramolecular manifold has been performed by tethering an aldehyde electrophile to allyl silane (Scheme 131).[414] Thus, the $TiCl_4$-induced cyclization of enone **424** to the hydrindane derivative **425** has been achieved in good yield and selectivity. The authors have explained the results by intramolecular allyl silane conjugate addition and ensuing intramolecular aldol annulation.

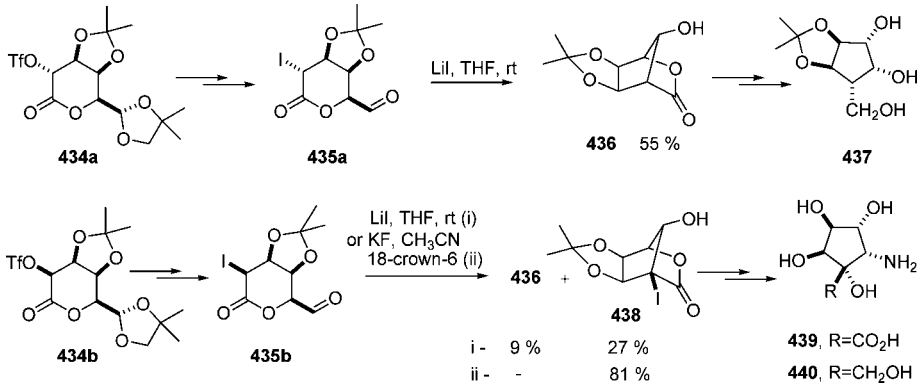
Scheme 132



Scheme 133



Scheme 134



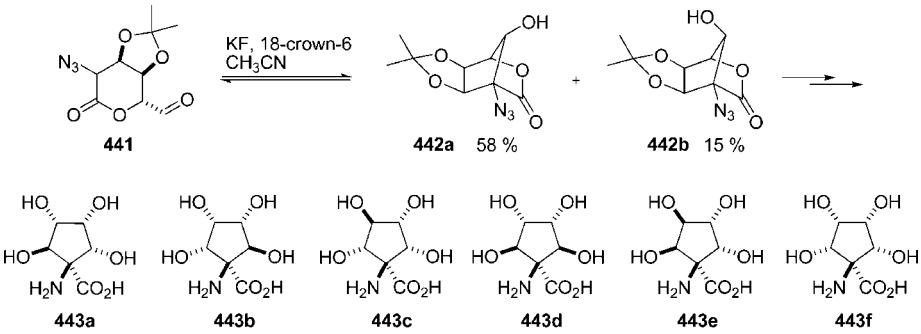
A series of highly functionalized cyclopentenes **428** have been obtained via organocatalytic cascade Michael−aldol condensation reactions (Scheme 132).[415] The new stereogenic center in **428** has been formed in high enantioselectivity via a one-pot protocol.

A 5-*exo* trigonal cyclization of zincated intermediates **430** of the ketone hydrazones **429** and lactam **432**, an olefinic version of the aldol reaction, has been achieved, and the corresponding 1,2-*cis*-substituted cyclopentanes **431** and **433** have been obtained with high levels of diastereoselectivity, 88−95% (Scheme 133).[416] It has been observed that the cyclization reaction took place smoothly in a manner that the hydrazone and the cyclization terminus were placed *cis* to each other and that the cyclization onto a disubstituted double bond (**429**, R = Ph) was much slower than that onto a terminal olefin (**429**, R = H). Additionally, the transformation has been achieved with the lactam **432**, and the corresponding aldol product **433** was obtained with 100% diastereoselectivity. The results indicated that both azaenolates and ordinary oxygen enolates took part in the olefinic aldol reaction studied.

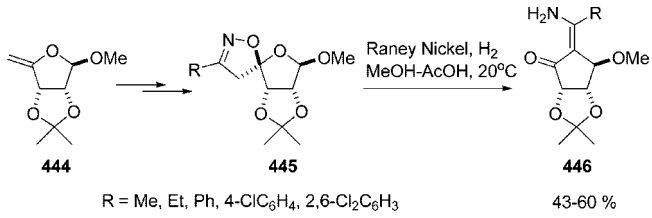
The reductive aldol cyclization is a powerful protocol for preparation of highly functionalized cyclopentanes. A fully substituted cyclopentane derivative **437** has been obtained from the epimeric sugar lactones **434** in relatively short sequences in an optically pure form.[417] The ring closing has been achieved via iodide ion-induced reductive aldol condensation of iodoaldehydes **435** (Scheme 134). Considerable difference was observed for the cyclization behavior of the epimeric iodoaldehydes **435a** and **435b**. While **435a** provided the required reductive aldol product **436** in moderate yield, very low yield was obtained from **435b** (9%) where the iodolactone **438** was isolated as a major product as a result of an intramolecular aldol condensation of the aldehyde. A possible explanation has been given by a combination of the relative ease of iodide attacking iodide to give iodine and the carbanion needed for the reductive aldol reaction and also of the relative acidities of the iodoaldehydes **435a** and **435b**, which would determine the relative ease for competition by the ordinary aldol cyclization. Because the nonreductive aldol product **438** also presents a convenient cyclopentitol precursor, its synthesis has been further improved.[418] The transformation has been successfully achieved, and **438** was isolated in much higher yield by applying the combination potassium fluoride/18-crown-6 instead of lithium iodide. Finally, the lactone **434** has been converted in several steps into the highly hydroxylated cyclopentane β-amino acid **439**, an analogue of the antifungal antibiotic *cis*-pantacin, and to the cyclopentitol **440**.

The analogous reaction of the epimeric azidoaldehydes **441** has been performed, and the corresponding epimeric aldol bicyclic azides **442** were isolated, the former being the major product (Scheme 135).[419,420] It has been shown that the reaction was reversible, and by application of a series of remarkable aldol equilibrations, the epimeric bicyclic lactones

Scheme 135



Scheme 136



442 have been converted to the stereoisomeric highly hydroxylated α-amino acids **443**.

A nitrile oxide approach for the carbocyclic ring closure of pentanofuranosides has been developed.[421] The conversion of spiro-isoxazolines **445** to the corresponding all-substituted cyclopentanones **446** has been achieved by Raney nickel-mediated N−O bond cleavage followed by spontaneous aldol-like condensation (Scheme 136).

The protocol presents a short and efficient route to convert D-ribose to densely functionalized cyclopentane derivatives suitable for further transformations including disaccharide preparation, as demonstrated by the authors.

6. Miscellaneous

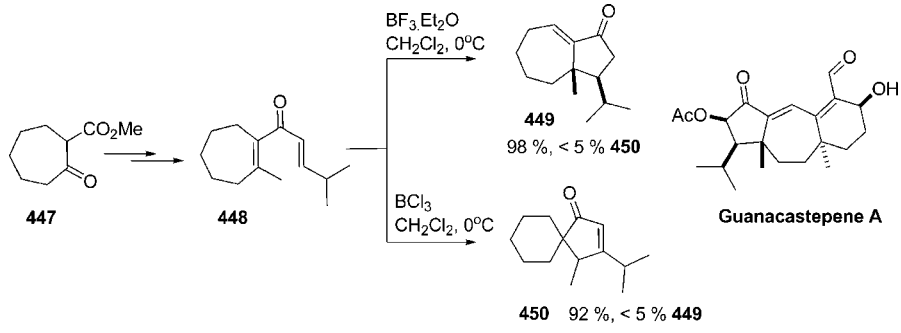
6.1. Nazarov Cyclization

The Nazarov cyclization is an efficient way to obtain cyclopentenones from divinyl ketones,[422] discovered in 1942.[423] It represents a rare example of a Lewis acid-catalyzed 4-π conrotatory electrocyclic reaction, which has been widely investigated in the synthesis of various types of molecules and reviewed.[424−430] Therefore, we will describe only a few examples of its application for the preparation of biologically active products.

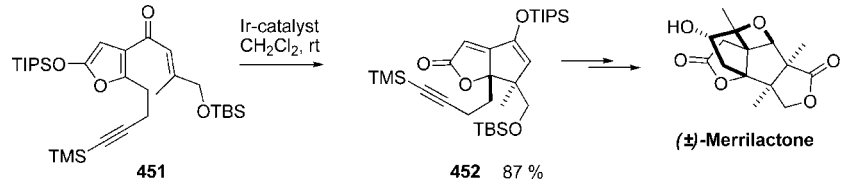
The hydroazulene core of the diterpenoid guanacastepene A, possessing potency against methicillin-resistant and vancomycin-resistant pathogens, has been synthesized from commercially available starting material **447** (Scheme 137).[431] A classical Nazarov cyclization has been applied as a key step, and hydroazulenone **449** was obtained from dienone **448** in high yield with *syn* relative stereochemistry of the methyl and isopropyl groups. Various acidic conditions have been examined, and it was found that the use of boron trifluoride etherate generated **449** as the sole product in quantitative yield, while the use of boron trichloride in dichloromethane favored the formation of **450** with a selectivity of >95:5, also in nearly quantitative yield. It has been shown that both Brønsted and Lewis acids in noncoordinating solvents favored carbocationic rearrangement leading to **450**, while acids in the presence of Lewis basic solvents such as ether and methanol induced deprotonation rapidly before rearrangement, generating **449**.

To examine the reaction, it has been further extended toward other divinyl ketone substrates, with both vinyl substituents and methyl groups and cyclohexadienone with the same vinyl substituents as **448**, and it was observed that fused bicyclic products were generated highly selectively

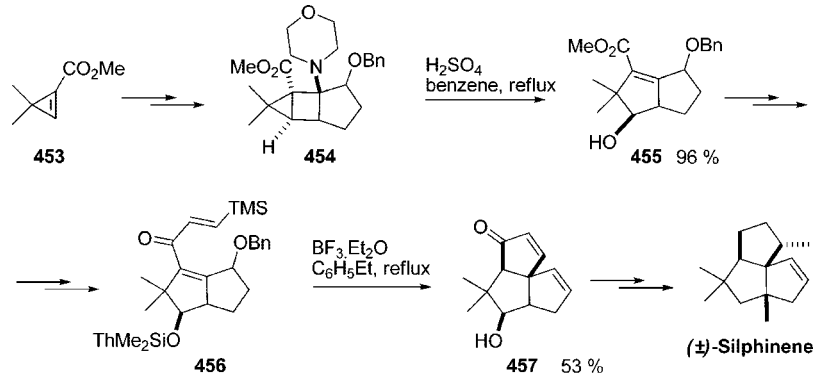
Scheme 137



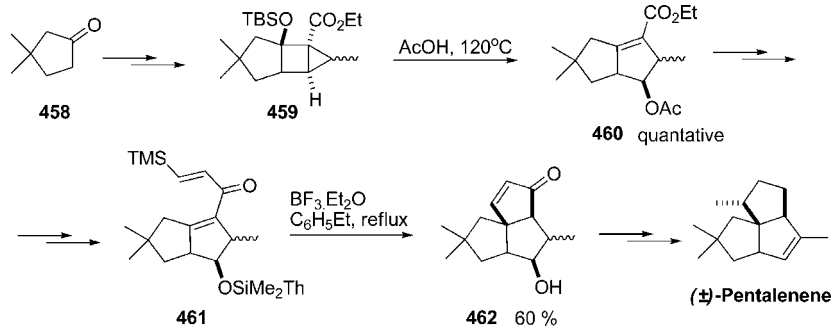
Scheme 138



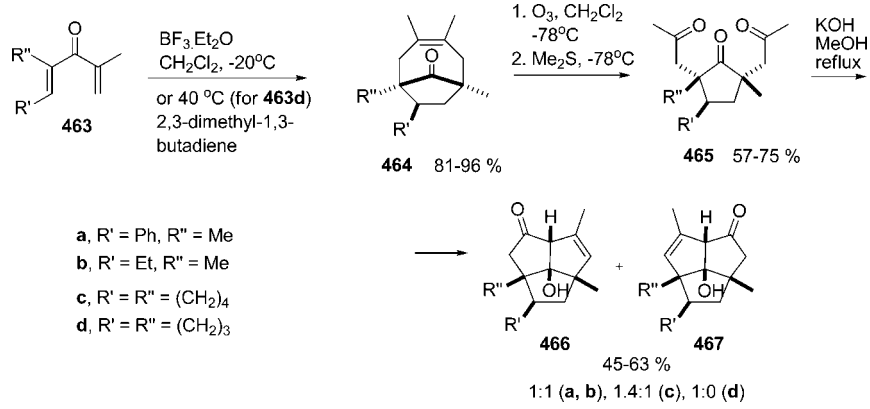
Scheme 139



Scheme 140



Scheme 141



under all conditions tested, even those that favored the formation of the rearranged product **450**.

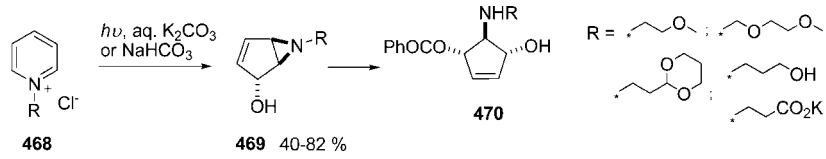
The total synthesis of a natural neurotrophic agent merrilactone A, possessing a sesquiterpene dilactone skeleton, has been achieved (Scheme 138).[432] A simultaneous creation of the C-4 and C-5 stereocenters has been accomplished stereospecifically using an unprecedented variant of the Nazarov cyclization. Therefore, the silyloxyfuran **451** has been converted into the unsaturated bicyclic lactone **452** with correct stereochemistry of the two quaternary centers in the presence of an iridium catalyst, where the cationic intermediate was quenched by silylenol ether.

The natural angular triquinane (±)-silphinene has been obtained from cyclopropene derivative **453** by consecutive acid hydrolysis and Nazarov cyclization (Scheme 139).[433] Thus, the bicyclic intermediate **455** has been isolated in quantitative yield and was further converted into bissilylated divinyl ketone **456**. The latter has been submitted to Nazarov cyclization to generate the tricyclic core of the final product in good yield and correct stereochemistry.

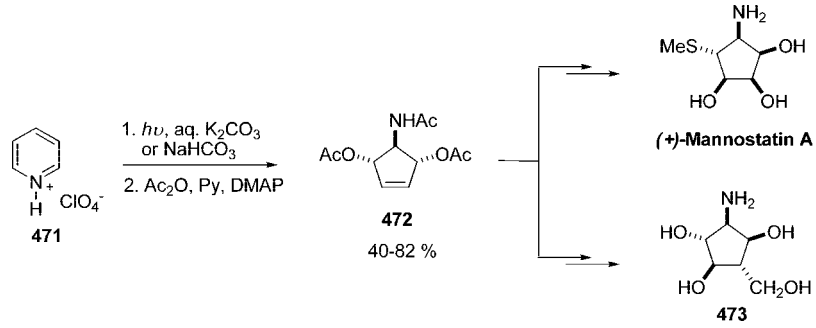
The same sequence has been applied to the synthesis of the natural antitumor and antibacterial agent illudine M[434] and linear triquinane hirsutene.[435] Similarly, an angularly fused natural triquinane (±)-pentalenene has been obtained from cyclopentanone **458** (Scheme 140).[436]

Centro-substituted triquinane skeletons have been prepared via an interrupted Nazarov reaction.[437] The [4 + 3]-cycloadducts, keto-bridged cyclooctenes **464**, have been obtained by trapping the Nazarov 2-oxidocyclopentenyl cation with symmetrical butadiene (Scheme 141). These adducts have been consecutively converted into triketones **465** and into an inseparable mixture of triquinane isomeric products **466** and **467**, possessing a hydroxyl group at the centro position, by an ozonolysis/aldol condensation sequence. The presumed mechanism for the formation of **466** and **467** was based on

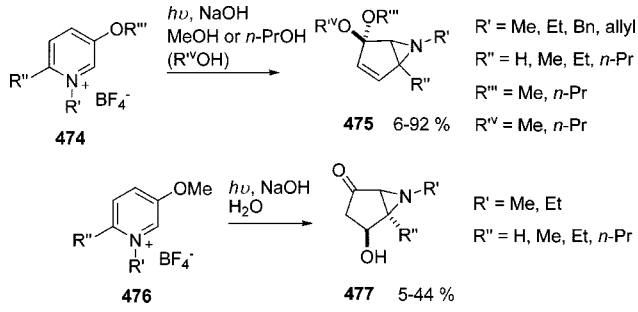
Scheme 142



Scheme 143



Scheme 144



an initial aldol closure, involving either methyl ketone side chain and the central cyclopentanone carbonyl.

6.2. Photochemical Approaches

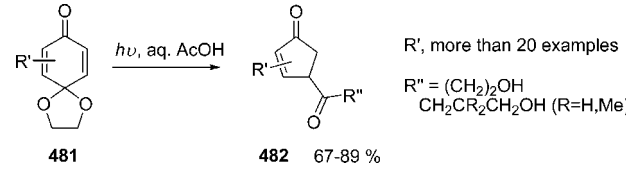
Photochemical reactions can transform structurally simple molecules into compounds with complex skeletons, often in high stereo- and regiocontrol.[438−441]

The irradiation of pyridinium salts provides the facile, stereocontrolled synthesis of a range of molecular architectures, such as bicyclic aziridines and various functionalized aminocyclopentenes.[442] A series of aminocyclopentitols **470** have been obtained by photolysis of *N*-alkylpyridinium chlorides **468** in aqueous alkaline media, leading to azabicyclic alcohols **469**, which were subsequently submitted to an opening of the aziridine ring (Scheme 142).[443] It has been found that N-substituents bearing ether, acetal, and alcohol functions did not influence significantly the photochemical reaction course.

Procedures for the enantioselective synthesis of functionalized aminocyclopentenes with applications to the preparation of biomedically relevant cyclic targets have been developed. The methods have been based on the photolysis of pyridinium perchlorate **471** to an aminodiol that was converted without isolation to its amidodiacetate derivative **472** (Scheme 143).[444] This key molecule has been further converted into the α-mannosidase inhibitor (+)-mannostatin A and to the aminocyclopentitol unit **473** of (−)-allosamizoline.[445]

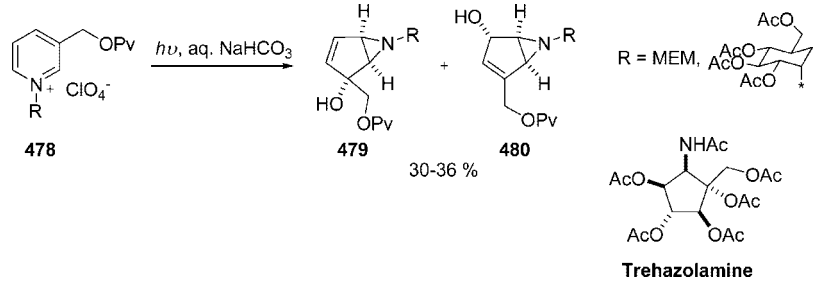
Similarly, photolysis reactions of a series of alkoxypyridinium tetrafluoroborates **474** and **476** have been studied (Scheme 144).[446] It has been shown that the irradiation performed in alcohol solution under basic conditions resulted in the formation of cyclopentenone ketal derivatives **475** by diastereoselective incorporation of the alcohol solvent while the irradiation performed in water solution yielded stereoselectively β-hydroxycyclopentanones **477**. The former reaction has been found to be much more efficient than the latter one.

Scheme 146

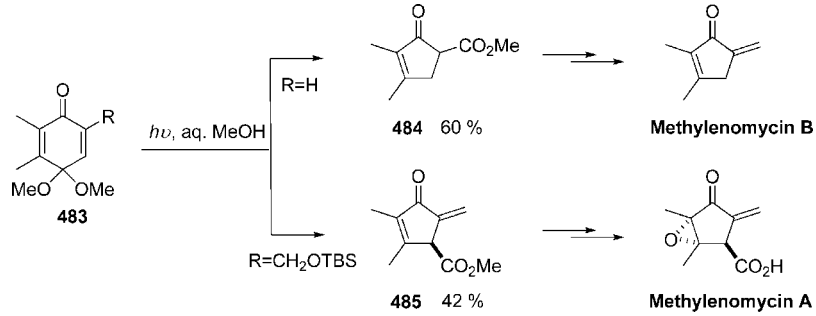


The photochemical conversion of alkoxypyridinium perchlorates **478** into bicycloaziridines **479** has been applied as a key step in the enantio-divergent sequence for the synthesis of the natural (+)-trehazolamine, the aminocyclitol core of the potent trehalase inhibitor trehazolin, and its unnatural (−)-enantiomer. The aziridine intermediates **479** and **480** have been obtained as a separable mixture in the case of the

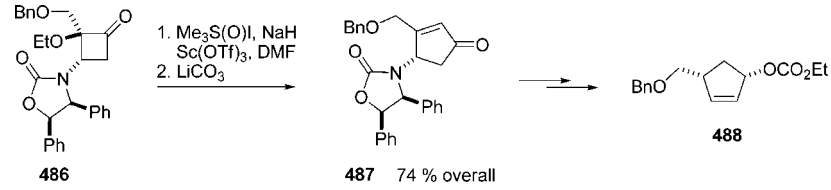
Scheme 145



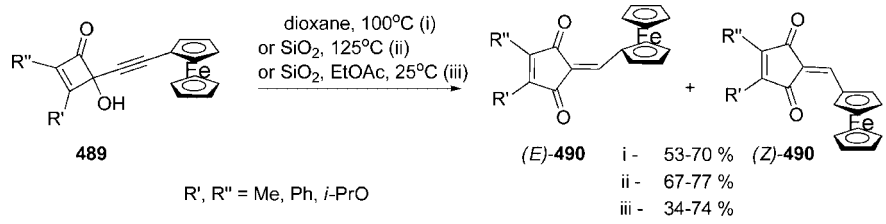
Scheme 147



Scheme 148



Scheme 149



N-methoxymethyl derivative, while only a partial separation was achieved with the tetraacetylglucosyl substituent (Scheme 145).[447]

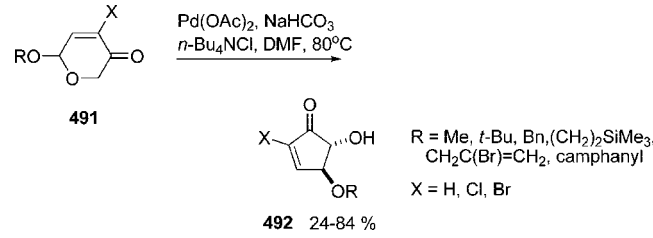
The photochemical rearrangement of quinone cyclic monoketals **481** to the corresponding carboxy-substituted cyclopentenones **482** has been studied (Scheme 146).[448] The reactions performed in acidic media have been generally explained by the classical mechanism for cyclohexadienone photochemical (di-π-methane) rearrangements: photocyclization to a cyclopropane-oxyallyl cation that is protonated, followed by solvolysis. It has been found that with a substituent at the β-position of the quinone monoketal, the rearrangement selectivity was modestly in favor of the more substituted alkene product, while with a substituent at the α-position of the quinone monoketal, the rearrangement selectivity was strongly in favor of the less substituted alkene product.

Photochemical rearrangements of masked *p*-benzoquinones **483** have been achieved as key steps in the formal synthesis of natural antibiotics (±)-methylenomycins A and B (Scheme 147).[449] It was suggested that the photorearrangement of **483** occurred via their n → π^* triplet states and cyclopentenones **484** and **485** were formed through bicyclo[3.1.0]hexenone intermediates.

6.3. Ring-Size Modifications

A one-pot ring expansion of cyclobutanones and subsequent elimination of ethanol leading to cyclopentanones has been developed (Scheme 148).[450] It has been proposed that the ring expansion occurred as a two-step process, involving conversion into spiro epoxides by reaction with a sulfur ylide, followed by Lewis acid-catalyzed iodohydrin formation, and rearrangement to the cyclopentyl compounds. Application

Scheme 150



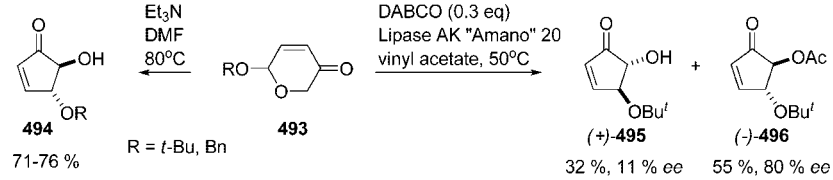
of the methodology to known cyclobutanone **486** provided the corresponding cyclopentenone **487** as the sole regioisomer, which was successfully converted to (+)-carbovir and (+)-aristeromycin carbocyclic core **488**.

A squarate-based synthesis of ferrocenylidene cyclopentenediones **490** has been reported (Scheme 149).[451] The rearrangement has been achieved both by a typical thermolysis procedure and under solvent-free conditions. The products have been obtained predominantly as the *E*-isomers in good yields.

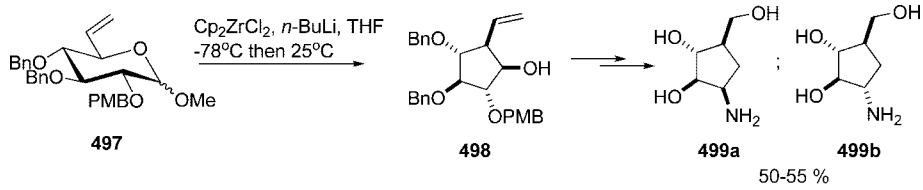
A practical procedure for the preparation of highly functionalized cyclopentenones **492**, based on palladium-assisted diastereoselective ring contraction of alkoxy-substituted dihydropyranones **491**, has been reported (Scheme 150).[452] The target carbohydrate building blocks **492** have been obtained in good yields and excellent *trans* selectivity.

The rearrangement has been further optimized,[453] and it has been found that homogeneous conditions reduced the reaction times and substantially improved reproducibility and yield. The scope and limitations with respect to the substitution pattern of the alkoxy-oxacyclohexenone **492** have been explored, and it was shown that the product yield increased with decrease in the leaving ability of the C-alkoxy group.

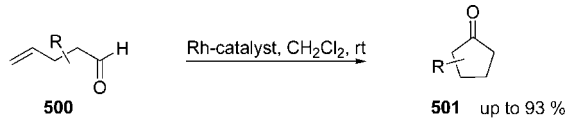
Scheme 151



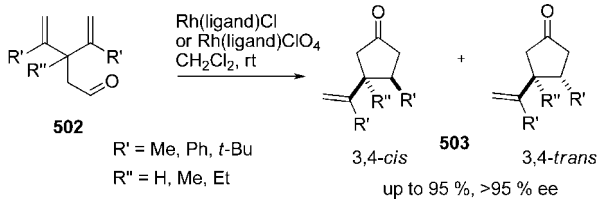
Scheme 152



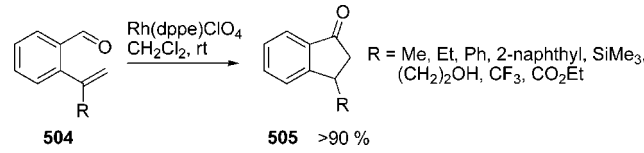
Scheme 153



Scheme 154



Scheme 155



Additionally, the potential of the resulting cyclopentenones **492** in natural product synthesis has been demonstrated.

The protocol has been applied as a key step in the synthesis of the cyclopentane motif of natural dienediyne chromoprotein antibiotics.[454] The base-mediated isomerization of pyranones **493** has been achieved stereoselectively and 1,2-*trans* dihydroxylated cyclopentenones **494** were isolated in good yields on large scales (Scheme 151). It has been observed[455] that the reactivity of a pyranone was dependent on the substrate structure or the reaction conditions, on the nature of the amine base, and on the solvent as well. By variation of all these factors, it was found that the optimum conditions involved treatment of the pyranone **493** with triethylamine in hot DMF. Recently, it was found that the rearrangement could be performed under milder conditions by using DABCO as organocatalyst with simultaneous enzymatic kinetic resolution.[456]

The ring contraction of the 6-enopyranoside **497** has been achieved in the presence of zirconocene equivalent reagent, and the corresponding highly hydroxylated cyclopentane derivative **498** was obtained without cleavage of the protecting group (Scheme 152).[457] The product has been further converted into aminocyclopentitols **499**, and it was found that (1*R*,2*R*,3*R*,5*R*)-isomer **499a** possessed high activity against α-mannosidase.

6.4. Transition Metal-Catalyzed Transformations

The rhodium(I)-catalyzed intramolecular hydroacylation of unsaturated aldehydes **500** has been investigated and a series of cyclopentanones **501** with a variety of substitution patterns has been obtained (Scheme 153).[458] Three catalyst systems have been obtained by addition of aryl or alkyl phosphines to chlorobis(cyclooctene)rhodium(I) and applied to the efficient preparation of the target cyclopentanones **501**, including spirocyclic and fused bicyclic products. It has been shown that alkyl substitution in either the 2 or the 5 position substantially reduced the yield of ketone, while disubstitution in the 2 position gave rise to ethyl ketones instead. Furthermore, it has been demonstrated that the transformation was tolerant of almost all important organic functionalities except amines.

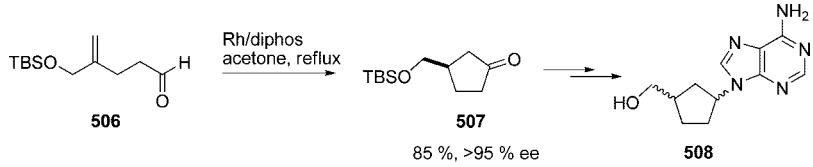
An asymmetric version of the cyclization has been achieved by using Rh-complexes with (*R*)- or (*S*)-BINAP ligands.[459] Thus, the symmetrically 3,4-disubstituted (**502**, R″ = H) and 3,3,4-trisubstituted 4-pentenals (**502**, R″ ≠ H) have been converted into the corresponding cyclopentanones **503** with excellent stereocontrol (Scheme 154). It has been found that the use of a neutral Rh[(*R*)-BINAP]Cl provided *cis*-3,4-disubstituted (4*R*)-cyclopentanones, while a cationic Rh[(*R*)-BINAP]ClO_4 led to *trans*-3,4-disubstituted (4*S*)-products.

Similarly, a series of chiral 3-substituted indanones **505** has been prepared from 2-vinyl benzaldehydes **504** (Scheme 155).[460] The indanone products **505** were obtained in very high yields without the formation of any side products. It has been shown that additions proceeded efficiently using only 1 mol % of the rhodium(I) catalyst and that simple aliphatic and aromatic substituents as well as electron-withdrawing and electron-donating groups were compatible with the reaction conditions.

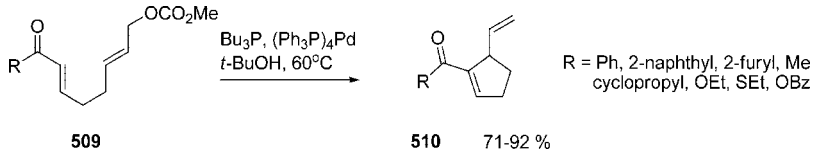
The enantioselective rhodium/DuPhos-catalyzed hydroacylation reaction has been applied as the key step in the synthesis of D- and L-carbocyclic nucleosides **508** (Scheme 156).[461] In this context, the pentenal **506** has been converted into cyclopentenone **507** in high yield and excellent stereoselectivity. The reaction conditions have been optimized, and the best results were obtained by using 5 mol % catalyst at 65 °C. Several catalysts have been examined, and the highest activity was achieved with 1,3-bis(diphenylphosphino)propane as ligand, which formed a five-membered ring upon coordination at the metal.

Organic and transition metal catalysis have been merged in the intramolecular enone cycloallylation of monoenone

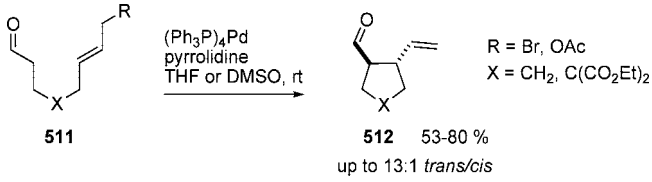
Scheme 156



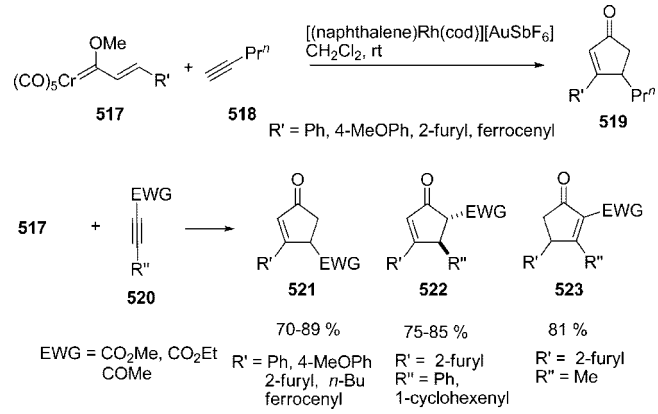
Scheme 157



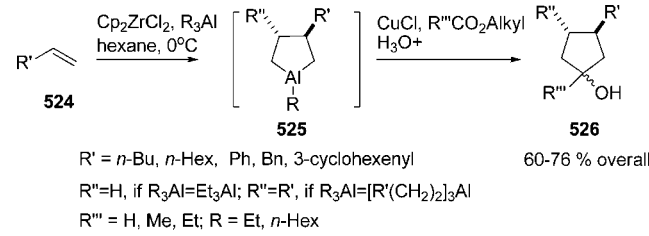
Scheme 158



Scheme 160



Scheme 161



monoallylic acetate **509** (Scheme 157).[462] The cyclopentene derivatives **510** have been obtained in high yields by using tributylphosphine and $Pd(Ph_3P)_4$ as nucleophilic and electrophilic activators, respectively. The transformation combined the nucleophilic features of the Morita−Baylis−Hillman reaction with the electrophilic features of the Trost−Tsuji reaction.

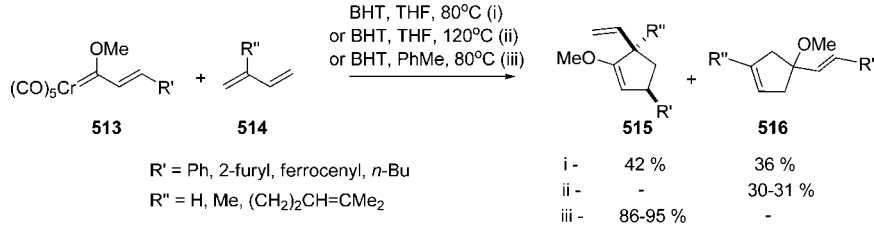
Similarly, Pd/amine catalytic synergic combination has been applied to the synthesis of a series of cyclopentane carbaldehydes **512** by Tsuji−Trost cyclization of aldehydes **511** (Scheme 158).[463] The transformation has been achieved stereoselectively, with up to 13:1 ratio of *trans*/*cis* diastereoisomers. It was suggested that the reaction evolved via an enamine intermediate of the π-allyl palladium complex. Additionally, the cyclization has been efficiently performed as an asymmetric protocol by using (BINAP)Pd, with up to 91% ee.

The intramolecular cycloaddition of chromium carbene complexes **513** with electronically neutral 1,3-dienes **514** has been studied, and a concurrence between [3 + 2] and [4 + 1] reactions was observed (Scheme 159).[464] Nearly equimolar mixtures of tetrasubstituted cyclopentene enol ethers **515** as single diastereoisomers and trisubstituted cyclopentenes **516** have been obtained in THF at 80 °C. On the other hand, the reaction performed at 120 °C led in moderate yields to [4 + 1] products **516** only, while [3 + 2] cycloaddition occurred diastereoselectively in toluene at 80 °C with high efficiency.

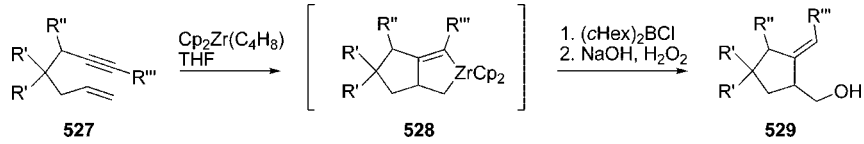
A cationic Fischer carbene of rhodium(I) has been synthesized from chromium carbene complexes via a double transfer of carbene and CO ligands, which have revealed a different reactivity than other transition metal carbenes, including their chromium precursors, toward neutral and electron-poor alkynes.[465] Thus, polysubstituted cyclopentenones **519** and **521**−**523** have been readily synthesized (Scheme 160) from chromium Fischer carbene complexes **517** and alkynes by a [3 + 2] cyclization mediated (for neutral alkynes **518**) or catalyzed (for activated alkynes **520**) by rhodium(I).

A one-pot catalytic method for the synthesis of cyclopentanols **526** based on successive transformations of olefins in the presence of Zr catalysts, evolving via *in situ* generated aluminacyclopentanes **525**, has been reported (Scheme 161).[466] The reaction represents a convenient route for the

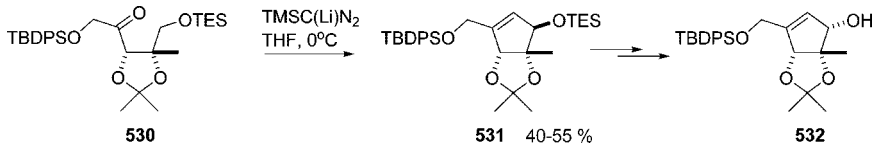
Scheme 159



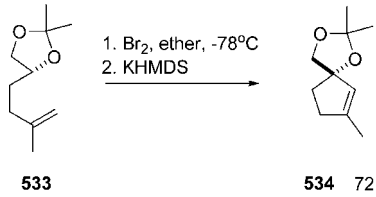
Scheme 162



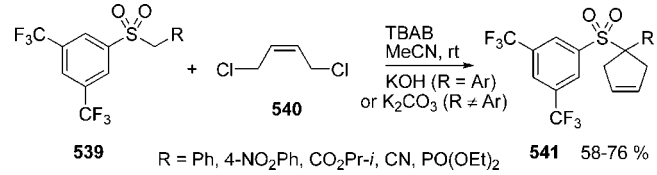
Scheme 163



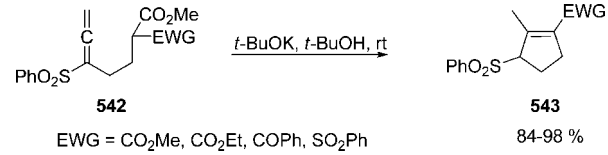
Scheme 164



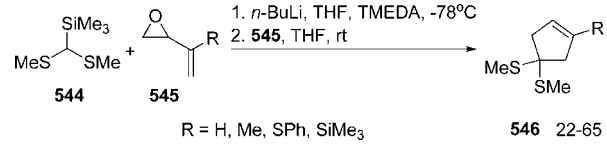
Scheme 166



Scheme 167



Scheme 168



synthesis of cyclopentanols with substitution patterns determined by the structure of the starting olefins.

The cycloalumination of olefins with triethylaluminium has been found to generate 3-substituted aluminacyclopentanes (**525**, R″ = H), while in the presence of dichloroethylaluminium, *trans*-3,4-dialkyl products were obtained (**525**, R″ = R′). These metallocycles have been converted to the corresponding cyclopentanols **526** under the action of alkyl formate and catalytic amounts of CuCl, and it was shown that the formation of two additional C−C bonds proceeded with retention of the relative configuration of the alkyl substituents.

A series of alkylidene cyclopentanes **529** has been obtained by a one-pot zirconocene-mediated enyne cyclization, boron transmetalation, and oxidation sequence (Scheme 162).[467] The oxidation of zirconocyclopent-2-enes **528** has been achieved selectively at sp^3 carbon by efficient transfer to electrophilic (^{c}Hex)$_2$BCl followed by oxidation of the resulting organoboranes. It has been shown that the protocol was compatible with a variety of enyne representatives.

6.5. Others

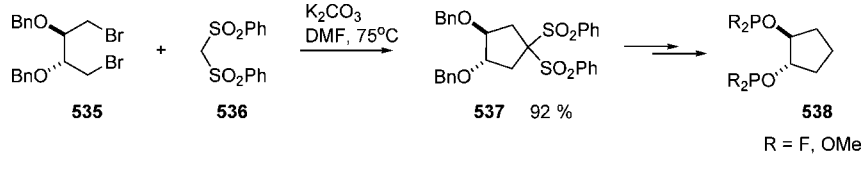
Several examples of C−H insertion without using rhodium catalysts have been reported. The carbocyclic core **532** of 2′-*β*-C-methyl-neplanocin derivatives has been obtained in correct geometry from a sugar (Scheme 163).[468] As a key step, an intramolecular C−H insertion of ketone **530** has been achieved by exposure to lithiotrimethylsilyl-diazomethane and the tetrahydroxylated cyclopentene **531** was formed as a single isomer.

The cyclization of alkene **533** to cyclopentene **534** has been applied as a key step for the total synthesis of angiogenesis inhibitor (−)-fumagillin (Scheme 164).[469] The alkylidene carbene has been generated by potassium hexamethyldisilazide from *in situ* formed bromo alkene.

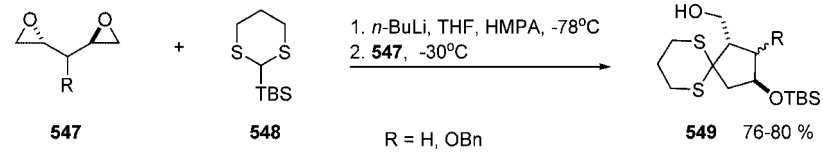
The tetrasubstituted cyclopentane **537** has been obtained from chiral dibromide **535** and bissulfonyl methane **536** as a step for the preparation of enantiomerically pure bidendate phosphate derivatives **538**, having electronic properties quite different from the classic bidendate ligands (Scheme 165).[470] The reaction conditions have been optimized, and almost quantitative conversion was achieved by using 10% excess of dibromide.

The cyclopentenes **541** were prepared in good yields under phase-transfer conditions by α,α-dialkylation reaction of the sulfone **539** with (*Z*)-1,4-dichlorobut-2-ene **540** (Scheme 166).[471] The transformation has been performed in very mild conditions due to the strongly electron-withdrawing character of the 3,5-bis-(trifluoromethyl)phenyl sulfonyl group. Therefore, the benzylic sulfones (**539**, R = Ar) were submitted to the dialkylation process by using KOH, while the activated compounds (**539**, R ≠ Ar) required a much weaker base.

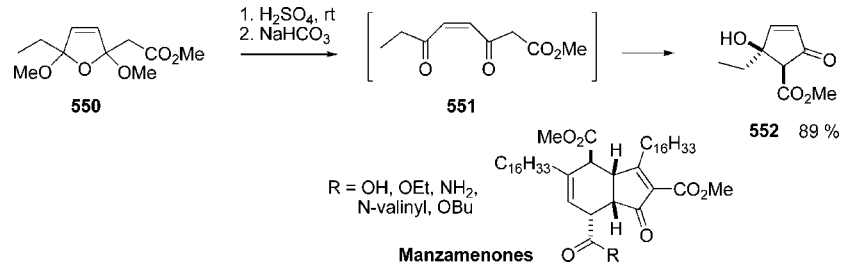
Scheme 165



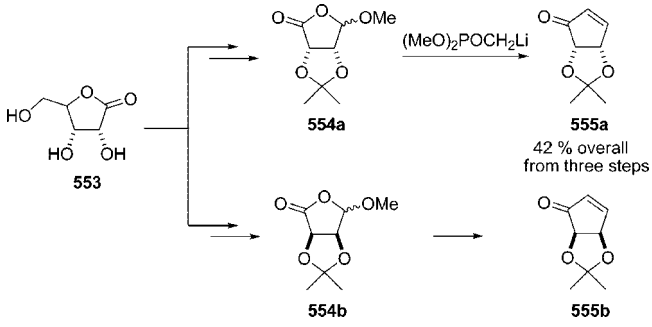
Scheme 169



Scheme 170



Scheme 171

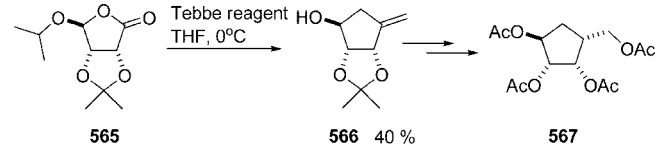


The protocol demonstrated the chemical versatility of BTFP sulfones for the synthesis of highly functionalized 3,5-disubstituted cyclopent-2-enones.

A simple and convenient procedure for the preparation of cyclopentene frameworks **543** possessing distinguishable functionalities from allenyl sulfone derivatives **542** with the active methine moiety has been developed (Scheme 167).[472] The author suggested that **543** were formed via an *endo*-mode ring closure at the sp-hybridized carbon center, followed by demethoxycarbonylation of the resulting malonate derivative.

A series of trisubstituted cyclopentenes **546** has been obtained by using the silylated thioacetal **544** as a masked

Scheme 174

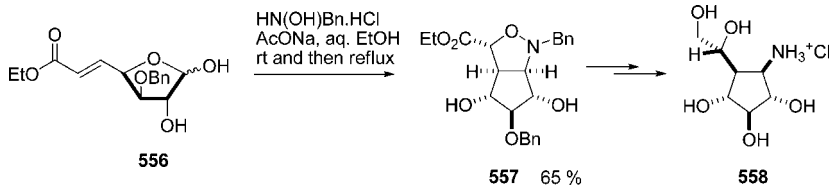


dianion and vinyloxiranes **545** as bis-electrophiles (Scheme 168).[473] The transformation proceeded as a domino process based on a 1,4-C → O shift of a silyl group and Michael-induced 5-*exo*−*trig* ring-closing reaction.

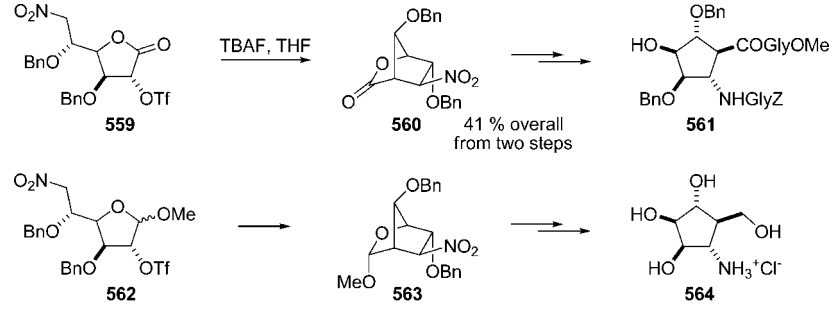
A concise synthesis of highly functionalized cyclopentane derivatives **549** has been achieved via a stereoselective linchpin cyclization reaction involving *tert*-butyldimethylsilyl-1,3-dithianyllithium **548** and homochiral 1,4-bis-epoxides **547** (Scheme 169).[474] The products were further converted into carbanucleosides[475] and carbafuranose sugars.[476]

Several approaches are based on the replacement of a heteroatom of a cyclic compound by a carbon unit. An efficient six-step protocol for the preparation of manzamenone analogues from 2-furanacetonitrile has been reported.[477] As a key step, furanone derivative **550** has been converted in excellent yield and diastereoselectivity into cyclopentenone **552** in mild acidic conditions followed by a brief base treatment. It has

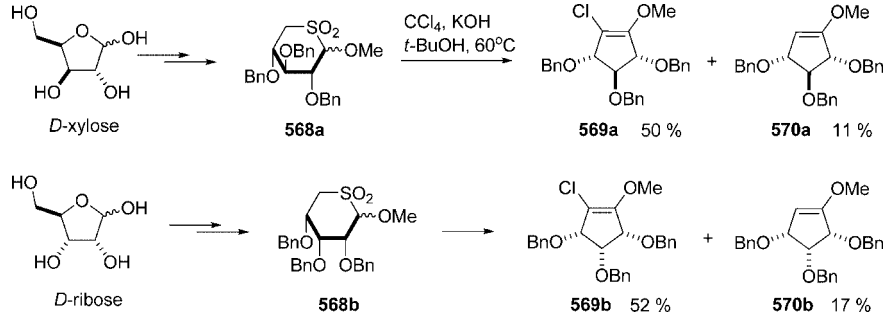
Scheme 172



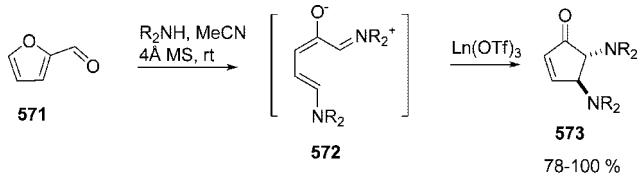
Scheme 173



Scheme 175



Scheme 176



R_2NH = Bn_2NH, $(4\text{-}MeOC_6H_4CH_2)_2NH$, $(allyl)_2NH$, morpholine, indoline, tetrahydroquinoline, tetrahydroisoquinoline

been proposed that the transformation proceeded via a 1,4-diketone intermediate **551** (Scheme 170).

A simple and efficient enantioselective preparation of hydroxylated cyclopentenones **555** has been achieved by reaction of sugar derivative **554** with lithium dimethyl methylphosphonate (Scheme 171).[478] The products are useful intermediates for the synthesis of various carbocyclic nucleosides and prostaglandins, directly from a readily available sugar **553**.

A diastereo- and regioselective synthesis of an aminocyclopentitol **558** has been achieved from D-glucose (Scheme 172).[479] The cyclopentane core was built by intramolecular [1,3]-dipolar nitrone olefin cycloaddition. Thus, the unsaturated ester **556** has been converted *in situ* to the corresponding *N*-benzyl nitrone at the hemiacetal carbon, which underwent spontaneous cycloaddition to form **557** with excellent selectivity.

An intramolecular alkylation of nitrohexofuranoses **559** and **562** to cyclopentane derivatives **560** and **563** has been achieved by treatment with tetrabutylammonium fluoride as a step in a total synthesis of a polyfunctionalized carbocyclic β-amino acid, which was further incorporated into a peptide **561** (Scheme 173).[480] The strategy also afforded an efficient route to a cyclopentylamine **564** with well-known glycosidase inhibition properties.

An efficient and highly diastereoselective approach for the synthesis of 1,2,3,5-tetraacetylcarba-α-D-lyxofuranose **567** from D-ribose has been reported.[481] As a key step, the one-pot conversion of five-membered carbohydrate lactone **565** to cyclopentitol **566** has been achieved by using Tebbe reagent (Scheme 174). The transformation involved a cascade reaction sequence of methylenation, cleavage of isopropyl group, carbocyclization, and again methylenation.

Enantiopure polyoxygenated cyclopentenes **569** and **570** have been synthesized by the Ramberg−Bäcklund rearrangement of sulfones **568** prepared from readily available thiosugars (Scheme 175).[482] The major products **569**, formed as a result of double chlorination followed by episulfone formation and loss of sulfur dioxide, have potential application in Pd-catalyzed coupling reactions, while the minor products **570** are suitable precursors for the synthesis of prostaglandin-type molecules. The protocol has been further applied to the formal synthesis of the aglycone trehazolamine from thioglucose.

A practical preparation of diaminocyclopentenones **573** via a domino ring-opening Nazarov-type electrocyclization process of 2-furaldehyde **571** and secondary amines catalyzed by Ln(III) and Sc(III) triflates has been developed (Scheme 176).[483] It has been found that secondary amines were highly efficient in the presence of Ln-triflate, while primary aliphatic amines were not reactive in general and primary anilines led to low to moderate formation of **573** by using Sc-catalyst.

The authors proposed that the transformation proceeded through a pathway involving initial ring-opening of the furan ring, presumably from the iminium ion, which would be activated toward nucleophilic attack at the 5-position followed by ring-opening to form intermediate **572**. Ring closing of the latter then led directly to the cyclopentenones **573**.

7. Conclusions

This review attempted to combine the most significant results concerning the ring-closing routes for cyclopentitol formation. The wide range of incorporation of the polyhydroxylated cyclopentane derivatives as structural subunits in biologically active substrates determines the actual interest in the development of new synthetic protocols for the construction of these fascinating molecules. More efficient synthetic methodologies are in many cases still required for short efficient enantioselective synthesis of cyclopentitols that allows more straightforward scale up under more environmentally friendly conditions.

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