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Quinic acid as a chiron in total synthesis†

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Covering: 1980 up to 2025.

Quinic acid became a versatile, accessible chiral building block for asymmetric synthesis, offering a functionalized, stereochemically rich scaffold that enables the creation of many natural products and bioactive compounds. This review covers synthetic strategies from the 1980s to 2025, highlighting quinic acid's ongoing importance in organic synthesis. It discusses its role in synthesizing carbocyclic frameworks, vitamin D analogues, carbasugars, cyclitols, aminocyclitols, lactones, alkaloids, and macrocyclic fragments. The review summarizes four decades of progress and emerging trends that reinforce quinic acid's status as a key chiral building block for complex molecule synthesis.

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1. Introduction

(−)-Quinic acid is the most naturally occurring stereoisomer of quinic acid and is systematically named as (1*R*,3*R*,4*S*,5*R*)-1,3,4,5-tetrahydroxycyclohexane-1-carboxylic acid. The D/L symbology developed by Fischer, in which the descriptor is based on its relation to a reference carbon with one of the D-(+)-glyceraldehyde, has resulted in the widespread use of "D-quinic acid" to describe such a levorotatory substance. This nomenclature issue was covered in multiple articles,[1–3] and the natural levoratory isomer (−)-quinic acid was recently identified as L.[2] Nevertheless, the natural isomer is frequently described in the recent literature and by chemical suppliers as D-quinic acid. Fig. 1 shows the IUPAC numbering system for cyclitols,[4] where the lowest numbered carbon is assigned to the substituent other than an unmodified hydroxyl group. Additionally, numbers 3 and 5 follow Maquenne's fractional system.[5]

The molecular structure of quinic acid features four stereocenters, three of them being contiguous, and with four hydroxyl groups arranged on a cyclohexane ring. This dense stereochemistry provided synthetic chemists with a ready-made, enantiopure platform for constructing complex molecules, particularly those requiring strict stereochemical control, allowing avoidance of challenging asymmetric synthesis steps. Its fixed configuration allows for regio- and stereoselective modifications using established protection, oxidation, reduction, elimination, and substitution protocols. Its value as a chiral starting material was soon recognized by the synthetic community, as demonstrated by several reviews on the use of quinic acid as a starting material for the synthesis of natural products.[6–9]

Despite the above-mentioned existence of different literature reviews demonstrating the synthetic value of quinic acid, namely the 1998 report by Barco and co-workers[6] and Enev's reviews,[8,9] there has not been a compilation on the topic since 2012. The present literature review aims to comprehensively cover all the uses of quinic acid as a starting point for total or

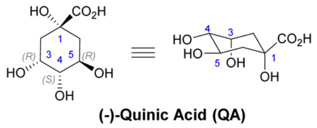

Fig. 1 Structure and numbering of (−)-quinic acid.

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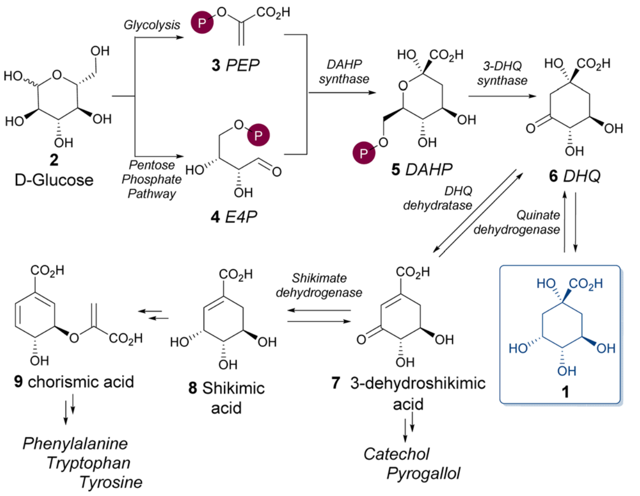
† In memory of Professor Ana M. Lobo (1945–2024).

formal synthesis of natural products and some selected related compounds, namely vitamin D derivatives. To facilitate readability, and in recognition of the impact that introducing acyl or other substituents to quinic acid's hydroxyl groups may have on the IUPAC systematic nomenclature—particularly the carbon skeleton numbering—the numbering system of unsubstituted quinic acid will be adopted throughout this manuscript. The manuscript is organized according to the type of natural product synthesised.

Quinic acid (**1**) is a secondary metabolite of the shikimate pathway (Scheme 1).[10,11] This metabolic pathway is responsible for the biosynthesis of aromatic amino acids in plants and microorganisms. Although not a direct precursor in the main shikimate pathway, quinic acid can be reconverted into 3-dehydroquinate in microorganisms,[12] serving as an alternative carbon source and establishing regulatory links with the biosynthesis of aromatic compounds. The shikimic acid pathway initiates with the condensation of phosphoenolpyruvate (**3**, PEP) and erythrose-4-phosphate (**4**, E4P), both derived from the metabolism of glucose (**2**) or other carbohydrates. This aldol-type reaction is catalyzed by DAHP synthase, an enzyme subject to feedback inhibition by the three aromatic amino acids ultimately produced through this pathway.

The product, 3-deoxy-D-arabino-heptulosonate 7-phosphate (**5**, DAHP), undergoes a complex transformation into 3-dehydroquinic acid (**6**). This conversion involves a sequence of oxidation, β-elimination of phosphate, reduction, ring opening, and intramolecular aldol condensation—all orchestrated by a single enzyme, 3-dehydroquinase synthase. 3-Dehydroquinic acid (**6**, DHQ) can either reversibly convert into quinic acid (the biosynthetic quinate pathway) or proceed towards shikimic acid (**8**) formation (shikimate pathway) *via* dehydration and reduction, catalyzed by DHQ dehydratase and shikimate dehydrogenase, respectively. Shikimic acid then undergoes a series of transformations into chorismic acid, ultimately taken into the synthesis of the aromatic amino acids.



Scheme 1 Biosynthetic pathway for the production of quinic acid (shikimate pathway). Abbreviations: PEP, phosphoenolpyruvate; E4P, erythrose-4-phosphate; DAHP, 3-deoxy-D-arabino-heptulosomate-7-phosphate; DHQ, 3-dehydroquinic acid.

Quinic acid was first isolated as an impurity in crude quinine in 1790,[13] but its structure and stereochemistry were fully assigned only in 1932, by Fischer and Dangschat[14] when isolating 3-*O*-caffeoylquinic acid from green coffee beans. Structural elucidation was further complemented by Haslam and Turner in 1971, with NMR studies[15] and by Allen and coworkers in 1988 with a crystal structure.[3]

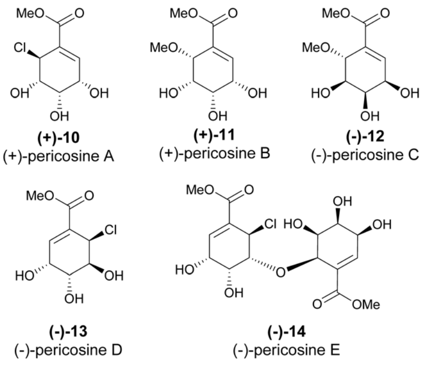
2. Synthesis of carbacycles

Carbacycles, which are ring systems made exclusively of carbon atoms, are fundamental in organic chemistry and natural product synthesis. Quinic acid, featuring a cyclohexane ring heavily substituted with hydroxyl groups and a carboxyl group, offers a valuable starting point for such frameworks. This chapter discusses approaches that utilize quinic acid as a chiral template for carbacycle synthesis, highlighting the synthesis of carbacycles with biological relevance.

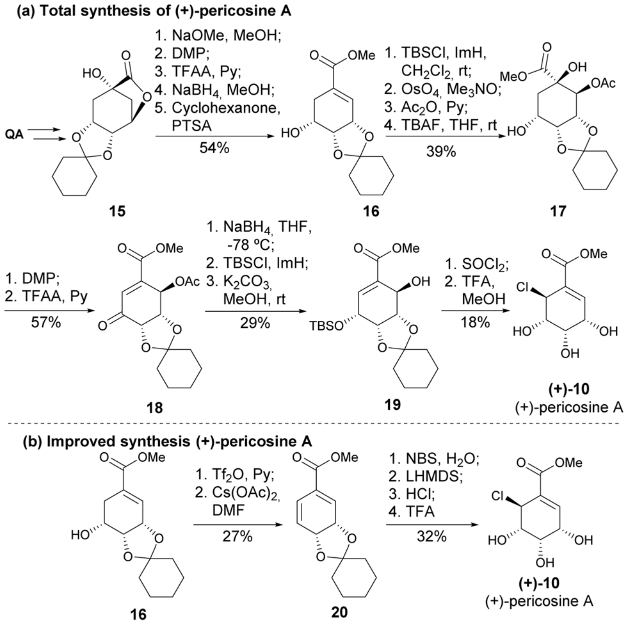
Usami and coworkers conducted extensive research on the total synthesis of pericosines (A to E) from quinic acid. Pericosines (Scheme 2) are natural products isolated from fungus *Periconia byssoides*, found in the gastrointestinal tract of *Aplysia kurodai* sea hare, and display *in vitro* antitumor activity.[16,17]

Usami's research on the total synthesis of (+)-pericosine A resulted in a revision of its original stereochemical assignment, as well as clarifying the structures of other pericosines due to spectral discrepancies between the synthetic sample and the naturally isolated molecule.[16,18] The group designed another synthetic strategy to obtain the *de facto* (+)-pericosine A from quinic acid (Scheme 3a), as well as two other diastereomers.[19,20] The synthetic strategy relied first on the oxidation followed by reduction, aiming at the inversion of the configuration of C5 and regioselective TFAA-mediated dehydration; however, the large number of protection steps highly impacted the overall yield. Later, Usami and his team devised a more efficient route with fewer protection steps, thus significantly increasing the overall yield of the natural product from quinic acid from 0.57% to 11.7% (Scheme 3b).[21]

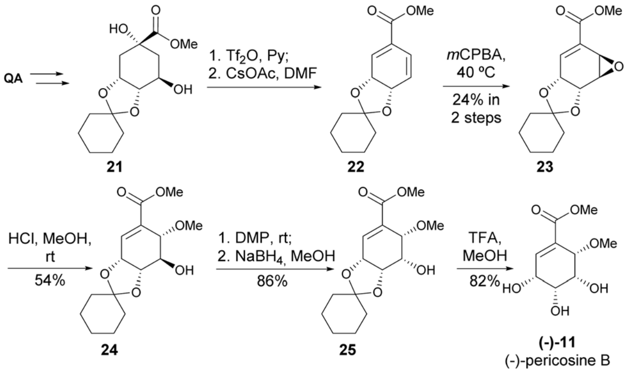
While initially thought that only (+)-pericosine B existed in nature, it was later discovered that both pericosines B and C exist as enantiomeric mixtures when isolated from *Periconia byssoides*.[22] The synthesis of (−)-pericosine B (Scheme 4) was



Scheme 2 Structures of some naturally occurring pericosines.



Scheme 3 (a) Total synthesis of (+)-pericosine from quinic acid; (b) improved total synthesis of (+)-pericosine A.

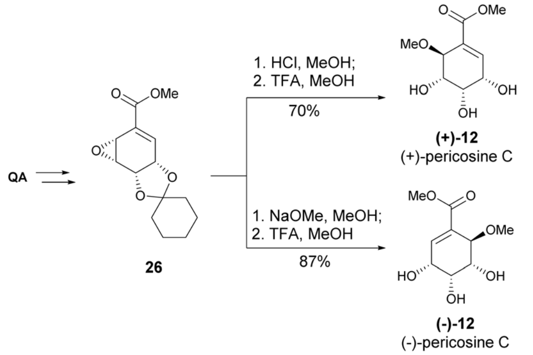


Scheme 4 Total synthesis of (−)-pericosine B.

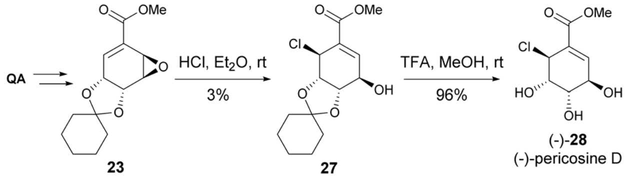
accomplished within seven steps from cyclohexylidene-protected methyl quinate **21**, where *m*CPBA demonstrated low conversion and regioselective epoxidation of **22**. The acid-catalysed opening of the epoxide **23** was accomplished with moderate yield. As the final significant step, the stereocenter at C5 was inverted with oxidation of **24** with DMP, followed by reduction with $NaBH_4$.[23,24]

Both enantiomers of pericosine C were synthesized from quinic acid-derived epoxide **26**, where, after cyclohexylidene ketal deprotection, the acid- and base-catalysed epoxide opening yielded (+) and (−)-pericosine C, respectively (Scheme 5).[21]

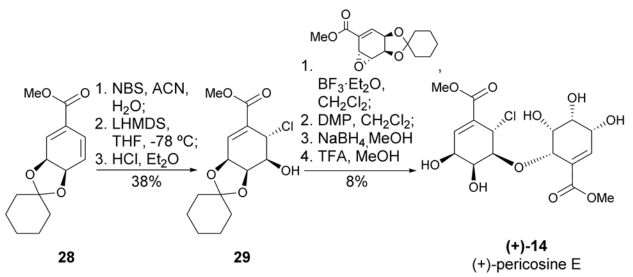
The synthesis of the diastereomers of pericosine A mentioned above proved useful in the confirmation of the relative configuration of pericosine D.[25] Although the synthetic strategy was not optimized, it provided enough material to



Scheme 5 Total synthesis of (+) and (−)-pericosine C.



Scheme 6 Total synthesis of pericosine D.

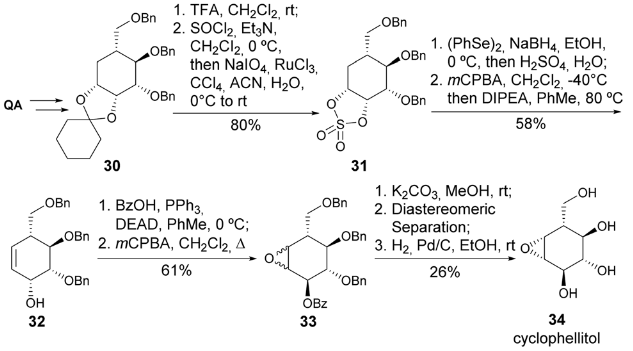


Scheme 7 Synthesis of (+)-pericosine E.

compare to the spectroscopical data (aside from specific rotation) of (−)-pericosine D (Scheme 6).[26]

Chlorohydrin **29** was prepared from QA, which, following its reaction with an epoxide derived from shikimic acid, permitted the synthesis of (+)-pericosine E – the only *O*-linked carbohydrate identified in pericosines (Scheme 7).[27] The formation of the ether bond was achieved in 52% by using $BF_3 \cdot Et_2O$ as a catalyst (10 mol%), whilst the oxidation-reduction sequence resulted in a more modest yield of 34%.

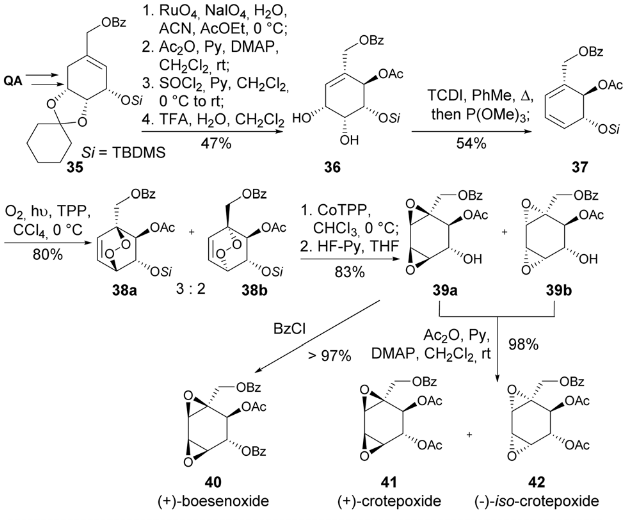
Shing and colleagues have reported the total synthesis of cyclophellitol, initially isolated from the culture filtrates of the mushroom *Phenellinus* sp. and known as a potent inhibitor of β-D-glucosidase.[28,29] The main steps for the synthesis of cyclophellitol involved regiospecific sulphate opening, regiospecific oxidative elimination, and epoxidation in 15 steps from quinic acid (Scheme 8). In the same work, the synthesis of the (1*R*,6*S*) and (1*R*,2*S*,6*S*) diastereomers was also reported, similarly achieved in 15 steps from quinic acid. Later, Shing and coworkers prepared 6-deoxy-1,2-anhydro analogs of cyclophetilol and evaluated their anti-glycosidase activity.[30]



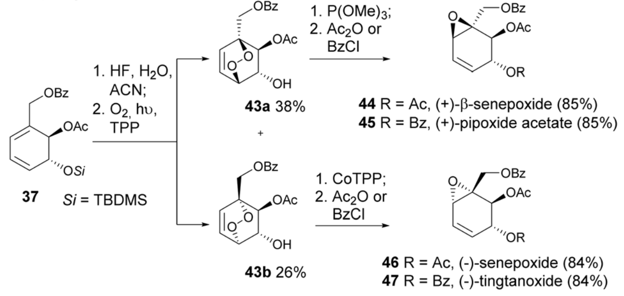
Scheme 8 Total synthesis of cyclophellitol.

(+)-Crotepoxide and (+)-boesenoxide are naturally occurring cyclohexene oxides found in the fruits of *Croton macrostachys* and *Piper futokadzura*.[31,32] (+)-β-Senepoxide and (+)-pipoxide, have been isolated from *Piper hookeri* and *Uvaria catocarpa*, respectively.[33] These cyclohexene oxides and related analogues display significant biological properties, such as tumour inhibition, anti-leukemic effects, and antibiotic activity. They were synthesized from quinic acid, primarily through a strategy where the main steps of the synthetic strategy involved Corey–Winter olefination with thiocarbonyldiimizadole (TCDI) and trimethyl phosphite, singlet photooxygenation mediated by tetraphenylporphyrin (TPP) and endoperoxide rearrangement facilitated by cobalt-TPP (Scheme 9).[33,34]

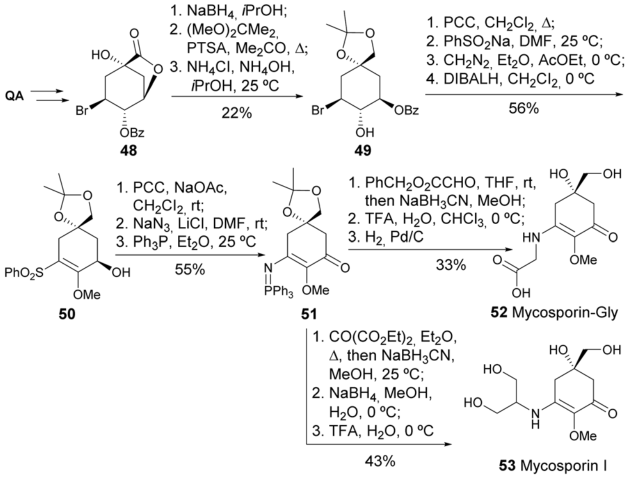
(a) Synthesis of (+)-crotepoxide, (-)-*iso*-crotepoxide and (+)-boesenoxide



(b) Synthesis of (+)-β-senepoxide, (+)-pipoxide acetate, senepoxide and (-)-tingtanoxide



Scheme 9 (a) Synthesis of (+)-crotepoxide, (−)-iso-crotepoxide and (+)-boesenoxide; (b) synthesis of (+)-β-senepoxide, (+)-pipoxide acetate, senepoxide and (−)-tingtanoxide.



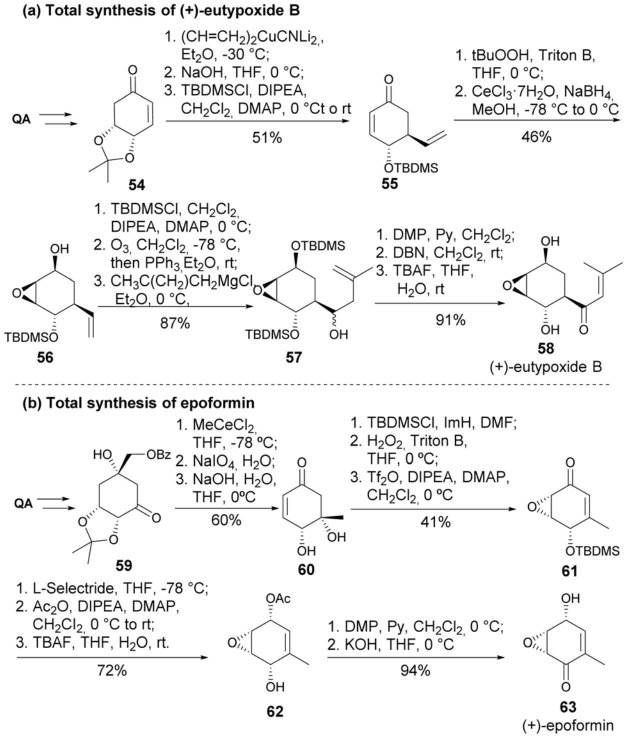
Scheme 10 Synthesis of Mycosporin-Gly and Mycosporin-l.

The mycosporin-like amino acids represent a structurally unique class of metabolites produced by various aquatic organisms, making them very attractive to the cosmetic industry, particularly as UV blockers.[35] Quinic acid was used as a chiral scaffold for the synthesis of Mycosporin-Gly and Mycosporin-l, where the key steps were the Staudinger reaction followed by Aza–Wittig reaction (Scheme 10).[36,37]

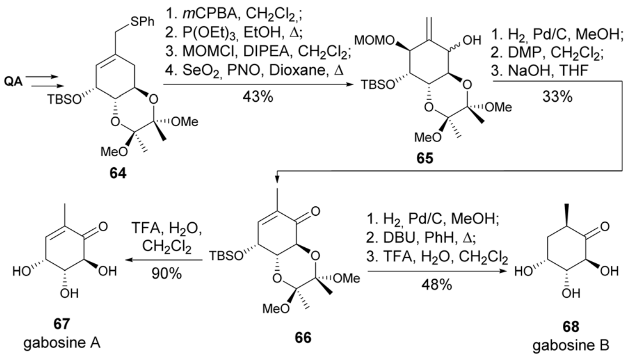
Barros and coworkers presented the synthesis of a metabolite isolated from the culture medium of the fungus *Eutypa lata*, (+)-eutypoxide B. The key step was the epoxidation of TBDMS-enone (**55**), where the bulkiness of the silyl-protecting group and the oxidizing agent were crucial for achieving good diastereoselectivity at the epoxide intermediate (Scheme 11a).[38] Additionally, reports from the same group described the total synthesis of (+)-epoformin (Scheme 11b), an antibiotic derived from the culture broth of *Penicillium claviforme*. The key step, again, was the epoxidation, and in this case, using a less bulky oxidizer (H_2O_2) has been shown to yield better diasteroselectivity.[39]

The gabosines are secondary metabolites isolated from various strains of *Streptomyces* bacteria. Quinic acid was used in the enantioselective synthesis of gabosines A and B (Scheme 12) and the synthesis of enantiomers of gabosines D and E. The key steps involved a Mislow–Evans rearrangement to reach the *exo*-methylene alcohol **65** and a DBU-assisted epimerization in the synthesis of gabosine B.[40]

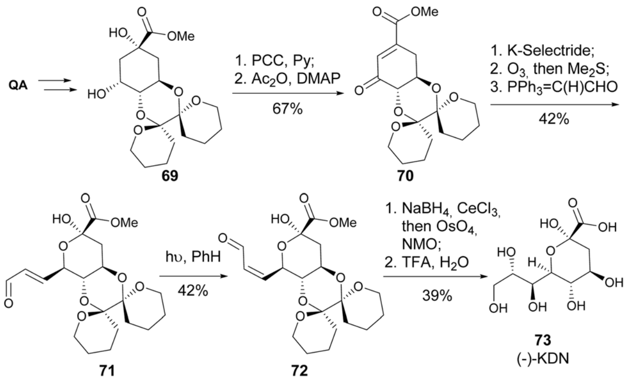
3-Deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (Kdn) is a member of the sialic acid family, which plays a crucial role in mediating and regulating a wide range of physiological and pathological processes.[41] Banwell and co-workers synthesized (−)-Kdn and two of its epimers from quinic acid, where the key step was the photoisomerization of the unsaturated aldehyde **71** to its *Z*-isomer. The enal **72** was submitted to Luche reduction, OsO_4-catalysed dihydroxylation and, after removal of the



Scheme 11 Natural products synthesized by Barros *et al.* (a) total synthesis of (+)-eutypoxide B; (b) total synthesis of epoformin.



Scheme 12 Total synthesis of gabosines A and B.



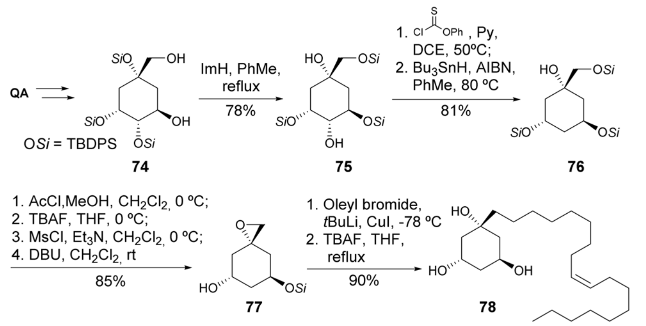
Scheme 13 Total synthesis of (−)-Kdn.

protecting group, (−)-Kdn was obtained as a single diastereomer (Scheme 13).[42]

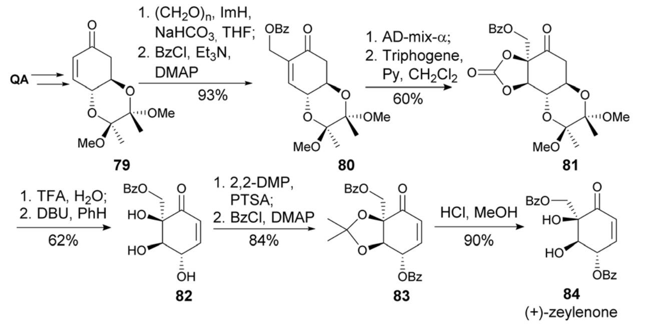
Holmstedt *et al.* reported the use of quinic acid for the total synthesis of a metabolite[43] isolated from the African ant *Crematogaster nigriceps*.[44] The main step in this process was the base-promoted silyl migration, where three types of migration could be obtained and optimized by varying the silyl group, base, and solvent. Two other key steps were the Barton–McCombie deoxygenation and the epoxide opening with oleyl lithium (Scheme 14).

(−)-Zeylanone, a natural product isolated from *Uvaria grandiflora*,[45] demonstrated to be a potent antitumor agent, suppressing myelogenous leukemia, cervical carcinoma, prostate and gastric cancer.[46,47] Motivated by the need to clarify the structure-activity relationship of zeylanones, Sun and coworkers developed a synthesis of the (+)-enantiomer in 13 steps from quinic acid with a 10% overall yield. The main step was the Sharpless asymmetric dihydroxylation (Scheme 15).[48]

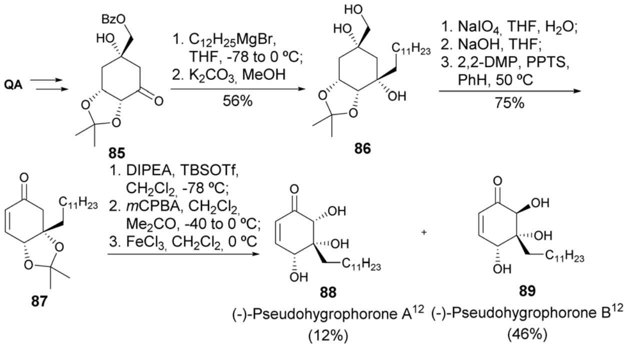
Pseudohygrophorones A[12] and B[12] were derived from the fungus *Hygrophorus abieticola*, and showed notable activity against the plant pathogenic fungi *Septoria tritici* and *Botrytis cinerea*, as well as the oomycete *Phytophthora infestans*.[49] A total synthesis of those compounds, starting from quinic acid, had as key steps the diastereoselective 1,2-addition of dodecylmagnesium bromide to a quinic acid-derived cyclohexanone **85**, producing a single diastereomer of the tertiary alcohol. The use of *m*CPBA afforded good chemoselectivity toward Rubottom oxidation over epoxidation of the less activated C=C bond



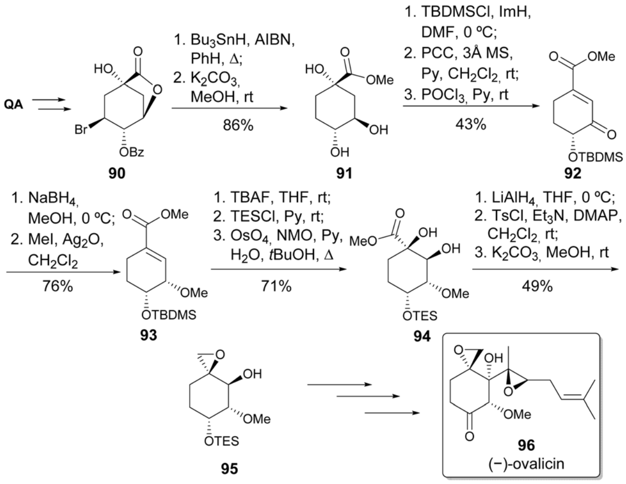
Scheme 14 Total synthesis of a metabolite isolated from the African ant *Crematogaster nigriceps*.



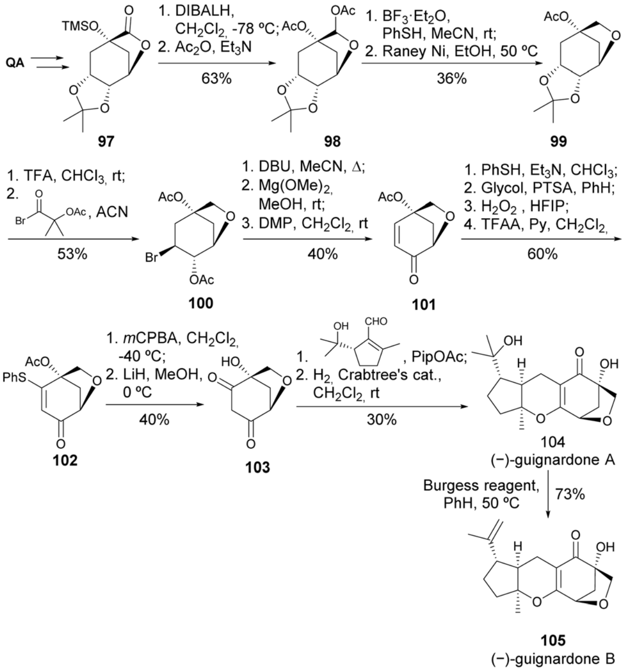
Scheme 15 Total synthesis of (+)-zeylenone.



Scheme 16 Total synthesis of (−)-pseudohygrophorones A^{12} and B^{12}.



Scheme 17 Formal synthesis of (−)-ovallicin.



Scheme 18 Total syntheses of guignardones A and B.

(Scheme 16). The removal of the acetonide with FeCl$_3$ resulted in the formation of the epimeric forms of pseudohygrophorones A^{12} and B^{12}.[50]

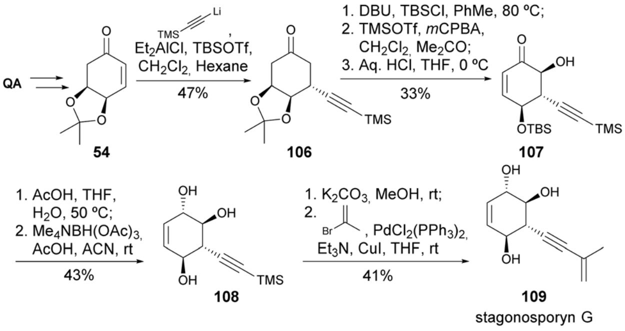
Barco *et al.* reported the formal synthesis of (−)-ovalicin,[51] a sesquiterpene isolated from the culture of the fungus *Pseudorotium ovalis* Stolk.[52] The main steps in this synthetic sequence for the formation of synthetic intermediate **95** were the debromination of **90** with Bu$_3$SnH and the formation of the epoxide by intramolecular Williamson ether synthesis (Scheme 17).[51] The epoxide **95** had been previously converted into (−)-ovalicin by Barton and co-workers in three additional steps (oxidation, Shapiro reaction with the corresponding vinyl lithium, and Sharpless epoxidation).[53]

Guignardones A, B, and C were first isolated by Tan *et al.* from *Guignardia mangiferae* cultures, and they possess a characteristic 6-oxabicyclo[3.2.1]octane framework.[54] There are at least 12 types of guignardones with a wide range of bioactivities, but guignardone B stood out among the others by having the most potent inhibition of *Candida albicans*, with an MIC of 15.5 μg mL^{-1}.[55] QA was used as a chiral scaffold for the synthesis of guignardones A and B, in 19 and 20 steps, respectively. The main stages of this synthetic route involved constructing the 6-oxabicyclo[3.2.1] octane core and performing the Knoevenagel condensation-6π-electrocyclization with the unsaturated aldehyde. Dehydration of guignardone A with Burgess reagent yielded guignardone B in 73% yield (Scheme 18).[56]

Stagonosporynes can be isolated from *Parastagonospora nodorum* fungus, being the major pathogen of wheat. The synthesis of stagonosporyne G was recently achieved from quinic acid-derived enone **54** in 8 steps, with the key steps being carefully studied, namely the conjugate addition of lithium TMS-acetylene to the enone and the Rubottom oxidation with TMSOTf and *m*CPBA (Scheme 19).[57]

3. Synthesis of vitamin D and derivatives

Vitamin D, in its active form, calcitriol, broadly affects calcium metabolism and immune regulation. Novel analogs can be engineered to selectively target specific pathways, to improve certain biological functions while reducing side effects. This is

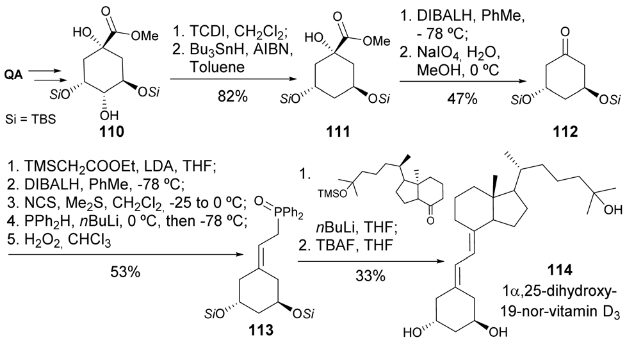


Scheme 19 Total synthesis of stagonosporyne G.

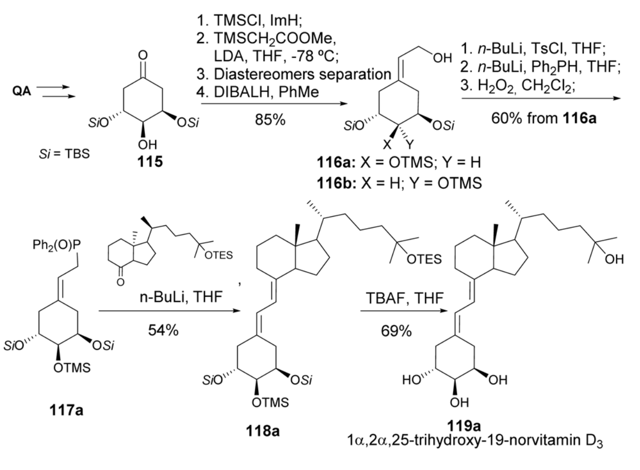
especially vital for diseases like osteoporosis, rickets, and chronic kidney disease, where vitamin D is essential for maintaining balance in calcium and phosphate levels.[58] The reader is directed to other reviews on the synthesis of 19-nor type vitamin D derivatives, in which QA takes a role other than the one covered in the present article.[59,60]

DeLuca and his team have significantly contributed to the synthesis of new vitamin D analogs since the early 1990s. Quinic acid has been extensively utilized as a chiral scaffold for constructing the ring A of vitamin D. In their initial research, quinic acid was transformed into di-TBS cyclohexanone **112** by deoxygenating the hydroxyl groups on C1 and C4 through oxidative cleavage using $NaIO_4$ and Barton–McCombie conditions, respectively (Scheme 20). Cyclohexene phosphine oxide **113** was synthesized through a laborious yet effective method, which, under Wittig–Horner conditions, followed by TBDMS deprotection, yielded 1α,25-dihydroxy-19-nor-vitamin D3 **114**.[61] The same coupling was used for the synthesis of both pure diastereomers of triol 1α,2,25-trihydroxy-19-norvitamin D3. The diastereomers were subjected to the same transformations after separation by HPLC, which was followed by the Peterson reaction with methyl (trimethylsilyl)acetate (Scheme 21).[62]

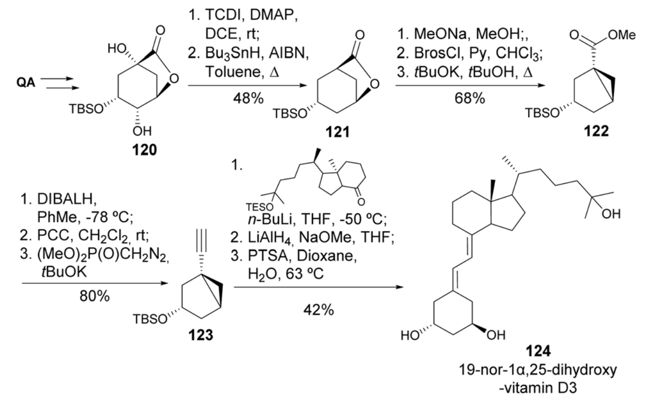
An alternative method for modifying QA during the preparation of 1α,25-dihydroxy-19-nor-vitamin D3 was reported by Vandewalle and co-workers (Scheme 22).[63] The silyl-protected lactone **120** was submitted to Barton–McCombie deoxygenation of both exposed hydroxyl groups to provide **121**. The lactone ring was opened by methanolysis, and the hydroxy group was transformed into brosylate, followed by an intramolecular alkylation of the ester-enolate formed by treatment with *t*BuOK. The carboxylic ester **122** was converted into the corresponding aldehyde, to follow a Seyferth–Gilbert homologation to the terminal alkyne **123**. Coupling of the two fragments, followed by reduction and solvolysis of the obtained allylic alcohol under acidic conditions, afforded the 1α,25-dihydroxy-19-nor-vitamin D3 **124**. The bulkiness from the ring derived from quinic acid was found to be crucial to obtain the desired *trans*-configuration.



Scheme 20 Synthesis of 1α,25-dihydroxy-19-nor-vitamin D3.

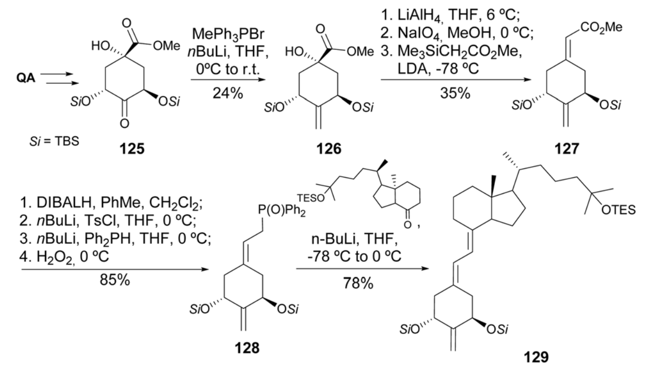


Scheme 21 Synthesis of 1α,2β,25-trihydroxy-19-norvitamin D3.

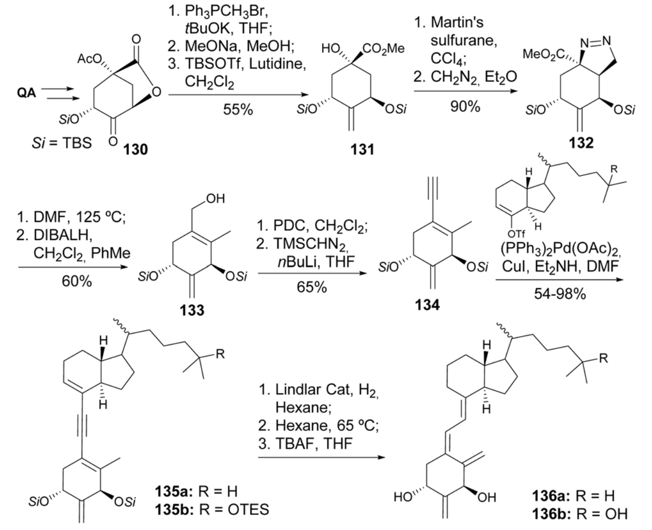


Scheme 22 Vandewalle synthesis of 19-nor-1α,25-dihydroxy-vitamin D3.

The preparation of norvitamin D3 derivatives containing 2-hydroxymethyl, 2-methyl, and 2-methylene substituents was achieved starting with the synthesis of the QA-derived ketone **125**, and its conversion into 2-methylene unit **127** (Scheme 23). The coupling of the QA and the 9,10-*seco* steroid skeletons was achieved through the same Peterson olefination of the cyclohexanone derivative, followed by installation of the phosphine oxide moiety and Wittig–Horner reaction. The 2-methylene-substituted analogue **129** was hydrogenated or hydroborated with 9-borabicyclo[3.3.1]nonane (BBN) to afford the 2-methyl or 2-hydroxymethyl moieties, respectively.[64] The same synthetic pathway was used for the introduction of other substituents at



Scheme 23 Synthesis of 2-methylene-19-norvitamin D3.



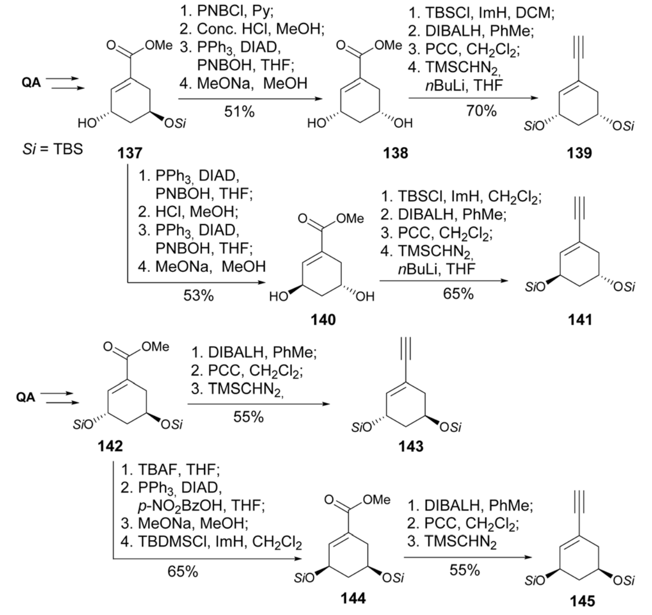
Scheme 24 Synthesis of 2-methylene analogues of calcitriol.

position 2, such as 3′-alkoxypropylidene,[65] 3′-alkoxypropylidene,[66] pegylated alkylidene chains[67] and the formation of an additional dihydropyran[68,69] and dihydrofuran[70] rings. The 9,10-*seco* steroid moiety has also been modified in its alkyl side chain, to have the hydroxyl group removed or replaced by a methyl substituent,[71] to include an alkyne[72] or ether[73] moieties, and in the synthesis of the (22*Z*)-isomer of paricalcitol.[74]

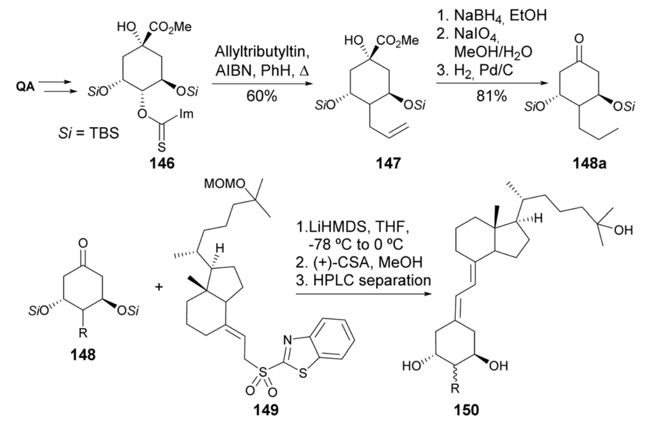
A series of 2-methylene-substituted vitamin D derivatives has been produced by the same research group (Scheme 24). The introduction of the additional exomethylene group was achieved by dehydration of the tertiary hydroxyl in **131** using Martin's sulfurane, followed by 1,3-dipolar cycloaddition of diazomethane to yield a single diastereomer of the diazole **132**, which was submitted to thermolytic nitrogen extrusion, forming the tetrasubstituted cyclic olefin derivative **133** with 34% of the cyclopropyl isomer. The carboxylic ester was converted to the aldehyde functionality by a full reduction-oxidation sequence, and then the carbonyl functionality reacted with the anion of trimethylsilyldiazomethane to provide the dienyne **134**. Coupling of the two carbon skeletons was achieved by Sonogashira reaction with the corresponding vinyl triflates.[75–77]

In their quest for the preparation of locked analogues of 6-*s*-*cis* conformer of 1α, 25-dihydroxyprevitamin D$_3$, Gotor and co-workers[78–80] have prepared the four stereoisomers of the QA-derived enyne, namely **139**, **141**, **143**, **145** (Scheme 25). Those were coupled with vinyl triflates in the same way as later explored by DeLuca.[75–77] The preparation of such isomers was based on the inversion of the hydroxyl stereocenters through Mitsunobu reactions, whilst the installation of the alkyne moiety followed the abovementioned reaction of the aldehyde functionality with the lithiated anion of trimethylsilyldiazomethane.

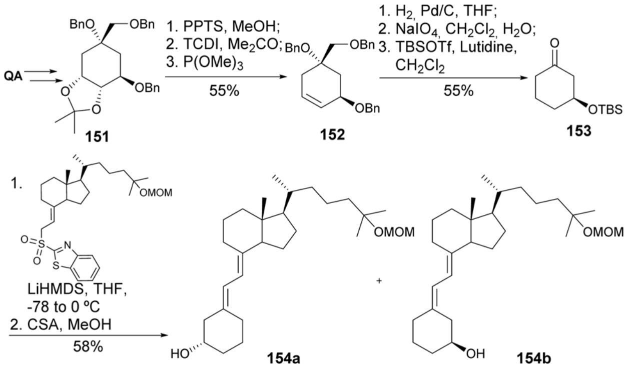
The synthesis of a similar type of 2-modified 1α, 25-dihydroxy-19-norvitamin D3 derivatives has been explored by Kittaka and co-workers. Faced with failures in using the Wittig–Horner reaction for the coupling of the QA-derived cyclohexane moiety and the 9,10-*seco* steroid skeletons, the authors have developed an alternative route using the Julia olefination reaction (Scheme 26). The introduction of the alkyl moiety in the C4 position of QA was achieved through allylation of thioimidazolide **146**. The QA derivative was then reduced to the diol to follow C–C oxidative cleavage and reduction of the olefin to yield **148a**, or the olefin was first hydroborated, then reduced and cleaved with periodate. Different cyclohexanones **148** were then reacted with sulfone **149** using LiHMDS to provide a mixture of 19-norvitamin D$_3$ epimers at C2.[81–85] The same olefination procedure was extended to the preparation of 25-hydroxy-19-norvitamin D$_3$ (Scheme 27),[86] in which cyclic *cis*-carbonothioate was heated in P(OMe)$_3$ to provide the cyclohexene derivative **152**. The synthesis of 1,3-*cis*-25-dihydroxy-19-norvitamin D$_3$, having a similar Julia olefination step, was also reported.[87]



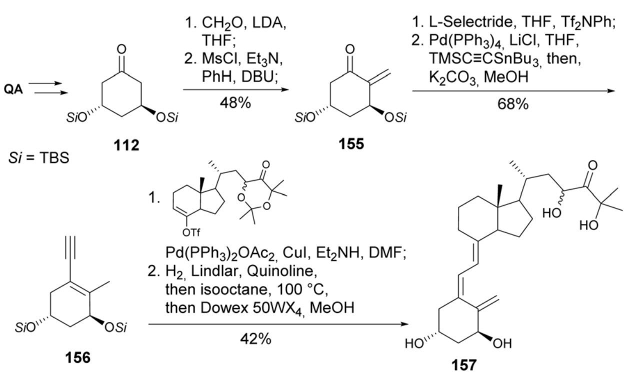
Scheme 25 Preparation of QA-derived enyne stereoisomers.



Scheme 26 Synthesis of 2-substituted-19-norvitamin D3 through Julia olefination.



Scheme 27 Synthesis of 25-hydroxy-19-norvitamin D_3.

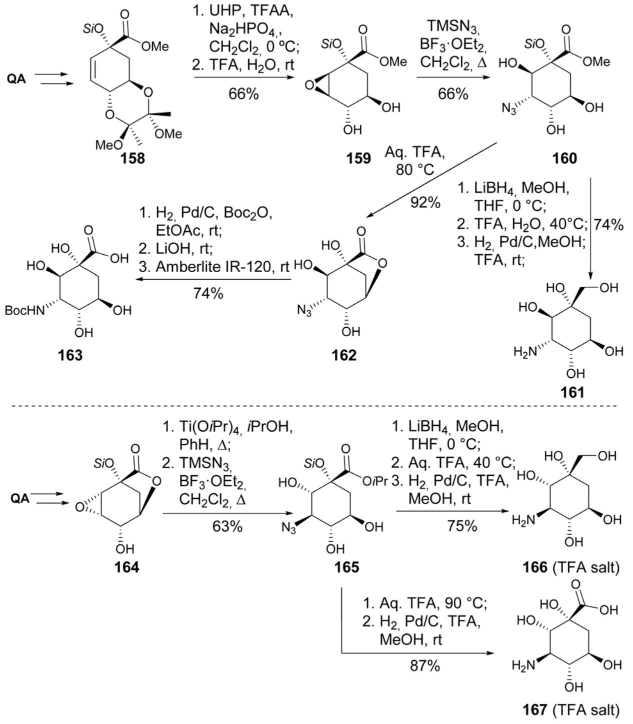


Scheme 28 α-Methylenation of QA-derived cyclohexanone.

Another approach for the installation of the methylene substituent was the one reported by Reddy and co-workers (Scheme 28). Ketone **112** was alkylated in the α-position through an aldol condensation with formaldehyde, followed by elimination of the primary mesylate. The enone was converted into its enol triflate and coupled with a stannylacetylene through Stille coupling. The enyne **156** was then coupled with the triflate in similar conditions to the above-mentioned Sonogashira coupling.[88]

4. Synthesis of cyclitols, aminocyclitols and carbasugars

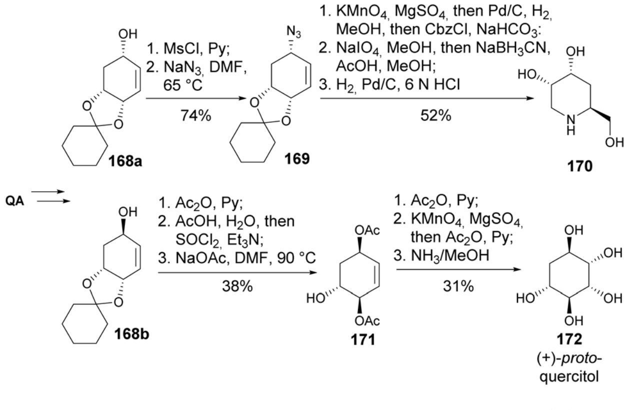
Cyclitols, a class of cyclic polyols, are widely distributed in nature and play crucial roles in biological and chemical systems. Aminocyclitols are a subclass of cyclitols, where the cyclohexane ring includes at least one amine moiety.[89,90] Considering the high number of hydroxyls and the cyclic nature of quinic acid, it is not surprising that it has been widely explored as a starting material for the synthesis of cyclitols and aminocyclitols.



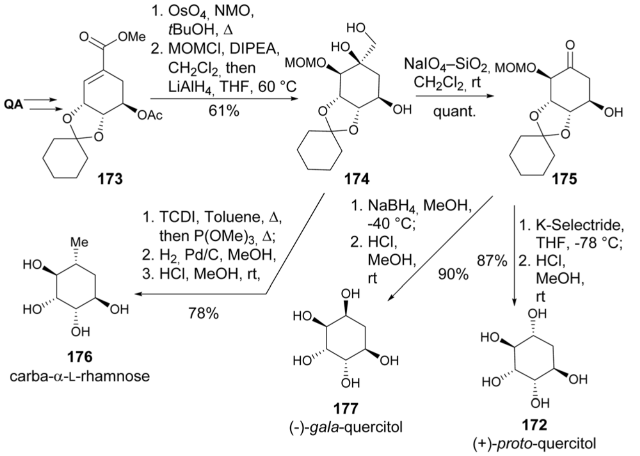
Scheme 29 Synthesis of aminocyclitols **161** and **166** and their corresponding γ-amino acids **163** and **167**.

A practical synthesis of positional stereoisomers of valiolamine **161** and **166** and their corresponding polyhydroxy γ-amino acids **163** and **167** has been obtained from quinic acid. The main steps include the stereocontrolled synthesis of the epoxides **159** and **164** and respective azidolysis, which afforded the azido-alcohols **160** and **165** (Scheme 29).[91] The opening of the lactone **164** was tested using methanol or methoxide as nucleophiles, resulting in the formation of the methyl ester in low yields, likely due to relactonization.

Two glycosidase inhibitors, 1,4,5-trideoxy-1,5-imino-D-*ribo*-hexitol **170** and (+)-*proto*-quercitol **172**, were synthesized from enones **168.** Luche reduction of the enone provided a mixture of the corresponding allylic alcohols **168a** and **168b** in a 1 : 1.4 ratio (Scheme 30). The piperidine ring was formed *via* the dihydroxylation of cyclohexene, followed by oxidative cleavage with $NaIO_4$, ending with reduction steps. The primary step in constructing the quercitol ring was the dihydroxylation by $KMnO_4$, with some complications arising in the previous steps



Scheme 30 Synthesis of trihydroxypiperidine **170** and (+)-*proto*-quercitol **172**.

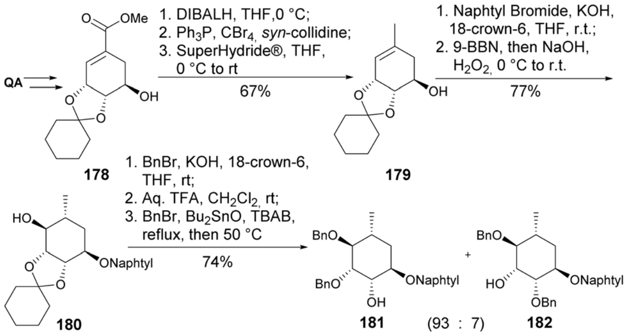


Scheme 31 Preparation of carba-α-L-rhamnose **176**, (−)-*gala* **177**, (+)-*proto*-quercitols **172**.

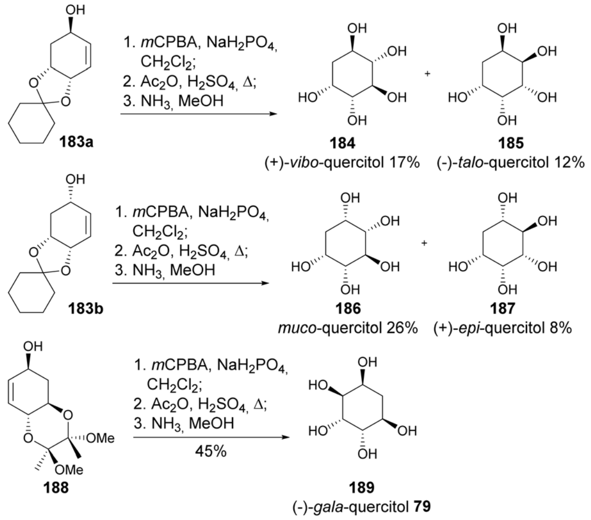
due to aromatization of the synthetic intermediates at high temperatures.[92]

Murugan *et al.* reported efficient syntheses of carba-α-L-rhamnose **176**, (−)-*gala* **177**, and (+)-*proto*-quercitols **172** from shikimic acid derivative **173** (Scheme 31). The unsaturated methyl ester was converted to the MOM-protected cyclitol **174** and, through a Corey–Winter protocol for installation of exocyclic olefin followed by hydrogenation and deprotection, yielded **176**. The ketone **175** was obtained *via* $NaIO_4$-oxidative cleavage of **174**. Cyclitols **177** and **172** were produced through the diastereoselective reduction of the ketone with K-Selectride and $NaBH_4$, respectively.[93]

Before the synthesis of carba-α-L-rhamnose, some of its derivatives have been prepared from the deacetylated analogue **178** (Scheme 32). The key steps for synthesizing **181** and **182** involved the highly stereoselective hydroboration of **179** (*c.a.* 97%), prepared upon reduction of the alkyl halide formed by the Appel reaction, and the regioselective benzylation facilitated by Bu_2SnO in the last step.[94]



Scheme 32 Preparation of regioisomers of protected carba-α-L-rhamnose.

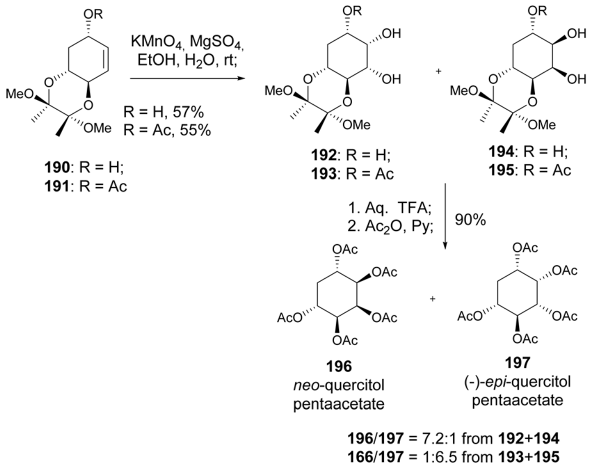


Scheme 33 Synthesis of various quercitols from quinic acid-derived allylic alcohols.

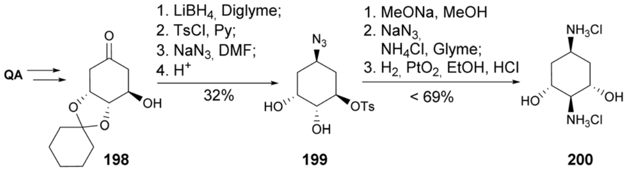
Following a similar approach for the synthesis of allyl alcohols **183**, Shih and co-workers reported the preparation of (+)-*vibo*, and (−)-*talo*, *muco*- and (+)-*epi*-quercitols, through epoxidation, followed by acetolysis and deprotection (Scheme 33). Starting from allyl alcohol **188**, in a similar approach, allowed the synthesis of (−)-*gala*-quercitol.[95] (+)-*Gala*-quercitol **189** was later prepared by the same authors through *syn*-dihydroxylation of allylic alcohol **183b**.[96]

A stereospecific synthesis of *neo* and (−)-*epi*-quercitols was also reported by Shih *et al.* (Scheme 34), upon deacetylation of **196** and **197**, respectively. When reacted with $KMnO_4$, allylic alcohol **190** and allyl acetate **191** gave significantly different diastereomeric ratios, which were attributed to the influence of the hydroxyl group in directing the dihydroxylation through intermolecular hydrogen bonding in the case of **190**.[96] Non-natural quercitol derivatives, namely deoxyfluoro quercitols, have been prepared from quinic acid using DAST-mediated fluorination of allylic alcohols.[97]

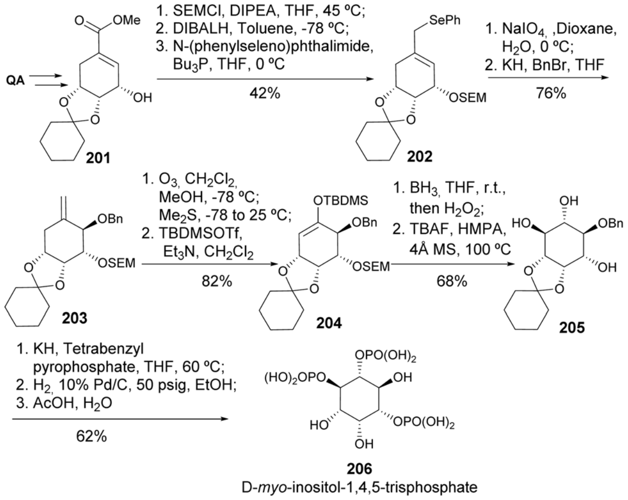
Gero and co-workers have reported the synthesis of dideoxy fortamine analogue **200** (Scheme 35).[98] The ditosylation analogue of diol **199** was reported to undergo selective replacement of the tosylate at C5 under carefully controlled conditions with sodium azide in DMF. Treatment with sodium



Scheme 34 Synthesis of *neo* and (−)-*epi*-quercitols.



Scheme 35 Synthesis of a fortamine analogue **200**.



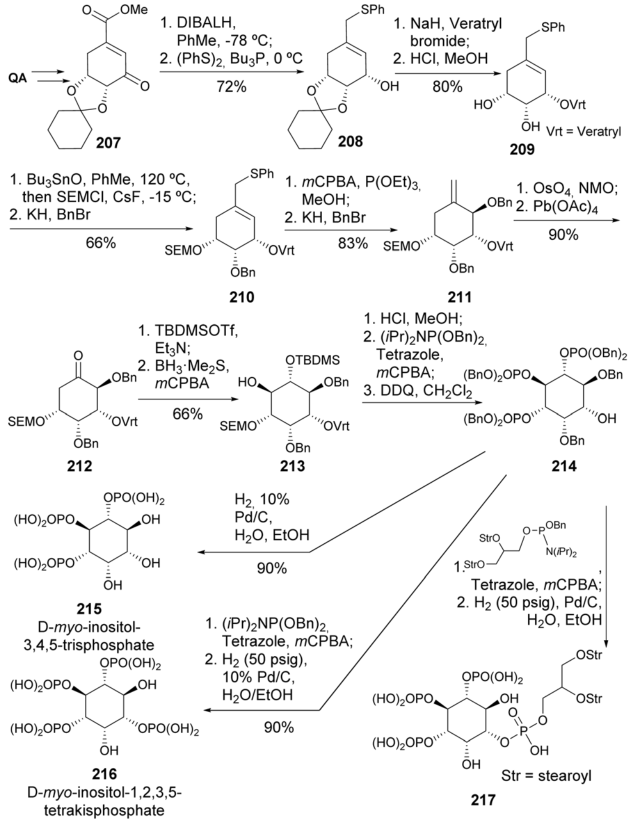
Scheme 36 Synthesis of D-*myo*-inositol-1,4,5-trisphosphate **206**.

methoxide resulted in the formation of epoxide **137**, upon benzoylation of the free hydroxy group, which underwent opening by a second azide moiety to provide the diamine dihydrochloride **200** after hydrogenation.

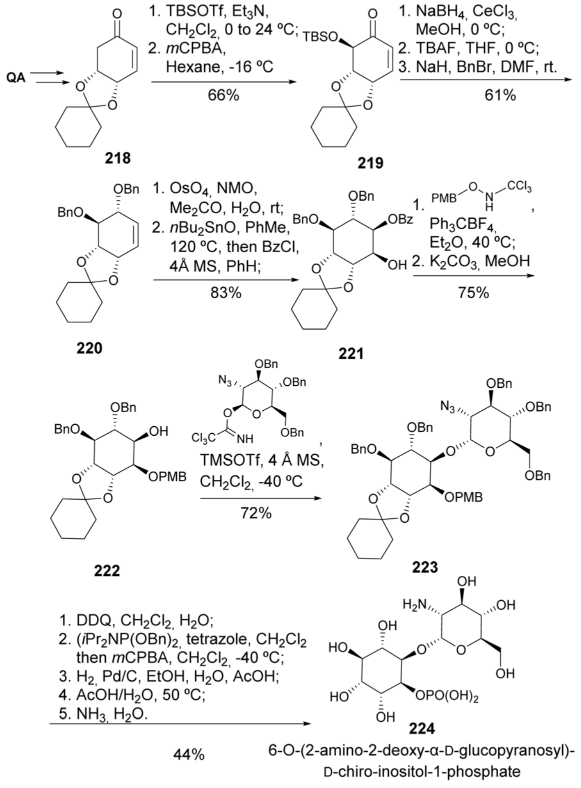
D-*myo*-Inositol-1,4,5-trisphosphate **206** was synthesized straightforwardly from quinic acid in 12 steps, through intermediate allylic alcohol **201** (Scheme 36). The additional hydroxyls were introduced through the stereoselective [2,3]-sigmatropic rearrangement of the allylic selenoxide **202** and hydroboration of the silyl-ether **204**.[99,100]

Under the same work, other inositol phosphates were prepared (Scheme 37).[100] Starting with shikimic acid derivative **207**, the additional oxygens necessary for the inositol core were introduced by Mislow–Evans rearrangement of **210** and hydroboration of the enol-silyl ether of **212**. The protected triphosphate **214** was the key intermediate to obtain the inositol phosphates **215–217** with different substitution patterns and degrees of phosphorylation. Of note, the introduction of a 1,2-di-*O*-stearoyl-glycerophosphate moiety in **214**, followed by hydrogenolysis, allowed the formation of **217**. A distinct protection strategy to selectively modify the inositol core, allowing for regioselective phosphorylation, was further explored.[101,102]

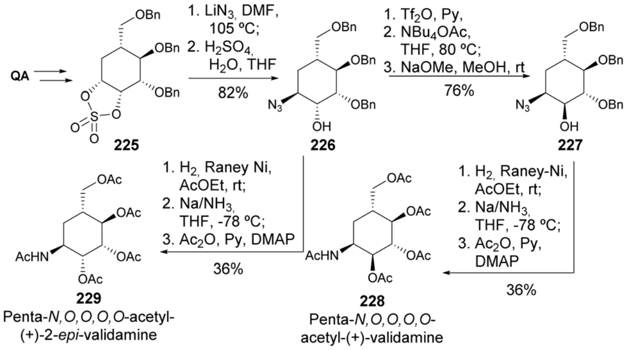
The cyclitol 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-chiro-inositol-1-phosphate **224**, an insulin mimetic, was prepared from enone **218** in 15 steps (Scheme 38).[103] The additional hydroxyl groups were added through stereoselective silylation of **218** with TBDMSOTf and OsO_4-mediated



Scheme 37 Synthesis of inositol phosphates with different substitution patterns and degrees of phosphorylation.



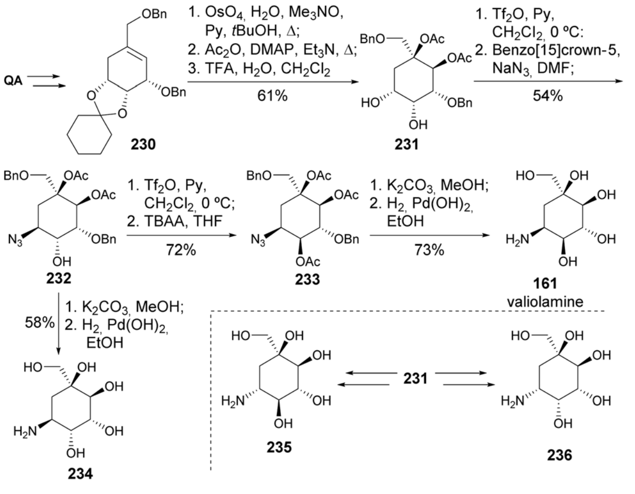
Scheme 38 Synthesis of D-*chiro*-inositol.



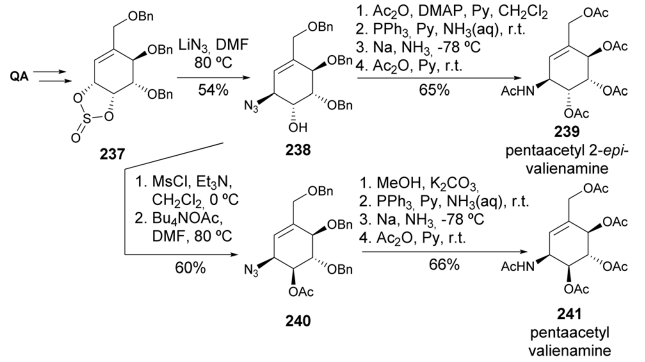
Scheme 39 Synthesis of pentaacetyl (+)-validamine **228** and pentaacetyl-(+)-2-*epi*-validamine **229**.

dihydroxylation of **220**. The disaccharide core was assembled by glycosylation with a sugar imidate, achieving good yield. A lengthy but effective deprotection route, along with phosphorylation between the sequences, led to **224**.

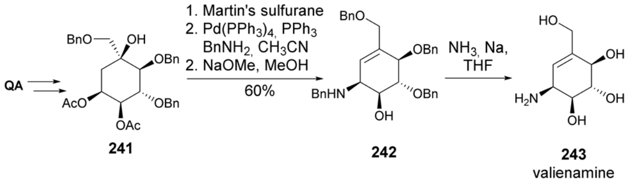
Penta-*N*,*O*,*O*,*O*,*O*-acetyl-(+)-validamine **228** and penta-*N*,*O*,*O*,*O*,*O*-acetyl-(+)-2-*epi*-validamine **229** were prepared from the sulfonate **225**, prepared from quinic acid, in 9 steps (Scheme 39). The azido alcohol was submitted to a two-step sequence of activation of the hydroxy group, followed by S_N2-type displacement of the triflate with tetrabutylammonium acetate in THF. Deacetylation by methanolysis to provide **227**, followed by azide reduction, debenzylation, and acetylation, provided the fully acetylated validamine **228**. As for the synthesis of the *epi*-analogue, the same azide reduction, debenzylation, and acetylation sequence was applied to azido alcohol **226**.[104]



Scheme 40 Synthesis of valiolamine **161** and three of its diastereomers.



Scheme 41 Synthesis of pentaacetylvalienamine **241** and its 2-epimer **239**.

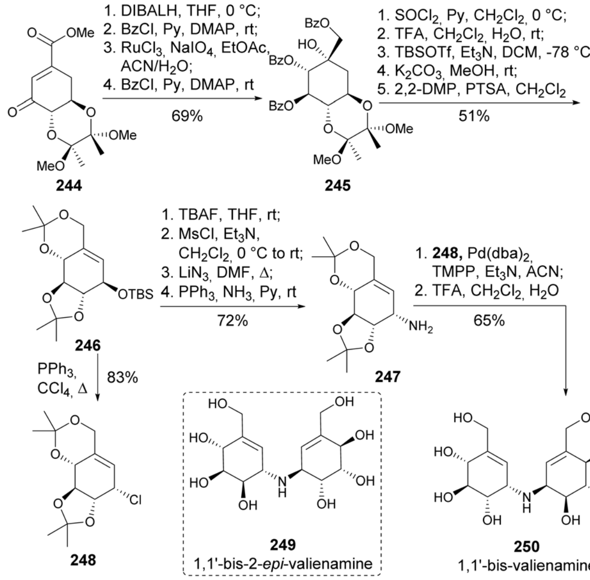


Scheme 42 Synthesis of valienamine.

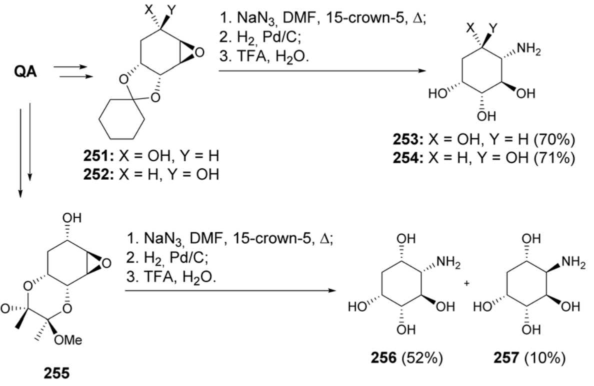
Valiolamine, along with three of its diastereomers, was synthesized by Shing and Wan (Scheme 40). Key steps in this process included azidolysis and OsO_4-catalyzed oxidations, whilst inversion of hydroxy-containing stereocenters was achieved through a sequence of activation with triflic anhydride followed by reaction with tetrabutylammonium acetate and methanolysis.[105,106] The same authors later reported the enantiospecific synthesis of valienamine using two different approaches. The first approach explored the regio and stereospecific ring opening of cyclic sulfite **237** with azide anion and also allowed the synthesis of 2-*epi*-valienamine (Scheme 41).[107] The second approach used a regio- and stereospecific palladium-catalysed allylic amination (Scheme 42), after the regioselective dehydration of **241**.[108] Specifically, Martin's sulfurane in refluxing benzene provided the allyl acetate through elimination of the more acidic ring methylene proton over the exocyclic methylene proton. The allyl acetate underwent amination with benzylamine in acetonitrile to afford **242** upon methanolysis, whilst the use of THF hindered the desired palladium-catalyzed amination of the allyl acetate. Full deprotection of the allyl amine provided the cyclitol in 11% overall yield and 20 steps from quinic acid.

An enantiospecific synthesis of 1,1′-bis-valienamine **250** and a first synthesis of 1,1′-bis-2-*epi*-valienamine **249** were achieved in 14 and 15 steps from QA with overall yields of 12% and 24%, respectively (Scheme 43). Both syntheses involved the stereospecific Pd-catalysed coupling reaction between an allylamine and the corresponding allyl chloride as the key steps, using tris(2,4,6-trimethoxyphenyl)phosphine (TMPP) as the ligand.[109]

Shih *et al.* detail the efficient synthesis of four aminocyclitols from quinic acid (Scheme 44).[110] A significant aspect of their method is the highly regioselective ring opening of epoxides with NaN_3, which allows for precise functionalization of the cyclitol framework. Interestingly, the opening of epoxides **251** and **252** by azide was regioselective, whilst the opening of epoxide **255** provided epimeric tetraols **256** and **257** upon deprotection. The latter was rationalized to be formed upon



Scheme 43 Synthesis of 1,1′-bis-valienamine **250**.

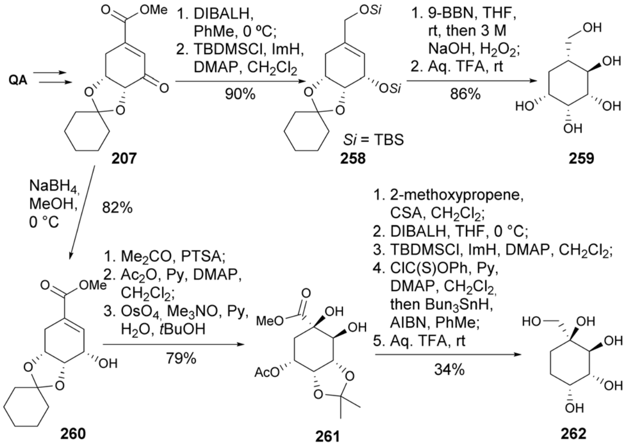


Scheme 44 Synthesis of aminocyclitols **253**, **254**, **256**, and **257**.

nucleophilic attack by the hydroxyl at C5 to form a new epoxide, opened by the azide nucleophilic attack at C4. This approach offers a streamlined pathway to producing structurally diverse aminocyclitols.

4.1 Synthesis of carbasugars

Pseudosugars, also known as carbasugars, are carbohydrate analogs that have garnered significant interest from medicinal chemists due to their potential as active pharmaceutical ingredients. These compounds exhibit structural resemblance to carbohydrates but contain a methylene group rather than a ring oxygen. Their structural similarity to conventional monosaccharides suggests they can bind to and inhibit the same protein targets.[111] A key advantage of carbasugar-containing compounds is their resistance to enzymatic degradation, as they lack a glycosidic linkage, which results in enhanced stability. Quinic acid provides a privileged skeleton and richness in stereocenters for synthesizing these compounds.[112] The first example of the synthesis of carbasugars from (−)-quinic acid was reported by Shin *et al.*, on its conversion into pseudo-β-D-mannopyranose **259** and pseudo-β-D-fructopyranose **262** (Scheme 45). The 4-*epi*-3-dehydro-shikimate **207** served as a precursor for the preparation of both polyols.[111,113]

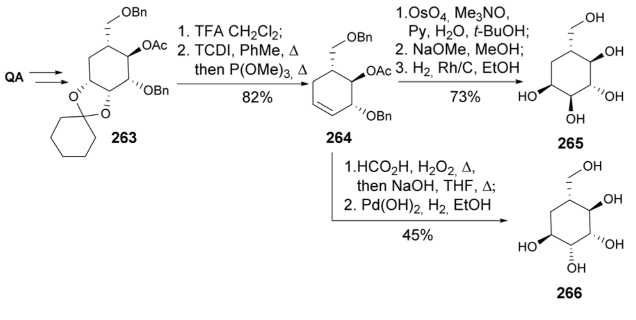


Scheme 45 Synthesis of pseudo-β-D-mannopyranose and pseudo-β-D-fructopyranose.

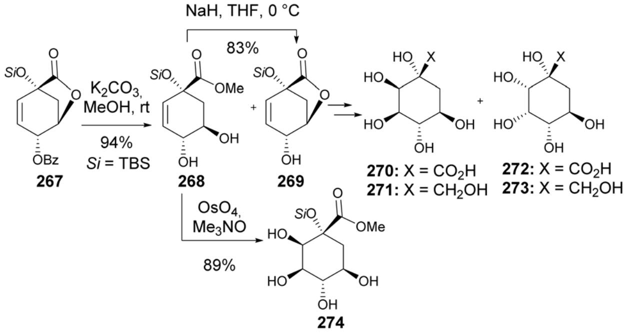
Later,[114,115] the same authors adopted a similar strategy for the synthesis of pseudo-α-D-glucopyranose **265** and pseudo-α-D-mannopyranose **266** (Scheme 46), through dibenzylated intermediate **263**. Removal of the acetal followed by Corey–Winter deoxygenation resulted in the formation of the cyclohexene derivative **264** that could then be transformed into both pyranoses through *cis* or *trans* dihydroxylations.

Carballido *et al.* presented the synthesis of carbasugars, outlining a strategy that incorporates selective functionalization and ring modifications to convert quinic acid into carbocyclic sugar analogs. The primary step involved OsO_4-catalyzed dihydroxylation of the unsaturated quinic acid derivative **269**, and in this work, 15 different carbasugars were prepared. The face selectivity for the dihydroxylation of **269** and analogs was controlled by the use of different co-oxidants, with $NaIO_4$ and NMO favoring the formation of *Si*-hydroxylation products. In the absence of the lactone ring, the sole diastereomer **274** was obtained independently of the reaction conditions (Scheme 47).[116]

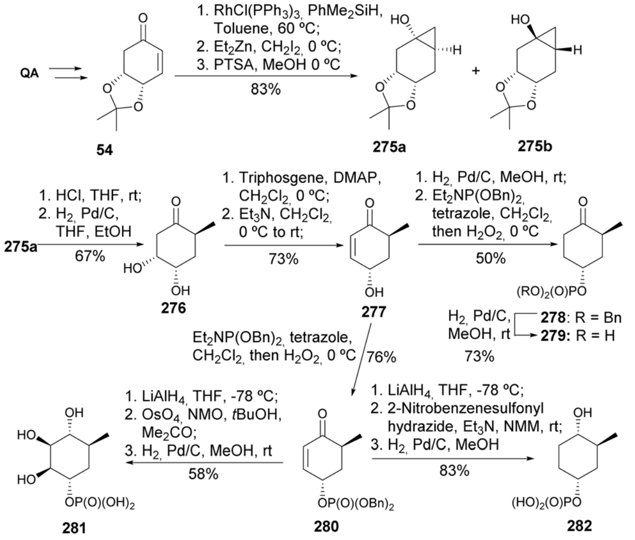
Shan *et al.* reported the synthesis of various cyclitol sugar phosphates (Scheme 48).[117] Hydroxyenone **277** was prepared from enone **54**, where the critical steps included the Simmons–



Scheme 46 Synthesis of pseudo-α-D-glucopyranose and pseudo-α-D-mannopyranose.



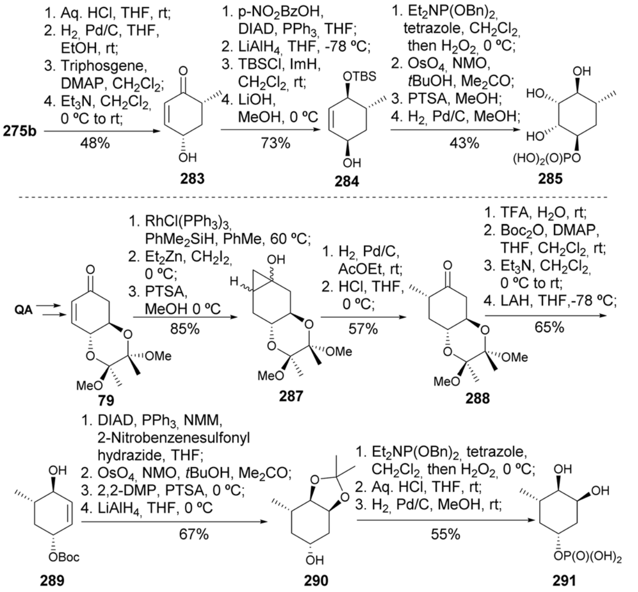
Scheme 47 Synthesis of (1*S*, 2*R*, 3*R*, 4*S*, 5*R*)-(**270**) and (1*S*, 2*S*, 3*S*, 4*S*, 5*R*)-1,2,3,4,5-pentahydroxy-1-hydroxymethylcyclohexane (**272**) and their corresponding carboxylic acids (**271** and **273**).



Scheme 48 Synthesis of carbasugar phosphates **280**, **281** and **282**.

Smith cyclopropanation and diastereospecific ring opening of cyclopropanol under Pd/C hydrogenation conditions to obtain the corresponding α-methyl ketone **276**. The one-pot hydrosilylation of **54**, followed by Simmons–Smith cyclopropanation, resulted in the formation of a separable mixture of cyclopropanes **275**, in a ratio that varied from 1 : 1 (at 0 °C) to 2 : 1 (at −20 °C). Deprotection of cyclopropanol **275a**, followed by hydrogenolysis, resulted in opening of the cyclopropane ring to provide ketone **276** that was dehydrated to the enone **277**, serving as a key intermediate to prepare 2,3-dideoxy-4-*oxo*-5*a*-carba-α-D-rhamnopyranose phosphate **280**, 5*a*-carba-α-D-rhamnopyranose phosphate **281**, and 2,3-dideoxy-5*a*-carba-α-D-rhamnopyranose phosphate **282**.

Cyclopropane derivative **275b** served as a synthetic intermediate for the synthesis of two other sugar phosphates (Scheme 49).[117] The synthesis of **285** started with the deprotection of the isopropylidene group of **275b**, followed by diastereoselective cyclopropane hydrogenolysis and deoxygenation at C3, which was achieved *via* carbonate formation and subsequent elimination. The stereocenter at C4 was inverted using the Mitsunobu reaction with *p*-nitrobenzoic acid, followed by reduction of the ketonic carbonyl with lithium aluminium hydride, with high diastereoselectivity (11 : 1). Compound **284** was obtained by TBS protection and hydrolysis of the nitrobenzoyl ester. In the final step, the free alcohol was phosphorylated with dibenzyl phosphate. The endocyclic double bond was dehydroxylated under Upjohn's oxidation conditions, and after deprotection of TBS and Bn groups, 5*a*-carba-α-L-rhamnopyranose phosphate **285** was obtained.

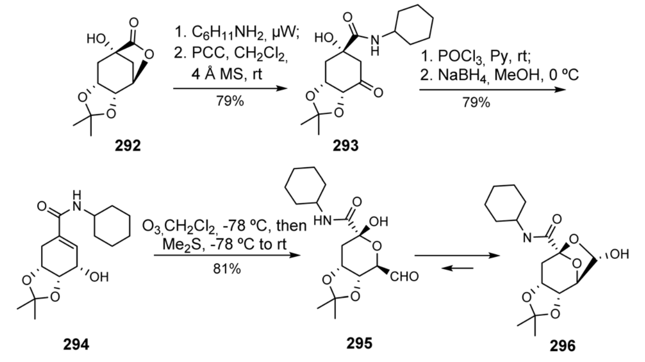


Scheme 49 Synthesis of 5*a*-carba-α-L-rhamnopyranose phosphate **285** and 5*a*-carba-β-D-digitoxopyranose phosphate **291**.

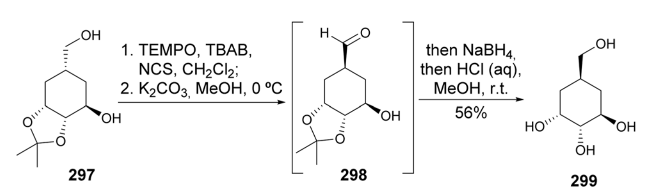
For **291**, its synthetic route started with an enone with butane bisacetal protecting group on the *trans*-vicinal diol **79**. This was converted to cyclopropanol **287** *via* a one-pot process comprising hydrosilylation, cyclopropanation, and desilylation, yielding a 1 : 1 diastereomeric mixture. Pd/C-mediated isomerization did not achieve diastereoselectivity, but epimerization with concentrated HCl led to the (*R*)-methyl ketone **288** in 57% yield. The allylic alcohol **289** was produced by reduction with $LiAlH_4$ and deoxygenation of C5, which involved removing the bisacetal protecting group, addition of Boc group, and then elimination under basic conditions. After two additional steps—similar to the last two steps used to prepare **285**—5*a*-carba-β-D-digitoxopyranose phosphate **291** was obtained.

Quinic acid has been explored in the synthesis of other non-natural carbasugar derivatives. Karukurichi *et al.* reported the synthesis of D-carbofructopyranosyl-1,2-diamines, for the preparation of chiral Co(III)-salen catalysts,[118] whilst Li *et al.* presented a synthesis of two analogues of the flavonoid glycoside natural product SL0101, with the carbasugar constructed using QA as a chiral scaffold.[119]

In a related note, quinic acid can also be converted to *de facto* sugar derivatives (Scheme 50). A careful stereoselective synthesis of a β-D-*ribo*-hept-6-ulopyranosuronamide derivative **296**, is a valuable intermediate for the synthesis of other higher sugars, as has been reported by Baptistella and Cerchiaro. The



Scheme 50 Synthesis of a β-D-*ribo*-hept-6-ulopyranosuronamide derivative.

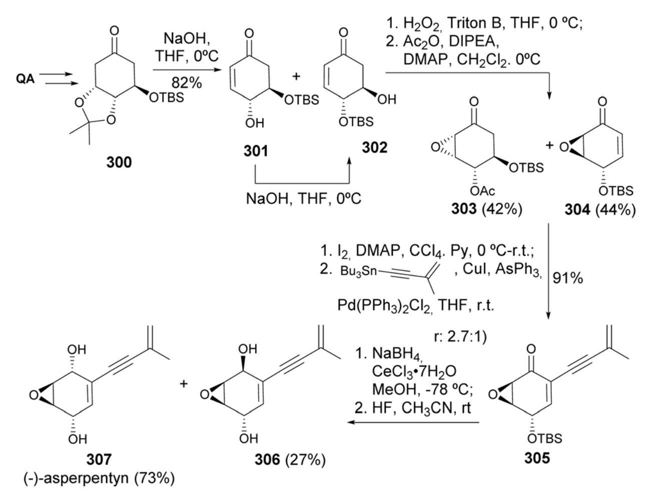


Scheme 51 Synthesis of *Streptomyces lincolnensis* carbasugar.

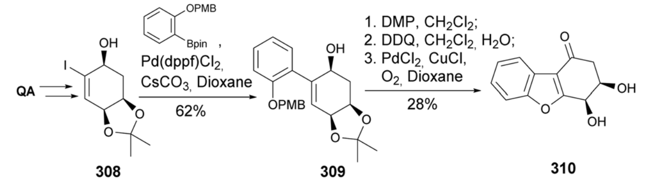
transformation of carbacycle to carbohydrate, an essential phase in this process, occurred in a one-pot reaction involving ozonolysis of the double bond of the α,β-unsaturated amide **294**, carried out under mild conditions.[120]

5. Synthesis of other carbacycles

Two carbasugars isolated from *Streptomyces lincolnensis* have been synthesised from quinic acid, upon reductive opening of a quinide derivative. The acetonide removal readily provided one of the natural carbasugars, whilst its epimer **299** (Scheme 51) could be obtained by oxidation of the primary hydroxyl, epimerization upon treatment with base, followed by reduction and acetonide removal.[121]

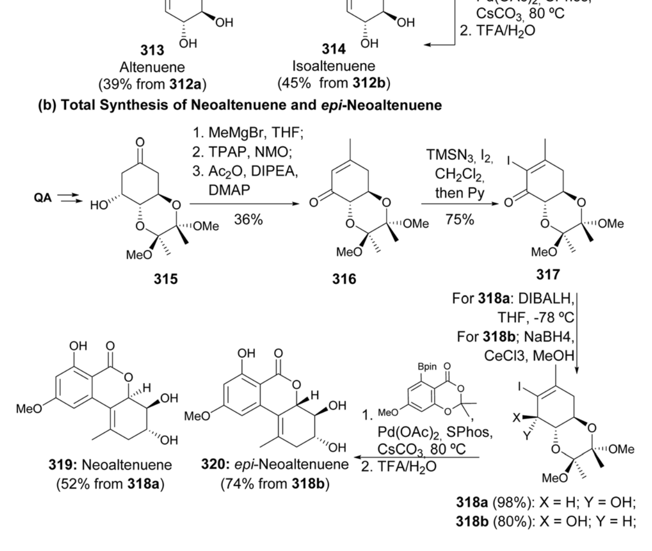


Scheme 52 Synthesis of (−)-asperpentyn **307**.



Scheme 53 Synthesis of previously assigned *ent*-ribisin F.

Maycock and co-workers have developed the first synthesis of (−)-asperpentyn, based on the conversion of quinic acid into epoxide **304**, followed by its conversion into the corresponding α-iodoenone, further submitted to Stille coupling with tetramethylstannane (Scheme 52). The acetonide elimination from **300** resulted in the formation of interconvertible isomers **301** and **302**, due to *O*,*O*-silyl migration. The enone isomers were epoxidized and, after separation, **304** was iodinated to be further submitted to Stille coupling conditions. Luche reduction of the enone resulted in the formation of both epimers of the allyl alcohol with some preference for the desired compound, which, upon deprotection and separation, allowed the isolation of enantiomerically pure (−)-asperpentyn. Some of the synthetic intermediates were taken in the synthesis of other cyclitols, namely (+)-harveynone, (+)-epieporformin, and (−)-theobroxide.[122]

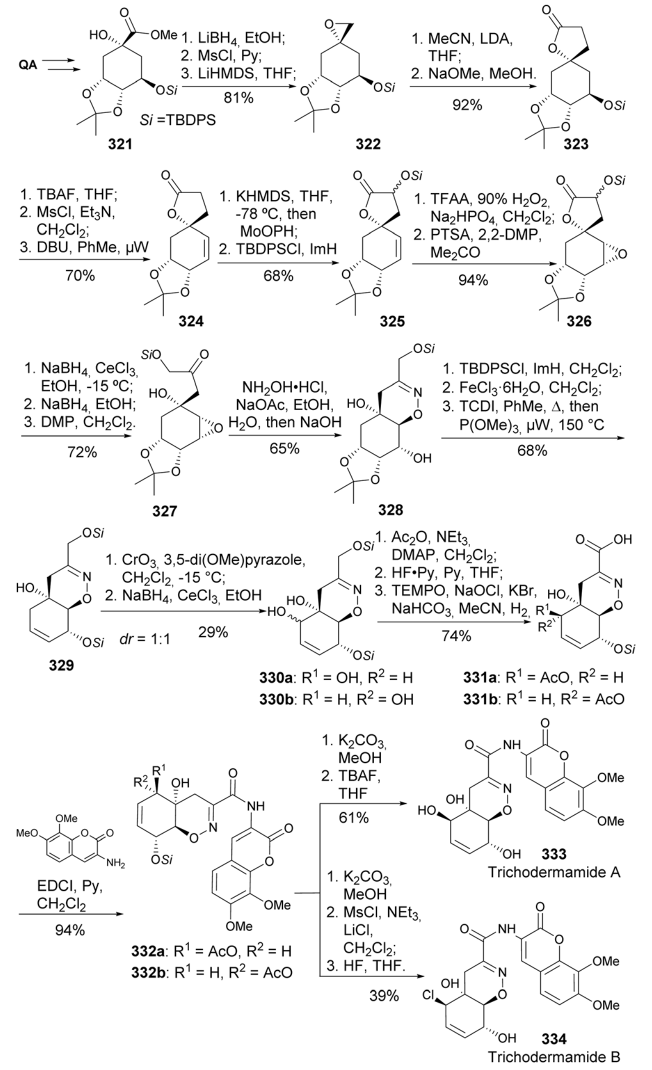


Scheme 54 Total synthesis of *Alternaria* fungi toxins: (a) altenuene and isoaltenuene; (b) neoaltenuene and *epi*-neoaltenuene.

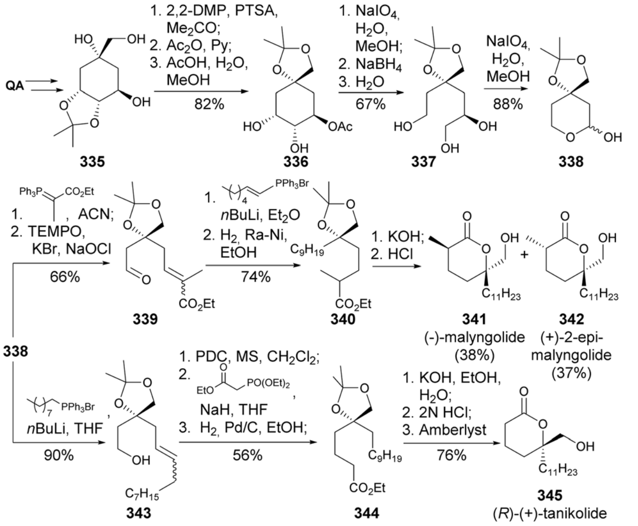
In an attempt to develop the first total synthesis of ribisin F, previously characterized upon isolation from the fruiting bodies of *Phellinus ribis*,[123] Badwell and co-workers took the acetonide-protected quinic acid as a starting material (Scheme 53). A mismatch in the spectral characterization of the synthesized compound (assisted by single crystal X-ray analysis) with the one from the natural isolate pointed to a wrongly assigned structure. The synthesis of the enantiomer of the envisioned natural product consisted on the formation of allyl alcohol **308**, followed by Suzuki coupling, oxidation to the corresponding enone, phenol deprotection, palladium-catalyzed oxidative cyclization, and acetonide removal.[124]

6. Lactones

Altenuene **313** and isoaltenuene **314** are minor toxins produced by various *Alternaria* fungi, and Altemöller reported their total synthesis from quinic acid (Scheme 54a). The iodo-cyclohexenone **311** was treated with MeMgBr at low temperatures to obtain a diastereomeric mixture of the alcohols **312**, which were separated by chromatographic methods.[125] In a different work,[126] the enone **316** was α-iodinated and then reduced stereospecifically to provide epimers **318a** and **318b** depending on the reducing agent. The four isomers of the vinyl iodide were submitted to Suzuki coupling with the same boronic ester, to provide toxins altenuene **313**, isoaltenuene **314**, neoaltenuene **319** and *epi*-neoaltenuene **320**, and (Scheme 54b).



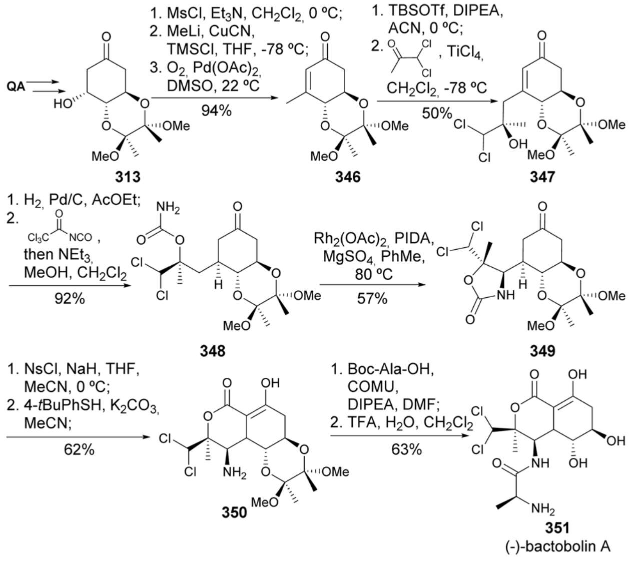
Scheme 55 Total synthesis of trichodermamides A **333** and B **334**.



Scheme 56 Total synthesis of (−)-malyngolide and (*R*)-(+)-tanikolide.

Trichodermamides A **333** and B **334** are modified heterocyclic dipeptides isolated from cultures of the marine-derived fungus *Trichoderma virens*. Wan and coworkers prepared both natural products from **321** (Scheme 55).[127,128] Spiro-lactone **323** was obtained by the addition of MeCN conjugate base to epoxide **322**, followed by treatment with NaOMe. A modified Rubottom oxidation, followed by protection, afforded the α-silyloxylactone **325**. The oxazine ring was formed by cyclization of the corresponding oxime of **328** in a basic medium. Allyl oxidation of **329** proved challenging, eventually resulting in the formation of the enone in ≈30% yield using CrO$_3$/3,5-dimethoxypyrazole. Luche reduction provided both diastereomers of allyl alcohol **330** that could be separated by chromatography. Protection of the allylic alcohol and installation of the carboxylic acid group provided **331**, which was coupled with aminocoumarin mediated by EDCI. Compounds **332** were subjected to deprotection conditions, resulting in **333** and **334**, with the latter requiring an additional step to convert the secondary alcohol to the corresponding chloride.

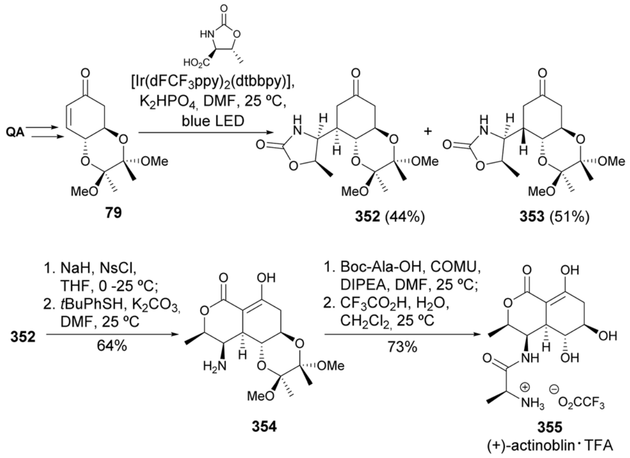
(−)-Malyngolide **341** and (*R*)-(+)-tanikolide **345** are two metabolites isolated from the lipid extract of a blue-green algae cyanobacterium, *Lyngbia mujuscula*.[129] (−)-Malyngolide **341** is an antibiotic, whilst (*R*)-(+)-tanikolide is an antifungal that can be prepared from the same synthetic intermediate. Matsuo and co-workers developed a synthetic route for the preparation of lactol **338** based on NaIO$_4$-mediated oxidative cleavages of the quinic acid triol moiety, followed by Wittig reactions and



Scheme 57 Total synthesis of (−)-bactobolin A.

hydrogenation of the prepared olefins. The use of different Wittig ylides and adjustments on the synthetic sequence allowed obtaining both metabolites[130,131] from the same lactol **338** (Scheme 56).

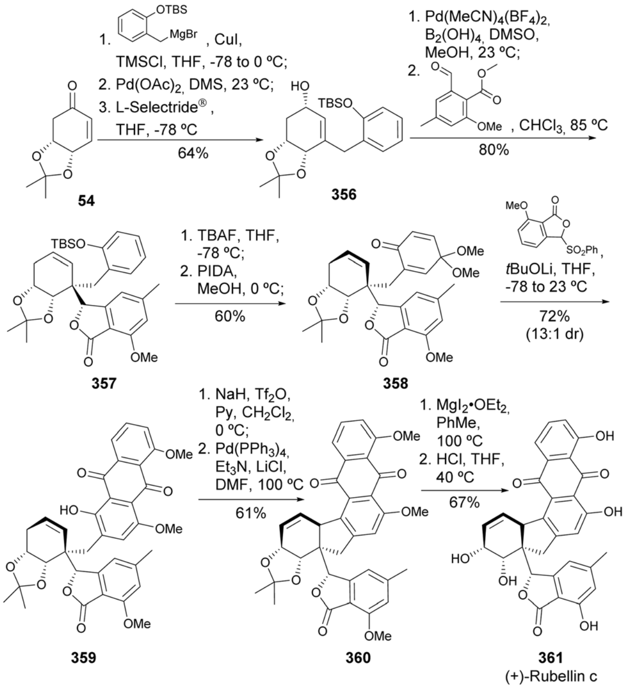
(−)-Bactobolin A **351** is a polyketide-peptide natural product first isolated in 1979 as a secondary metabolite of *Pseudomonas* sp. Vojáčková *et al.* reported a highly stereoselective synthesis of **351** from quinic acid (Scheme 57). The key transformations in this approach include a vinylogous aldol reaction of **346** to introduce the dichloromethyl group, a rhodium(II)-catalyzed C–H amination of **348**, and an intramolecular alkoxycarbonylation to obtain the bicyclic lactone **350**.[132] The final amide coupling step required screening different coupling agents due to the occupation of the amino group at the axial position. COMU ((1-cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino-morpholino-carbenium hexafluorophosphate)) delivered the amide in good 73% yield that could be deprotected with TFA to yield target **351**.



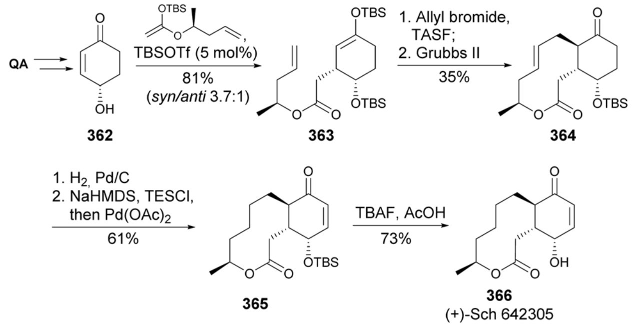
Scheme 58 Total synthesis of (+)-actinobolin.

Švenda and co-workers have reported an improved synthesis path for the preparation of (+)-actinobolin (Scheme 58).[133] Starting from the diol-protected QA-derived enone as radical acceptors, and exploring oxazolidinone derivatives as a source of carbon-centered radicals, the photocatalyzed Giese addition was used for the preparation of epimeric ketones **352** and **353**. Changing the diol protecting groups to a silyl-protected enone had some effect on the diastereoselectivity towards the desired epimer, although at the expense of the reaction yield. The *N*-sulfonylation of **352** triggered an intramolecular alkoxycarbonylation and, after nosyl removal, the amine group was coupled with Boc-protected L-alanine. The removal of the diol group with TFA resulted in the preparation of the trifluoroacetate salt of (+)-actinobolin in 9 steps and 18% overall yield from quinic acid.

(+)-Rubellin C **361** is an anthraquinoid with a distinct scaffold, characterized by a 6-5-6 ring system. Rubellins can inhibit and reverse tau protein aggregation, a therapeutically relevant target for Alzheimer's disease. The high synthetic complexity of this molecule, with five contiguous stereocenters, was addressed by Gartman *et al.*,[134,135] who converted the quinic acid-derived enone **54** in 8 steps into the stereochemically rich allyl alcohol **356** by Saegusa–Ito oxidation with addition of organomagnesium reagent, followed by oxidation of the ketone to the corresponding enone with $Pd(OAc)_2$. An additional ring was introduced through the borylation of the alcohol, followed by the addition of methyl 2-formyl-6-methoxy-4-methylbenzoate, resulting in a single diastereomer of the lactone **357**. Another crucial step involved forming the anthraquinone ring, where TBS-deprotection and oxidation of the phenolic moiety with phenyliodine(III) diacetate (PIDA) yielded the *p*-quinone monoketal **358**. Under Hauser–Kraus annulation



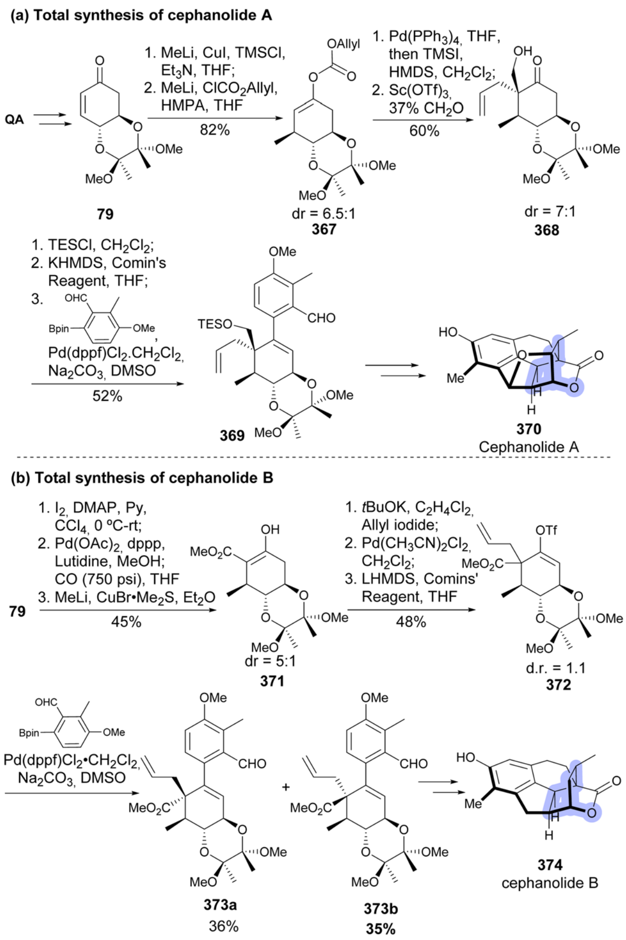
Scheme 59 Total synthesis of (+)-rubellin C.



Scheme 60 Synthesis of (+)-Sch 642305.

conditions, anthraquinoid **359** was obtained. The final key step entailed an intramolecular Heck reaction of the corresponding triflate of **359** with the endocyclic double bond, followed by total removal of the oxygen protecting groups (Scheme 59).

The 10-membered macrolide (+)-Sch 642305 **366**, isolated from *Penicillium verrucosum* and later found to inhibit bacterial DNA primase, was synthesized from quinic acid (Scheme 60).[136] The synthesis relies on a Mukaiyama–Michael addition between enone **362** and a silyl ketene acetal in the presence of TBSOTf as catalyst. The mixture of the two diastereomers was submitted to allylation with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) to provide the diallyl compound that was readily submitted to ring-closing metathesis reaction, resulting in the formation of 10-membered ring lactone **364**. Hydrogenation followed by dehydrogenation and deprotection with buffered TBAF finalized the synthesis of the antibiotic.



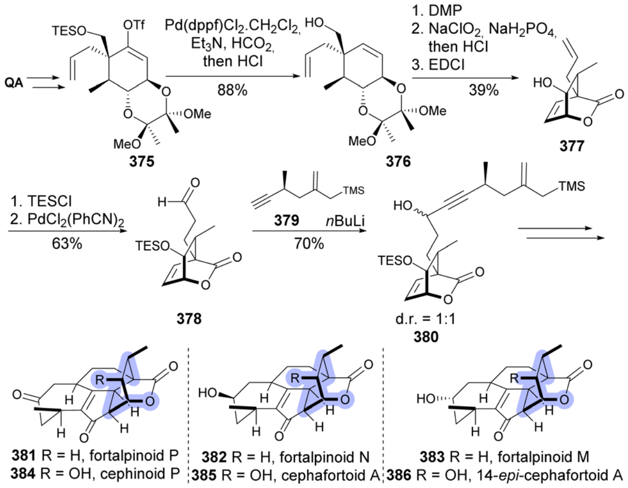
Scheme 61 Synthesis of cephanolides A and B.

Gao and co-workers have recently reported the total synthesis of cephanolides A (**370**) and B (**374**), exploiting quinic acid as the starting material for the construction of ring C of the natural products (Scheme 61).[137,138] The cyclohexene derivatives were obtained upon arylation of the vinyl triflates with the corresponding boronic acid. Two different methods were developed for the installation of the quaternary stereocenter in C-5. A Sc(OTf)$_3$-mediated hydroxymethylation was successful in forming the quaternary stereocenter in decent diastereoselectivity of 7 : 1 for the formation of **368**, taken for the total synthesis of chephanolide A. The other route consisted in C-5 carboxylation, C-4 methylation, and C-5 allylation to provide **372** as an equimolar stoichiometric mixture. After arylation, epimers of **373** were separated, and epimer **373a** was used in the total synthesis of cephanolide B **374**.

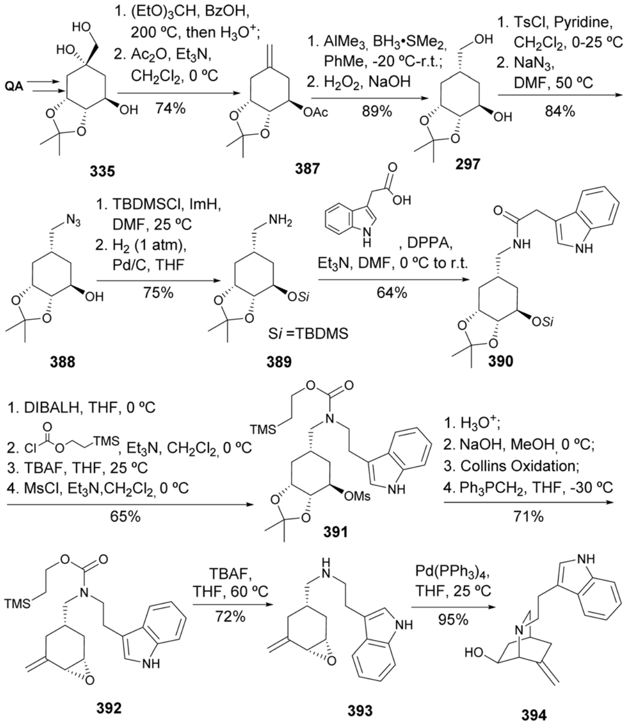
The vinyl triflate derived from **368** (Scheme 61) was later used in the design of a synthetic scheme that could provide the preparation of several *Cephalotaxus* diterpenoids (Scheme 62). The synthetic scheme encompassed a Nicholas/Hosomi–Sakurai cascade reaction and an intramolecular Pauson–Khand reaction to form the 7-5-6 tricyclic system. The vinyl triflate **375** was used both in the preparation of aldehyde **378** and in the synthesis of linear fragment **379**. Lactone **380** was further reacted with Co$_2$(CO)$_8$ to afford an organometallic cluster that was used in the synthesis of diterpenoids **381–386**.[139]

7. Alkaloids

Alkaloids represent a significant class of molecules due to their structural complexity and potent biological activities. Trost *et al.* reported the synthesis of an optically active isoquinuclidine, that could allow further cyclization to either enantiomeric series

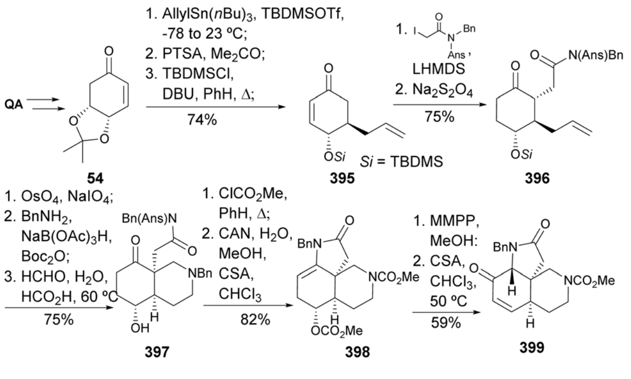


Scheme 62 Synthesis of *Cephalotaxus* diterpenoids.

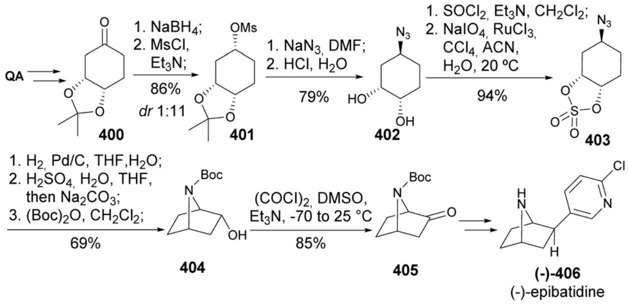


Scheme 63 Synthesis of optically active isoquinuclidine.

of the iboga alkaloids (Scheme 63). The crucial steps for controlling stereochemistry included the hydroboration of the exocyclic double bond with $AlMe_3$, which was essential for diastereoselectivity. The synthesis route involved tosylation of the primary hydroxy group, followed by installation of an azide at the primary carbon, and reduction to provide an amino group prone to condensation with a carboxylic acid. The amide **390** was reduced, and the resulting amine was protected with 2-trimethylsilyl chloroformate. Deprotection of the secondary alcohol, followed by mesylation, acetonide hydrolysis, and epoxide formation, followed by Collins oxidation and Wittig methylenation, afforded the vinyl epoxide **392**. Its cyclization using palladium catalysis allowed the synthesis of the isoquinuclidine fragment **394**.[140]



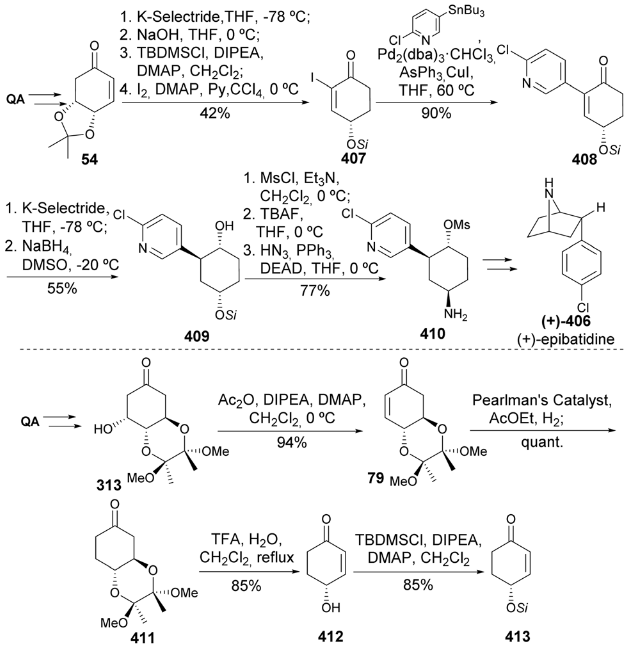
Scheme 64 Synthesis of the *cis*-decahydroisoquinoline core Manzanine **399**.



Scheme 65 Synthesis of a precursor of (−)-epibatidine **406**.

Manzamines are alkaloids that consist of a β-carboline heterocycle paired with polycyclic diamine moieties containing an isoquinoline ring.[141] Kamenecka *et al.*[142] reported the synthesis of the *cis*-decahydroisoquinoline substructure from quinic acid (Scheme 64). Key steps include the stereoselective addition of allyltributyltin to enone **395**, an acid-catalyzed Mannich cyclization with formaldehyde in formic acid, and lastly, the formation of the tricyclic system through debenzylation with methyl chloroformate, followed by cleavage of the *p*-methoxybenzyl group and an acid-catalyzed dehydration that afforded the enamide **398**. The oxidation of the enamide by magnesium monoperoxyperphthalic acid, followed by epoxide rearrangement and elimination, resulted in the formation of the tetracyclic core of (+)-manzamine A, although its final synthesis has not been reported through this route.

Albertini *et al.* developed a synthetic strategy to obtain a precursor of epibatidine,[143,144] an alkaloid with a 7-azabicyclo[2.2.1]heptane ring, isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolor*.[145] The uncommon 7-

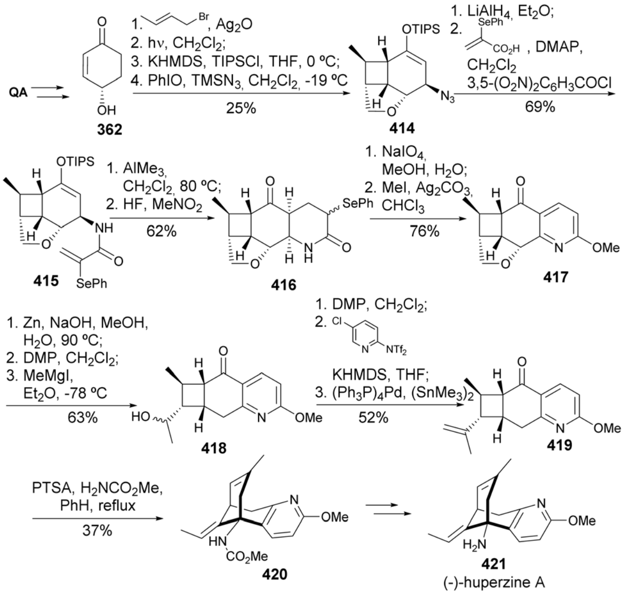


Scheme 66 Synthetic approaches to (+)-epibatidine, extendable to (−)-epibatidine.

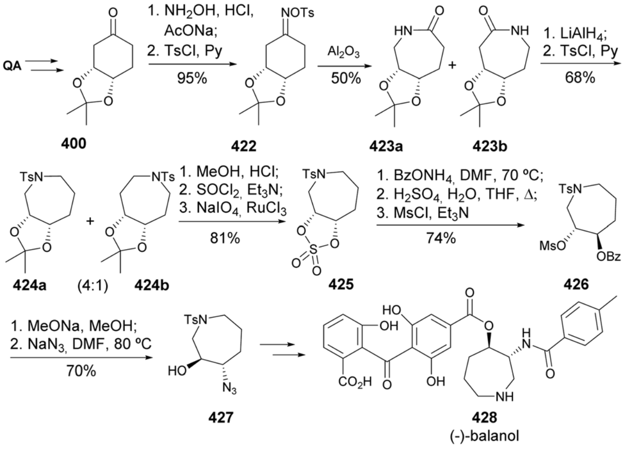
azabicyclo[2.2.1]heptane ring was built by an intramolecular transannular cyclization of a 1,4-*trans* disubstituted cyclohexane azido sulfate **403** (Scheme 65). The sulfate derivative was obtained upon diastereoselective reduction of **400** in a 1 : 11 ratio, mesylation, azide introduction by nucleophilic substitution, followed by reaction with thionyl chloride to afford a diastereomeric mixture of sulfites, readily oxidized by $NaIO_4$ using $RuCl_3$ as catalyst. Reduction of the **403**'s azido group was followed by the intended cyclization, *N*-protection and Swern oxidation to provide **405**, a synthetic intermediate previously reported for the synthesis of (−)-epibatidine **406**.[146]

Maycock and co-workers have later expanded the utility of quinic acid on the synthesis of both enantiomers of epibatidine (Scheme 66). The key step in this route was the diastereoselective reduction of the 4-chloropyridyl cyclohexanone **408** with $NaBH_4$, for which the most selective diastereoselective conditions were searched for.[147,148] Interestingly, reduction with $NaBH_4$ in the absence or presence of $CeCl_3$ did not affect the diastereoselectivity, whilst the presence of DMSO was determined to be more relevant for the desired selectivity. Mesylation of the hydroxy group and installation of the amino group through the Mitsunobu reaction provided intermediate **410** that could be taken up into the synthesis of (+)-epibatidine, similarly to the previously reported racemic routes.[149,150] For the synthesis of the other enantiomer, the authors have started from the *trans*-diol protected derivative of quinic acid **313** through a sequence of dehydration, hydrogenation, another dehydration, followed by silylation to provide **413**. Analogous iodination of **413** followed by a similar synthetic sequence as described for **407** would provide (−)-epibatidine.

White and co-workers[151,152] have reported a novel synthesis of (−)-huperzine starting from enone **362** (Scheme 67), prepared following Danishefsky's protocol.[153] The presented synthesis started with the installation of a cyclobutane unit by an intramolecular [2 + 2] cycloaddition, followed by the construction of tetracyclic compound **416**, oxidation, and methylation. Opening of the cyclic ether ring, oxidation, and carbonyl methylation provided secondary alcohol **418** that was further treated with Comins reagent, and the obtained enol triflate was submitted to Stille reaction. Treatment with anhydrous PTSA in hot benzene provided rearranged product **420**, to be taken up in the previously established synthetic route of (−)-huperzine.[154]



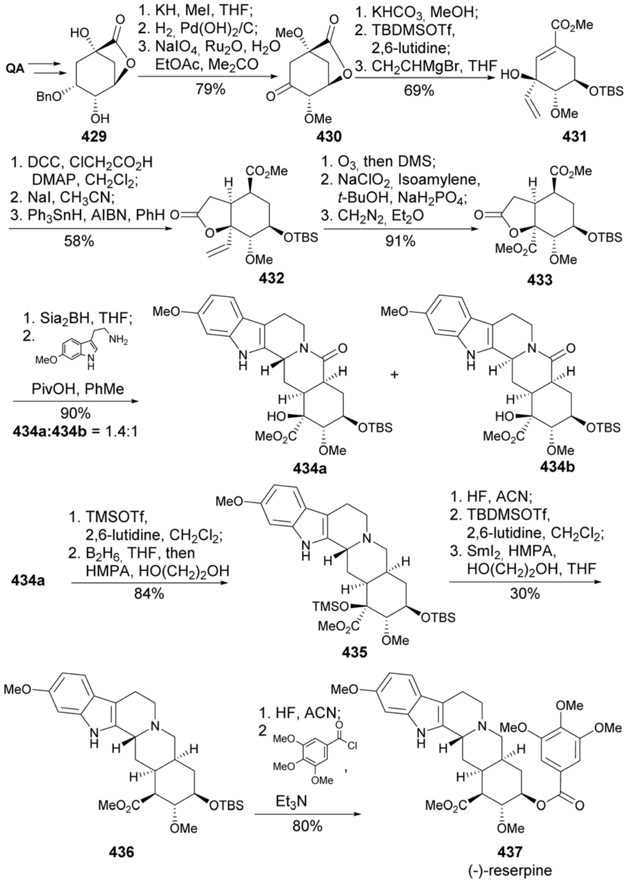
Scheme 67 Synthetic approaches to (−)-huperzine A.



Scheme 68 Synthesis of a precursor to (−)-balanol.

(−)-Balanol is a fungal metabolite derived from the fungus *Verticillium balanoides*[155] and was identified amid the search for novel PKC inhibitors. Barco and co-workers used the same quinic acid-derived precursor **400** used in the synthesis of epibatidine for the synthesis of (−)-balanol, relying on the Beckmann rearrangement of oxime sulfonate **422** (Scheme 68).[144] Despite the lack of regioselectivity of the rearrangement, both lactams could be separated by crystallization and the reduction of the isomeric mixture resulted in the preferred formation of hexahydroazepine **424a** over its meso isomer **424b**. After acetonide deprotection, the sulfate moiety was installed in the same manner as for the previous synthesis, followed by regioselective nucleophilic substitution with ammonium benzoate acid treatment for removal of the sulfate group. Epoxide installation followed by regioselective opening with sodium azide provided the cyclic skeleton in the form of synthetic intermediate **427**, prone to being included in the previously described synthesis of (−)-balanol upon stereoinversion.[156]

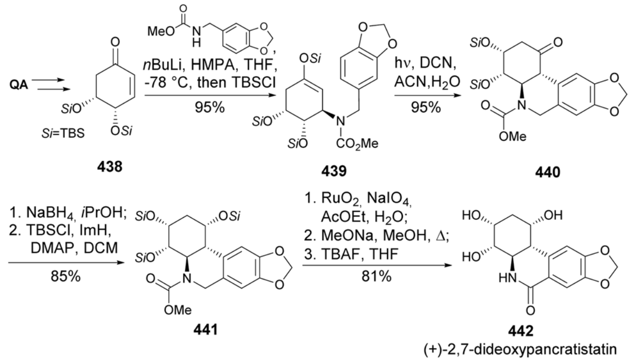
Following the chiron approach, Hanessian and co-workers have explored quinic acid as the chiral template for the construction of ring E in the enantioselective synthesis of (−)-reserpine **437** (Scheme 69).[157] Benzylated lactone **429** was transformed into its dimethoxy derivative, followed by debenzylation and oxidation to provide ketone **430**, prone to diastereoselective installation of a vinyl moiety in the conjugated ester to yield tertiary alcohol **431**. The alcohol was submitted to an intramolecular free-radical cyclization of the α-iodoacetate ester, resulting in the formation of both epimers of bicyclic lactone **432**, which could all be transformed into the β-epimer by treatment with DBU. Ozonolysis followed by oxidation and esterification resulted in the formation of lactone **433**,



Scheme 69 Hanessian's total synthesis of (−)-reserpine.

containing the carbon skeleton of rings D and E. The assembly of the pentacyclic ring skeleton was accomplished upon differentiation of the three carbonyl groups by conversion of **433** into its hemiacetal with disiamylborane, followed by reaction with the tryptamine derivative. The hexacyclic epimers of **434** were separated, and the desired one was submitted to lactam carbonyl reduction, upon the needed protection of the tertiary hydroxyl. Removal of the silyl ether was required for effective deoxygenation of **435** with SmI_2, and the natural product **437** was obtained upon silyl protecting group removal and installation of the trimethoxybenzoyl unit.

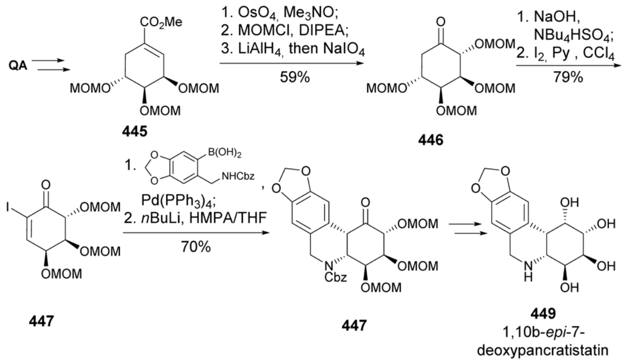
(+)-Pancratistatin occurs naturally in the Hawaiian spider lily with antineoplastic activity.[158] Due to its low natural abundance, efforts have been made toward its total synthesis and the synthesis of congeners. Pandey and coworkers developed a synthetic strategy for (+)-2,7-dideoxypancratistatin **442**, with a key step being the control of a *trans* cyclization *via* photoinduced electron transfer cyclization of silylenol **439** to an electron-rich aromatic ring **440** (Scheme 70).[159] Quinic acid was first converted to silyl ether-protected enone **438**, which undergoes conjugate addition of *N*-lithiated piperonylamine carbonate, followed by trapping of the enolate as TBS ether. The photoinduced cyclization of silylenol was achieved by using a >280 nm medium-pressure lamp in the presence of 2 mol% of 1,4-dicyanonaphthalene (DCN). The tetracyclic compound was reduced and protected as TBS ether, followed by benzylic oxidation and complete deprotection to provide the natural product.



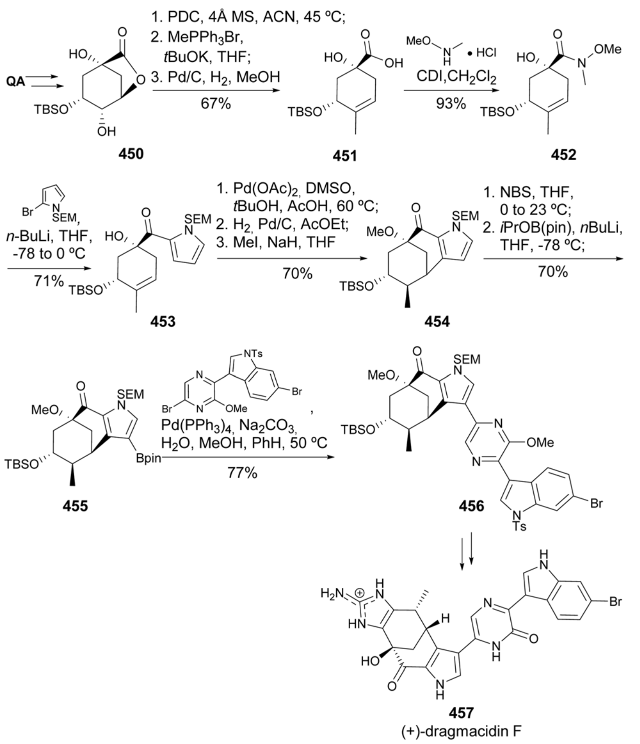
Scheme 70 Synthesis of (+)-2,7-dideoxypancratistatin.

The abovementioned strategy was in part adapted for the total synthesis of 1,10*b*-*epi*-7-deoxypancratistatin **449** (Scheme 71).[160] The key step was the Suzuki-cross coupling for the formation of the aza–Michael precursor that was readily cyclized upon base treatment, to provide the tetracyclic **447** as a single diastereomer. Attempts to epimerize the α-carbonyl position to reach the *trans*-fused ring junction resulted in retro-Michael reaction and ring aromatization.

Dragmacidins are a family of alkaloids that can be obtained from marine sponges, and they possess a wide range of biological activities.[161] The total syntheses of both enantiomers of dragmacidin F starting from quinic acid were developed by Stoltz and co-workers (Scheme 72).[162,163] The divergent approach started with the preparation of carboxylic acid **451** through oxidation of quinide derivative **450**, installation of an exocyclic olefin, followed by diastereoselective hydrogenation and base-promoted elimination of the carboxylate functionality. Upon conversion of the carboxylic moiety to the corresponding Weinreb amide, a pyrrole moiety was installed to provide **453**, prone to palladium-catalyzed intramolecular carbocyclization when employing DMSO as a palladium ligand. The pyrrole-fused bicycle was hydrogenated and *O*-methylated to provide **454**, to which the pinacol boronate was installed to be used in the Suzuki coupling with a brominated indole derivative. The

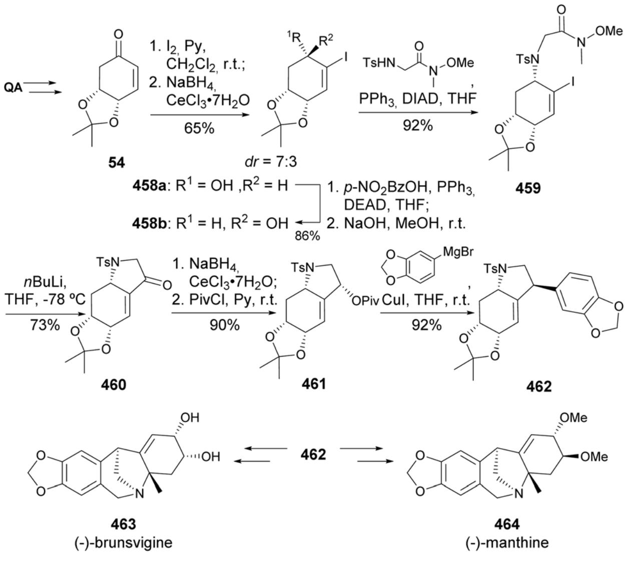


Scheme 71 Synthesis of 1,10*b*-*epi*-7-deoxypancratistatin.



Scheme 72 Total synthesis of (+)-dragmacidin F **457**.[163]

final steps of the synthesis, namely the removal of all protecting groups and the installation of the aminoimidazole moiety, followed the lessons previously learned from the total synthesis of dragmacidin D,[164] resulting in the use of a late-stage Neber rearrangement to provide (+)-dragmacidin F **457**. The conversion of quinic acid to the enantiomer of **453**, through desymmetrization of a pseudo-C2-symmetric compound, followed by formation of a bicyclic carbonate and hydrogenation, provided a new route for the synthesis of the antipode molecule.



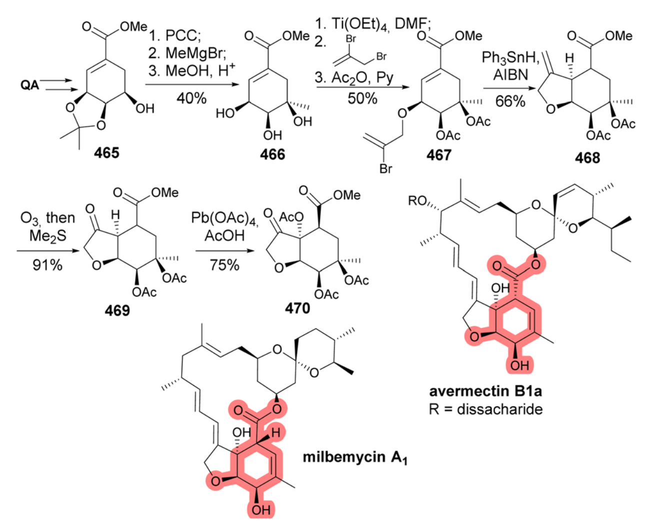
Scheme 73 Total synthesis of (−)-brunsvigine **463** and (−)-manthine **464**.

Montanine-type alkaloids found in the Amaryllidaceae family exhibit a broad range of biological activities, including antiviral, anxiolytic, antidepressant, and anticonvulsant effects. (−)-Brunsvigine **463** and (−)-manthine **464** were synthesized from quinic acid (Scheme 73), after its conversion into common enone **54**, iodination, and diastereoselective reduction of the iodoenone resulted in the formation of epimers **458** that were separated, and the undesired isomer **458a** was easily transformed to its epimer **458b** *via* a Mitsunobu reaction. The bicyclic structure **460** was obtained upon introduction of the Weinreb amide side chain, followed by anionic cyclization by treatment with *n*BuLi. The reduction of amine **460** with $NaBH_4$ in the presence of hydrated cerium chloride was shown to be diastereoselective, thus allowing the formation of pivaloate **461**, readily converted to synthetic intermediate **462** through a copper-mediated S_N2 reaction with an arylmagnesium bromide.[165]

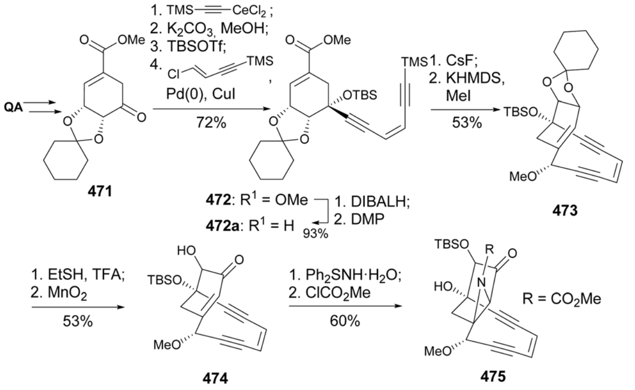
8. Macrocycle fragments

Hanessian *et al.* disclosed a new synthetic method for the hexahydrobenzofuran core found in avermectins and milbemycins (Scheme 74).[166] Such an approach utilized a radical-induced intramolecular Michael cyclization of a bromovinyl ether **467**, for which the installation of the vinyl bromide moiety was accomplished using thallium ethoxide in DMF, after failure with more common alkylation procedures.

The synthesis of the macrocyclic motif of espearmicin A1, an antitumor antibiotic, can be done by having quinic acid as the starting material (Scheme 75). The formation of the enediyne macrocycle occurred with the addition of an organocerium reagent to **472** as the first step, with the cyclohexylidene ketal being essential to promote *anti*-addition. Subsequently, the addition of vinylenthynyl chloride was aided by Pd-catalysis, while the intramolecular cyclization of **472a** was achieved by introducing the deprotected terminal alkyne to the aldehyde.[167]



Scheme 74 Synthetic route to tetrahydrobenzofurans.



Scheme 75 Synthesis of the macrocyclic motif of espearmicin A1.

Mulzer and coworkers have conducted extensive research on the synthetic pathways to the antibiotic branimycin **476** (Fig. 2), using quinic acid as a chiral scaffold for the synthesis of the *cis*-decalin system.[168–171]

In their studies, the *cis*-isoxazoline subunit can be obtained by an intramolecular nitrile oxide olefin cycloaddition (INOC) (mediated by either *t*BuOCl[168,169] or *N*-chlorosuccinimide[169,170]) or by ring-closing metathesis.[169,170] The former approach using *t*BuOCl (Scheme 76) was successfully applied to the preparation of model isoxazoline **483** from quinic acid, which included the diastereoselective hydroboration of **478** and the formation of allylic alcohol **480** using a Corey–Hopkins protocol that included the use of 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidene (DPD) for the elimination of a thionocarbonate. Upon successful formation of the desired isoxazoline, a similar approach was applied to the preparation of a more substituted derivative **489** (Scheme 77). The *cis*-isoxazoline **488** had its N–O bond cleaved to proceed with an Eschenmoser–Claisen rearrangement for the installation of the amide moiety.[170]

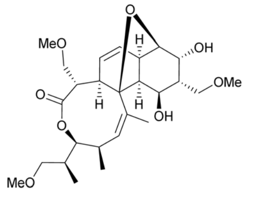


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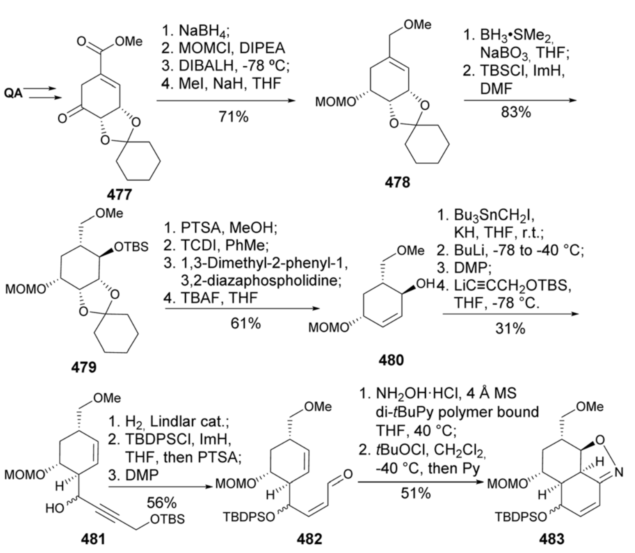
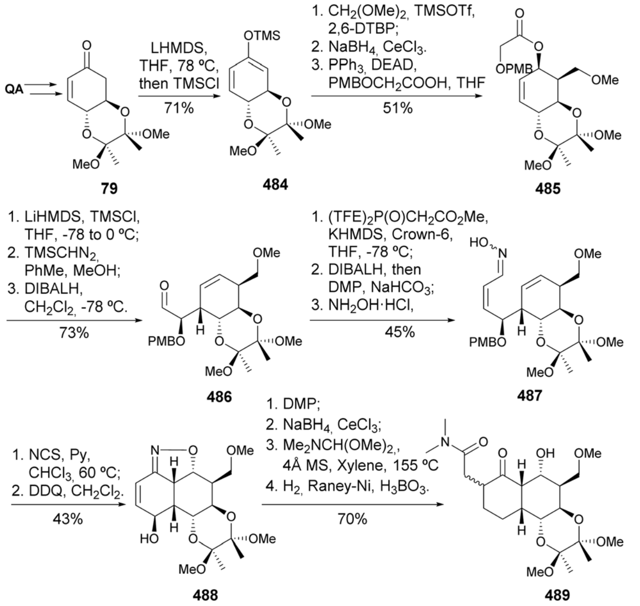
Fig. 2 Structure of branimycin.



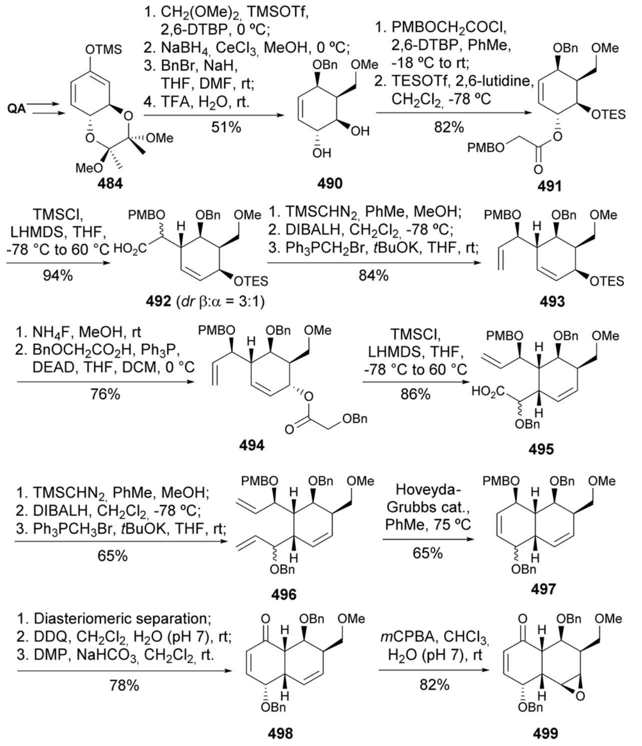
Scheme 76 Synthesis of highly substituted *cis*-decalin by INOC reaction mediated by *t*BuOCl.

The ring closing metathesis strategy encompassed the Mukaiyama-type condensation with dimethoxymethane, a diastereoselective process due to the conformational rigidity imposed by the *trans*-diequatorial-protected 1,2-diol (Scheme 78).[171] Ester **491** undergoes an Ireland–Claisen rearrangement, through a silylketene acetal, to provide **492** as a $\beta:\alpha = 3:1$ epimeric mixture. Installation of the alkene moiety was achieved *via* three steps, including a Wittig olefination, to provide **493**. A second Claisen–Ireland rearrangement to provide **495** was achieved upon desilylation of **493**, followed by ester installation through Mitsunobu inversion. The installation of the second cyclohexene moiety was achieved by RCM with Hoveyda–Grubbs catalyst, after the 2nd generation Grubbs failed to withstand 75 °C. PMB group was removed and the allyl alcohol oxidized to provide **498**, which was stereo- and regioselectively epoxidized to yield **499**, whose structure was confirmed by X-ray. Eventually, the first synthesis of branimycin was achieved by the same authors, starting from diepoxynaphthalene.[172]

Quinic acid has been converted into a dienyne and used in the preparation of taxadiene analogues by ring-closing metathesis (Scheme 79).[173] Enone **500** was converted into the α-iodoketone **501** and then treated with ethylmagnesium



Scheme 77 *Cis*-decalin by INOC reaction mediated by NCS.



Scheme 78 Preparation of *cis*-decalin by ring-closing metathesis.

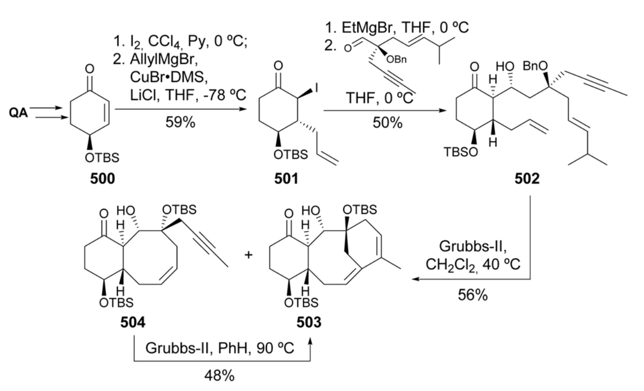
bromide and the aldehyde containing the required unsaturations. The ring closing metathesis was achieved with second-generation Grubbs catalyst in refluxing dichloromethane to provide the desired tricyclic structure **503** together with the bicyclic derivative **504** (in 40%). The latter could be easily converted into the desired taxadiene analogue **503** by further treatment with the same catalyst at higher temperatures.

9. Others

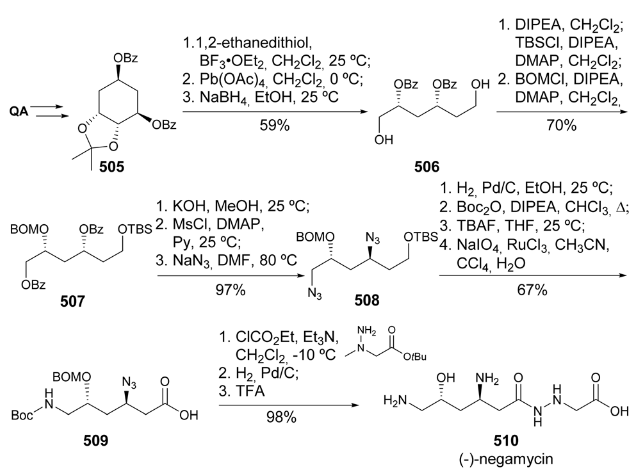
Although not so explored, QA has also been used in the total synthesis of linear natural products. One example is the synthesis of antibiotic (+)-negamycin **510** (Scheme 80). The oxidative ring cleavage of the cis diol was achieved using lead tetraacetate, followed by dialdehyde reduction. A series of protections, deprotections, nucleophilic substitution with azide, and reduction led to the synthesis of the linear natural product.[174]

A total synthesis of diterpene (+)-aphidicolin was reported by Fukumoto and co-workers,[175] by converting quinic acid into a synthetic intermediate used in the synthetic route developed by Smith.[176] A rather long synthetic sequence, starting from enone **511**, leads to the formation of enyne **512**, which undergoes a palladium-catalyzed cycloisomerization to provide bicyclic fragment **515**. This transformation enables the preparation of intermediate **516**, which can then be advanced *via* the reported Smith route (Scheme 81).

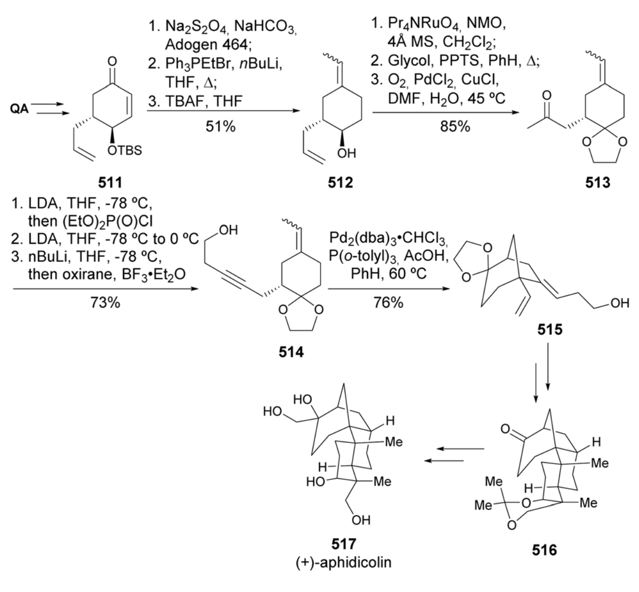
Notwithstanding the multiple previous syntheses of aquayamycin, Toshima and co-workers explored a new synthetic route in which the A ring fragment could be obtained from quinic acid (Scheme 82). This allowed shortening the previous



Scheme 79 Preparation of taxadiene analog.



Scheme 80 Synthesis of (−)-negamycin **510**.

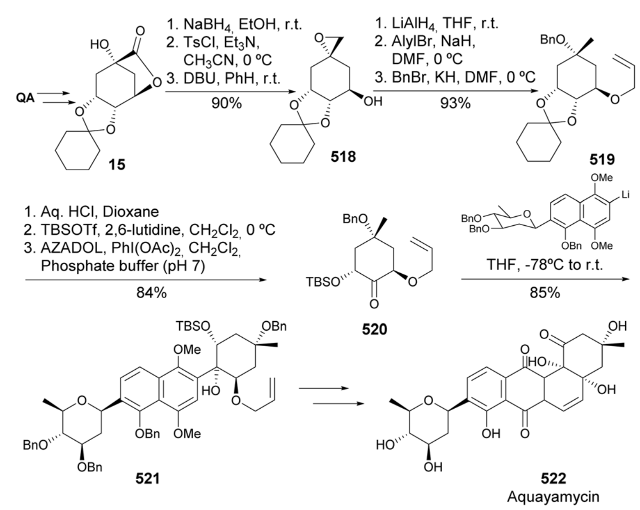


Scheme 81 Preparation of synthetic fragments for (+)-aphidicolin **517**.

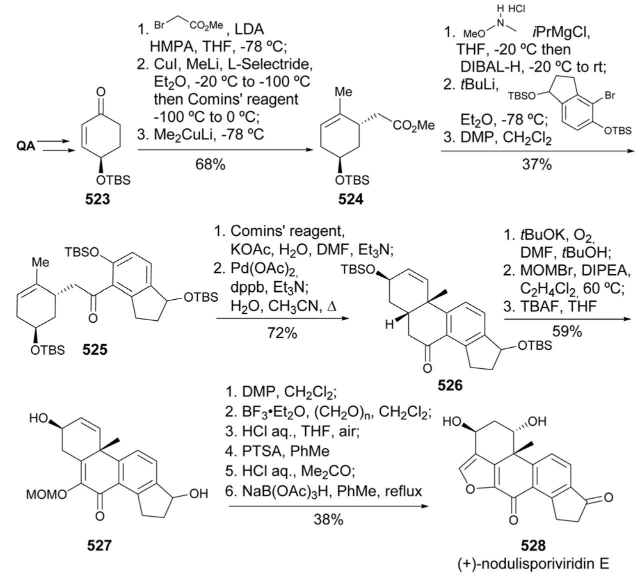
routes in 16 synthetic steps, having as a key step the diastereoselective 1,2-addition of a *C*-glycosyl naphthyllithium to the QA-derived ketone **520**. The construction of the B ring was achieved by an intramolecular pinacol coupling of a ketoaldehyde.[177]

The first total asymmetric synthesis of (+)-nodulisporiviridin E, reported by Gao and co-workers (Scheme 83),[178] started from the QA-derived enone **523**, obtained as previously reported by Maycock and co-workers.[147] The synthesis of this furanosteroid from the enone was based on an intramolecular Heck reaction for the construction of the tetracyclic core and the furan E ring built upon an intramolecular oxonium trapping reaction.

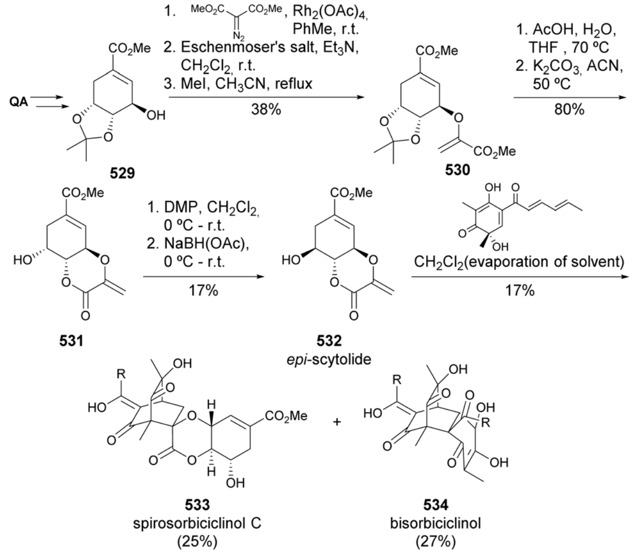
Quinic acid was used in the synthesis of the protected 4-epimer of shikimic acid, which, together with (−)-shikimic acid itself, was engaged in the synthesis of scytolide and multiple isomers (Scheme 84).[179] The scytolide epimer **532**, obtained from quinic acid, was submitted to Diels–Alder cycloaddition in the presence of sorbiclinol as the enophile to yield compound **533** in 25%, the endo compound, although with different spectral characterization than the previously reported natural product.



Scheme 82 Synthesis of aquayamycin **522**.



Scheme 83 Synthesis of (+)-nodulisporividin E.



Scheme 84 Synthesis of spirosorbiclinol C.

10. Conclusions and future perspectives

Quinic acid has established itself as a privileged chiral building block in total synthesis, enabling the efficient construction of structurally diverse and biologically relevant molecules. Its densely functionalized cyclohexane core, bearing four stereocenters, offers an inherent stereochemical advantage that reduces the need for complex asymmetric induction steps. Over the past decades, synthetic strategies have relied on key intermediates such as quinide lactones, decarboxylation-derived enones, and shikimic acid analogues, combined with transformations including oxidation-reduction epimerization, deoxygenation, and selective installation of exocyclic functionalities. These approaches have facilitated the synthesis of natural products ranging from carbacycles and alkaloids to vitamin D analogues, carbasugars, and cyclitols.

Despite these achievements, the chemoselective differentiation of hydroxyl groups remains the most significant challenge, often requiring extensive protection–deprotection sequences. To date, the most common methods rely on the selective protection of the *trans* diol moiety with butanedione[180,181] or the *cis* moiety with acetonide.[127,182]

While intramolecular protection and selective diol masking have improved efficiency, future progress will depend on the development of protecting-group-free methodologies and site-selective catalytic transformations. Such advances would dramatically reduce step count, improve atom economy, and align with the principles of sustainable synthesis.

Looking ahead, the adoption of greener processes, including catalytic and solvent-minimized reactions, will be essential to reduce environmental impact and improve scalability. Chemoenzymatic strategies hold promise for achieving unparalleled selectivity in hydroxyl functionalization and epimerization, complementing traditional chemical methods. Furthermore, the exploration of quinic acid derivatives in medicinal chemistry—especially for glycosidase inhibitors, vitamin D analogues, and alkaloid frameworks—will continue to drive innovation, as these scaffolds provide unique opportunities for tuning biological activity and pharmacokinetic profiles.

By combining these emerging approaches with the intrinsic stereochemical advantages of quinic acid, future synthetic strategies will not only enhance efficiency and sustainability but also expand the chemical space accessible from this versatile chiral building block, reinforcing its role as a key enabler in modern organic synthesis.

11. Author contributions

NRC performed the bibliographic search, curated the articles, organized the contents and revised the manuscript. MJV curated the articles, wrote the text and drew the schemes. ICV participated in the bibliographic search and revised the text.

12. Conflicts of interest

There are no conflicts to declare.

13. Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

14. Acknowledgements

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