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D-(−)-Quinic acid: a chiron store for natural product synthesis

Achille Barco*,[a,*] Simonetta Benetti,[a] Carmela De Risi,[b] Paolo Marchetti,[b] Gian P. Pollini*[b] and Vinicio Zanirato[b]

[a] Dipartimento di Chimica, Via L. Borsari 46, I-44100 Ferrara, Italy
[b] Dipartimento di Scienze Farmaceutiche, Via Fossato di Mortara 19, I-44100 Ferrara, Italy

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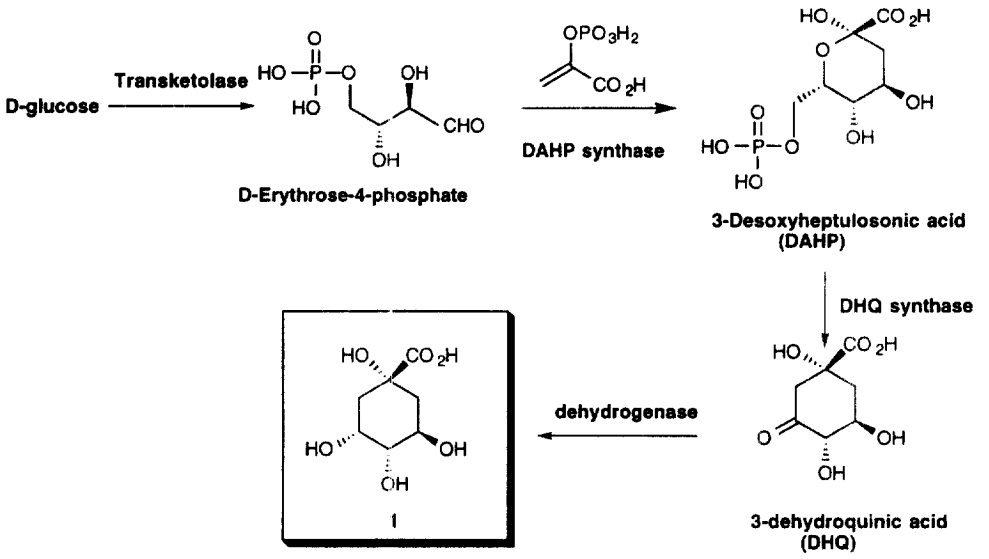
Abstract: Chemists have long been aware of the potential advantages of using chiral building blocks as starting materials in the synthesis of natural products. D-(−)-Quinic acid **1**, a widely occurring plant metabolite, has seen in the past only limited use as an optically active synthetic precursor in multistep chemical synthesis but has been particularly appreciated for the preparation of natural compounds featuring cyclohexane substituted skeletons. More recently, its applications as a chiral template in natural product synthesis have been rapidly growing, the serviceability of this highly functionalized substrate being easily extended to the preparation of open chain building blocks, which could be further transformed into optically active cyclopentane substituted skeletons and nitrogen containing targets. This review comprehensively covers quinic acid chemistry literature up to the beginning of 1997 and is aimed at stimulating the development of new chiral building blocks from a readily available, inexpensive starting material. © 1997 Elsevier Science Ltd

1. Introduction

(1*R*,3*R*,4*R*,5*R*)-1,3,4,5-Tetrahydroxycyclohexane-1-carboxylic acid, D-(−)-quinic acid **1**, first isolated as an impurity in crude quinine at the end of 18th century, occupies a prominent position among the primary metabolites originating from D-glucose. The pathway (Scheme 1) from D-glucose to

* Corresponding author. Email: pol@dns.unife.it

1 involves several enzymes including: (i) transketolase, which converts D-glucose to D-erythrose-4-phosphate; (ii) DAHP synthase, which adds phosphoenol pyruvate yielding 3-desoxyheptulosonic acid (DAHP); (iii) DHQ synthase, which converts the latter to 3-dehydroquinic acid (DHQ); (iv) quinic acid dehydrogenase, which eventually transforms 3-dehydroquinic acid to **1**.[1]



Scheme 1.

While its importance as a ubiquitous natural product is widely recognized, its role as a biogenetic precursor to more complicated secondary metabolites is less well defined. Although it does not appear as an intermediate on the main stem of the shikimic acid pathway, its presence can be related to a regulation of the shikimate pathway. Moreover, it can constitute an alternate source of carbon in several microorganisms (e.g. *Aerobacter aerogenes*, *Klebsiella pneumonia*) capable of converting it to 3-dehydroquinate. Interestingly, the ability of *Klebsiella pneumoniae* to live using quinic acid as the only carbon source has been cleverly utilized for producing quinic acid, simply through insertion of the gene coding for synthesis of the enzyme catalyzing the first metabolic step, the oxidation of **1** to 3-dehydroquinic acid, in bacteria unable to metabolize quinic acid, namely *Escherichia coli* modified by genetic engineering. Furthermore, a mutation suppresses the expression of the dehydratase responsible for the transformation of 3-dehydroquinic acid to dihydroshikimic acid.[1]

Quinic acid is widespread in the plant kingdom where it is found free or in the form of various esters with dihydroxycinnamic and gallic acid, the so-called depsides, the chlorogenic acids. However, the presence of significant amounts of quinic acid (more than 5% of the weight of the dried vegetal in some instances) suggests other possible metabolic activities and/or other relations with the shikimate pathway, for instance through quinate 3-phosphate.[2]

The structure and the stereochemistry of **1** were assigned in 1932 by H. O. L. Fisher and G. Dangschat,[3] who soon realized, simply on the basis of the structural relationships, the possibility that **1**, shikimic acid **2** and the aromatic phenolic acids, such as gallic acid **3**, should have a common biogenetic origin (Figure 1).

This intuition was confirmed 20 years later, when the shikimate pathway, through which the aromatic aminoacids are formed in plants and microorganisms, was fully elucidated.

Quinic acid, being easily isolated in a state of very high enantiomeric purity from plant sources through simple processes, is commercially available and its abundance in the chiral pool has made

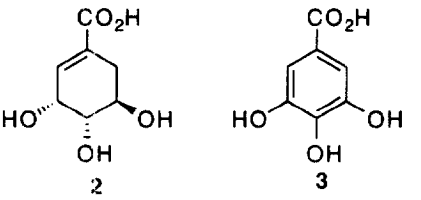
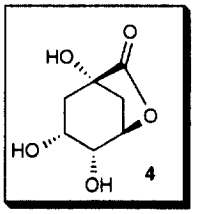


Figure 1.

it an attractive starting material for asymmetric multistep syntheses of naturally occurring substances and related compounds.[4]

2. D-(−)-Quinic acid and its transformations

The separation of the reactivity of the functional groups present in **1** may be easily accomplished through esterification of the carboxylic acid group both inter- or intramolecularly. Thus, Gorrichon *et al.*[5] were able to convert quantitatively quinic acid into the corresponding methyl ester simply by heating in methanol in the presence of Amberlyst. The same procedure applied to dehydroquinic acid affords less satisfactorily (50% yield) the corresponding methyl ester, the pattern of functionalities being less tolerant to acid conditions. However, much more attention has been paid to the intramolecular esterification of the C-1 carboxyl group with the C-5 hydroxyl group leading to the formation of the bicyclic γ-lactone **4**, commonly called quinide, leaving free the hydroxyl groups at C-1, C-3 and C-4.



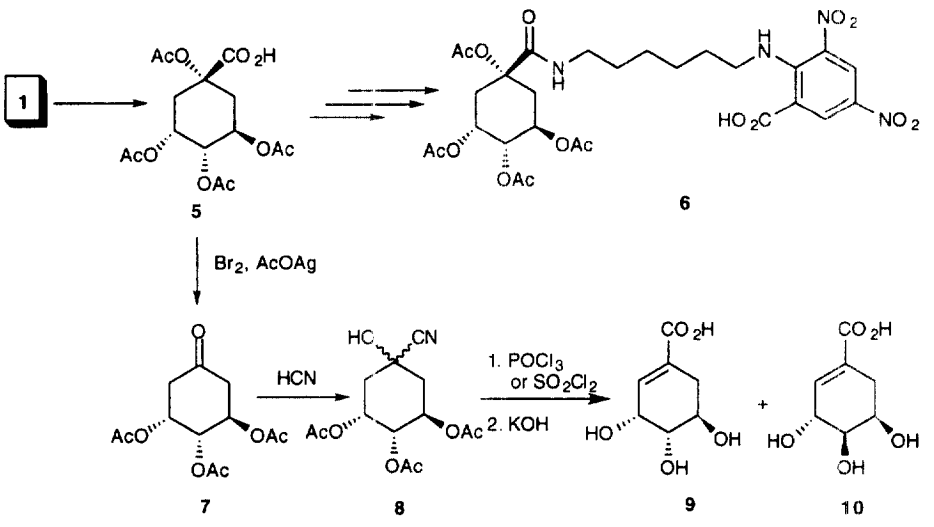
A detailed spectroscopic investigation (^{1}H and ^{13}C NMR) allowed Ernst *et al.*[6] to identify the different quinide isomers obtained by heating **1** in acetic acid in the presence of 90% sulfuric acid, after a careful separation. All these products are generated in the toasting coffee process.

The four hydroxyl groups of **1** could be acetylated as described by Grewe and Haendler[7] to give the tetraacetylated derivative **5**, on which several interesting transformations have been performed as summarized in Scheme 2. Thus, condensation of **5**, suitably activated as the benzotriazolyl derivative, with 2-(6-aminohexylamino)-3,5-dinitrobenzoic acid, produced the amide **6**[8] while the Hunsdiecker reaction converted it in good yield (77%) into the ketone **7**, the oxidative decarboxylation being effected with bromine and silver acetate.[9] The same authors[9] and later Rapoport *et al.*[10] investigated the formation of the cyanohydrin **8** by addition of hydrogen cyanide to **7** and subsequent dehydration, demonstrating that both processes are not stereospecific producing a mixture of **9** and **10**.

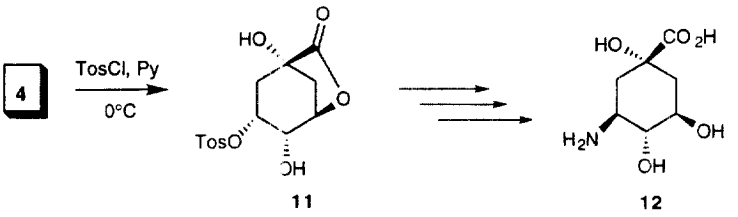
3. Quinide 4 as the starting material

The preparation of **4**, originally described by Fisher in 1921,[11] has been later improved, firstly by Gero *et al.*[12] by heating **1** in dimethylformamide solution in the presence of IR-120 Amberlyst (80% yield) and more recently by Vandewalle *et al.*,[13] by heating **1** in toluene in the presence of *p*-toluenesulfonic acid (96% yield). Gero *et al.* used **4** as the precursor of the cyclic γ-amino-α-hydroxy acid **12**, which has been subsequently introduced as a side chain in aminoglycoside antibiotics such as amikacin and butyrosin B (Scheme 3).

Interestingly, tosylation of **4** in dry pyridine at low temperature led to the selective formation of the tosylate **11**, the equatorial C-3 secondary hydroxyl group being less hindered than the axial C-4 one.



Scheme 2.



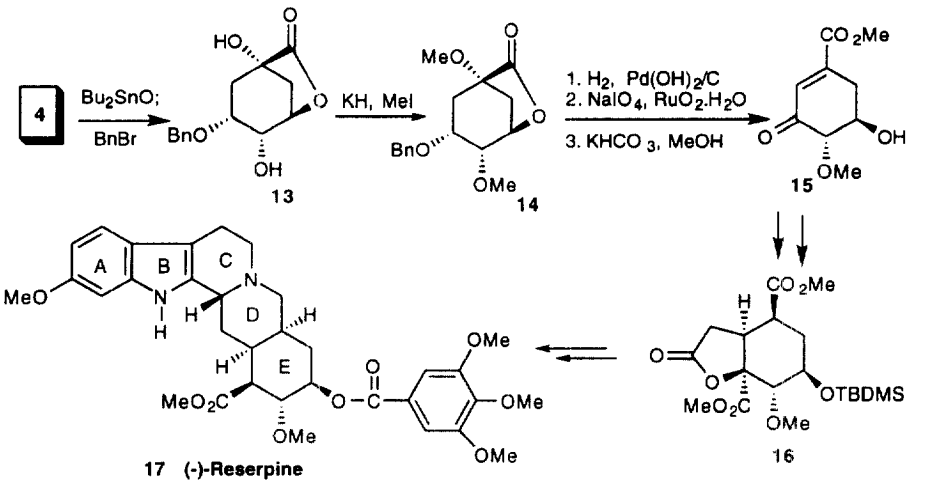
Scheme 3.

Selective benzylation of the equatorial hydroxyl group of **4** to give **13** has been also efficiently accomplished via the intermediacy of a stannylene acetal by Hanessian *et al.*[14] in the opening step of a total synthesis of (−)-reserpine. The approach entails the use of D-(−)-quinic acid as a chiral template for a stereocontrolled construction in 10 steps via the quinide **4** of the intermediate **16**, the carbon skeleton possessing the required functionalities for rings D/E of (−)-reserpine **17** (Scheme 4).

Methylation of the free hydroxyl groups of **13** gave the fully protected derivative **14**, which, after reductive removal of the benzyl protecting group and subsequent oxidation, produced a cyclohexanone derivative which underwent a clean transformation to the conjugate ester **15** through mild methanolysis of the lactone moiety followed by β-elimination.

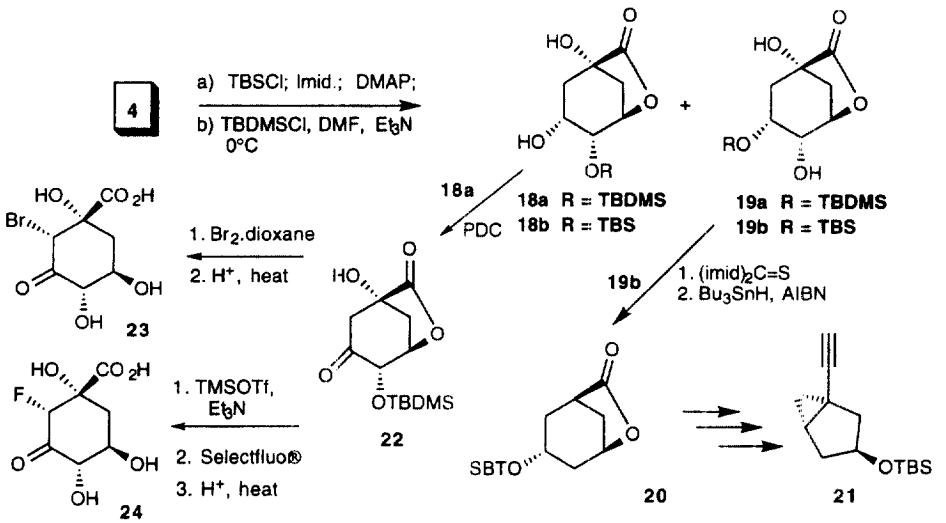
The carbonyl group of **15** will serve to introduce both the required carbomethoxy and tertiary hydroxy group, the latter being subsequently transformed into an α-haloacetate ester which was used as a branch for an intramolecular free-radical mediated conjugated addition across the α,β-unsaturated ester.

On the other hand, the selective protection of the C-4 hydroxy group of **4** was recently achieved using *tert*-butyldimethylsilyl (TBDMS) chloride in *N,N*-dimethylformamide containing tetrabutylammonium iodide and triethylamine at 0°C for 6 h (Scheme 5).[15] Under these experimental conditions a mixture of the monoprotected compounds **18a** and **19a** was obtained in a ratio 3:97. Moreover, carrying out the reaction at 90°C the selectivity was reversed (product ratio 2:1). In addition, submission of the kinetic product **19a** to the higher temperature conditions resulted in it being converted to a mixture of **18a** and **19a**. Curiously, the silylation of **4** with TBSCl using imidazole as the catalyst has been previously reported to give rise to a 4:1 mixture of the corresponding silyl derivatives **18b**



Scheme 4.

and **19b**.[13] The silylated quinide **18b** was separated from the isomer **19b** by preparative HPLC and the latter transformed into the bicyclic γ-lactone **20**, a convenient precursor of the key intermediate **21** in the route to Vitamin D3 analogs, through removal of the C-1 and C-3 hydroxyl groups through Barton–McCombie deoxygenation via the corresponding bis-thiocarbonyl imidazolide derivative.

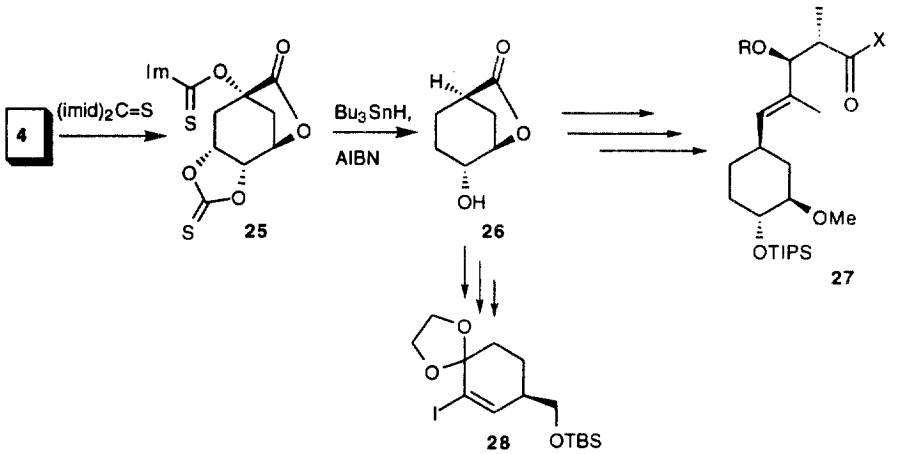


Scheme 5.

In addition, the free secondary hydroxyl group of **18a** could be oxidatively converted (PCC or TPAP–MNO or PDC) into the corresponding acid-sensitive ketone **22** which has been conveniently utilized for preparing interesting halogenated quinic acid derivatives such as (2*R*)-2-bromodehydroquinic acid **23** and (2*R*)-2-fluorodehydroquinic acid **24**.[15]

The bromine has been introduced directly into **22** using dioxane dibromide, while the introduction of fluorine with Selectfluor® required a two-step operation involving the prior formation of the silyl enol ether. Both compounds are inhibitors for 3-dehydroquinate dehydratase, the third enzyme on the shikimate pathway.

The same quinide **4** has been conveniently used by Mills *et al.*[16] as the starting chiral building block for the construction of the carbon backbone **27** featuring the immunosuppressant FK-506 (Scheme 6). The synthetic sequence required the stereo- and regioselective removal of the C-1 and C-3 hydroxyl groups. This operation has been successfully achieved through the intermediacy of the bis-thiocarbonyl lactone **25**, in turn obtained by a standard step, which reacted with tributyltin hydride to give in moderate overall yield (40%) exclusively the optically active lactone **26**. The regioselectivity of the Barton and McCombie opening of the cyclic thiocarbonate has not been explained.



Scheme 6.

The same intermediate **26** has been also transformed by Paquette *et al.*[17] to the enantiomerically pure acetal of 2-iodo-2-cyclohexenone **28**, bearing a hydroxymethyl side chain destined to become the C-16 carbon of the taxol skeleton. Unfortunately, the application of this intermediate to the synthesis of the taxane system has been frustrated by the congestion of substituents which hampers the planned reaction sequence.[18]

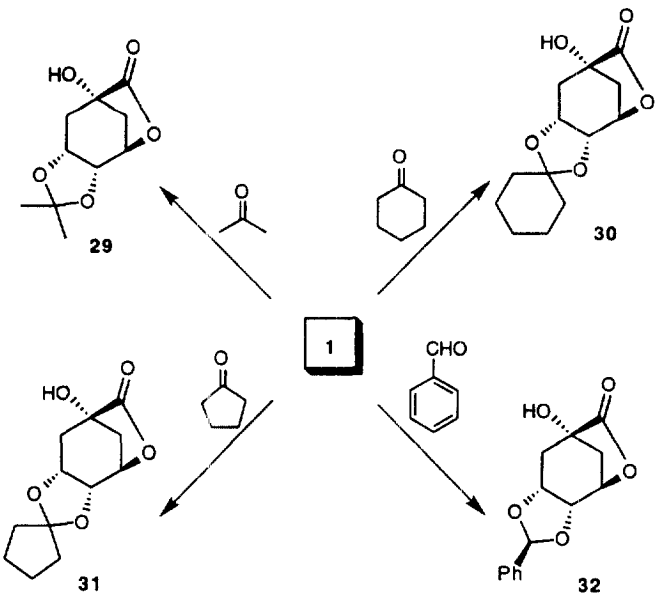
4. Natural products from quinide ketals and acetals

The acid-catalyzed reaction of quinic acid with different carbonyl compounds (acetone, cyclohexanone, cyclopentanone and benzaldehyde) allows the protection of the C-3 and C-4 hydroxyl groups as ketals or acetals with concomitant formation of a γ-lactone ring between the carboxyl group at C-1 and the C-5 hydroxyl group producing the different quinide acetals **29–32** (Scheme 7). Thus, sulfuric acid[19] and later hydrochloric acid[20] have been used as the catalyst to perform the reaction between quinic acid and acetone which proceeded at low temperature to give the isopropylidene lactone **29** in 80% yield, while cyclohexylidene- and cyclopentylidene lactones **30** and **31** have been obtained by azeotropic removal of water from a mixture of quinic acid and the required carbonyl partner in benzene solution in the presence of *p*-toluenesulfonic acid as the catalyst.[21,22]

Acid-catalyzed reaction of quinic acid with benzaldehyde[22–25] produced the benzylidene lactone **32** as a 3:1 mixture of diastereomers at the acetal carbon from which the major isomer could be obtained in crystalline form. The (*S*) configuration originally assigned to the newly created stereogenic centre, simply on the basis of steric arguments,[23] has recently been shown to be (*R*) on the basis of more convincing spectroscopic evidence through the observation of NOEs from H-4 and H-5 to the benzylidene hydrogen in the ^{1}H NMR spectrum.[15]

4.1. *Isopropylidene quinide ketal 29*

The simplest quinide ketal **29** has been widely used as a starting material in natural product synthesis. Standard functional group transformations allowed this compound to be conveniently transformed



Scheme 7.

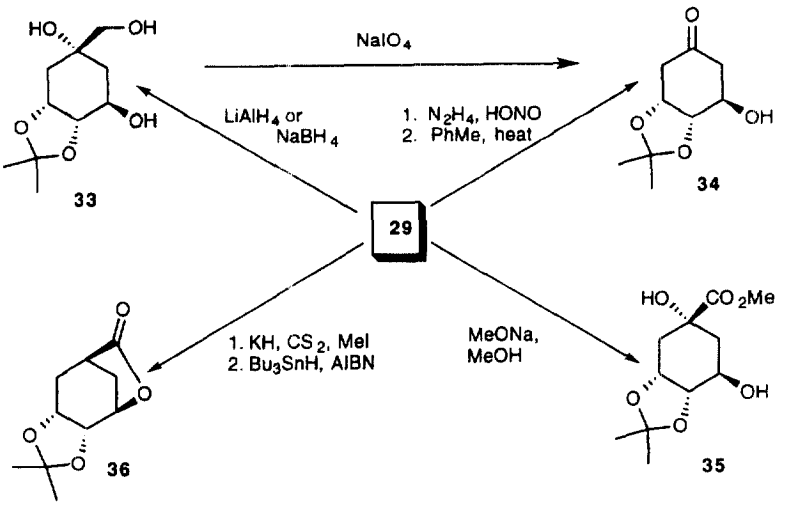
into a series of interesting synthons. Thus, its $LiAlH_4$[26] or $NaBH_4$ reduction leads to the almost quantitative formation of **33**, an important intermediate for further transformations, while Fisher *et al.*[3] were able to convert **29** through Curtius rearrangement of an intermediate acylazide into the the hydroxyketone **34**, later more conveniently prepared by oxidative cleavage of the vicinal diol with $NaIO_4$.[26,27] Methanolysis of **29** with NaOMe in methanol furnished the interesting intermediate **35** in good yield, the free secondary alcohol function, as we will see later, could be oxidized to the corresponding ketone under carefully controlled experimental conditions (short reaction times) in order to minimize the possibility of concomitant elimination.[28] Finally, deoxygenation of the C-1 tertiary alcohol could be conveniently achieved via the corresponding xantate by treatment with tributyltin hydride in the presence of catalytic quantity of AIBN to give **36** in 73% yield.[29] The synthetic operations leading to the chiral synthons **33–36**, which have been further transformed in natural targets, are summarized in Scheme 8.

The acetyl derivative **37** of the ketone **34** was acylated with the lithium salt of 2-methyl-1,3-dithiane to give the adduct **38**. Acid-promoted deprotection followed by Corey–Winter deoxygenation of the vicinal diol moiety afforded the allylic alcohol acetate **39**. The configuration of the allylic stereogenic center could be easily and quantitatively inverted under Mitsunobu conditions allowing the preparation of the protected A-ring system of both daunomycinone and 7-*epi* isomer (Scheme 9).[30,31]

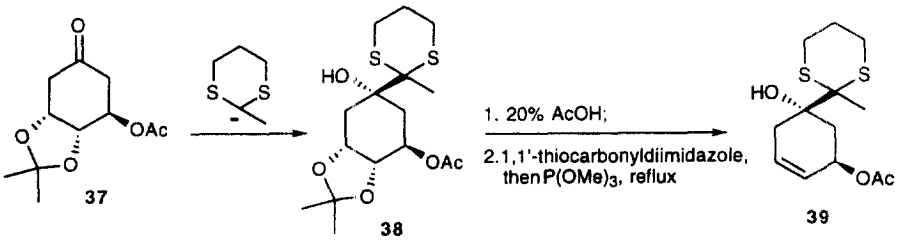
Quinic acid has been conveniently utilized by Steglich *et al.*[32] as a building block for ring A in the first stereoselective synthesis of preanthraquinones **45**, a class of compounds isolated from fungi and plants. In this case, deoxygenation of the diol moiety was performed thermally on the intermediate **41**, in turn obtained from the quinide **29** via acylation to give **40**, followed by a deprotection–reprotection sequence to give **41** (Scheme 10).

The unsaturated lactone **42** was subsequently reduced by treatment with $LiAlH_4$ into the triol **43**, which required suitable differentiation of the three alcoholic groups, the primary alcohol being destined to become the methyl group in the crucial cyclohexenone **44**.

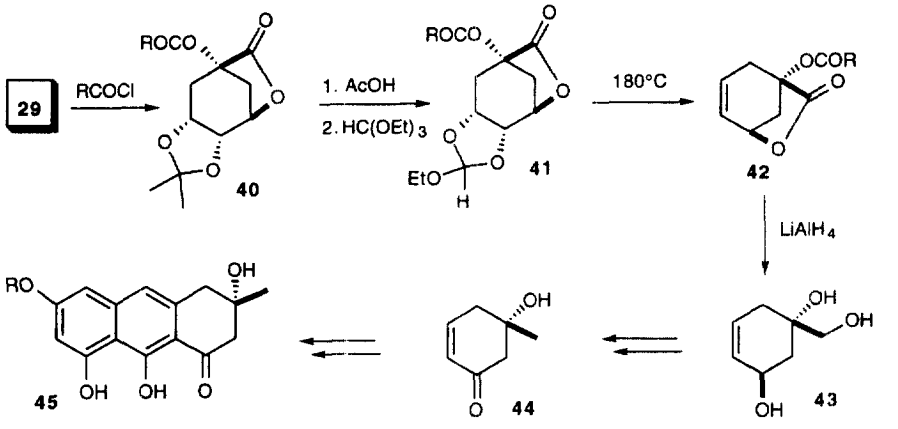
The interesting compound **35** has been both transformed into the carbocyclic analogue 3-deoxy-β-D-manno-2-octulopyranosidic acid **47** of β-KDO,[28] and successfully used as an intermediate for preparing



Scheme 8.



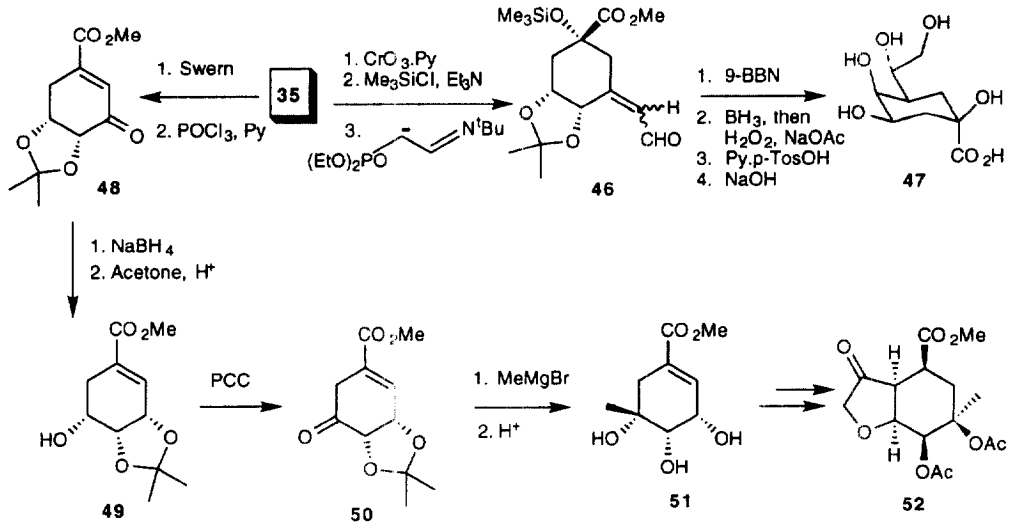
Scheme 9.



Scheme 10.

the triol **51**, a precursor of the hexahydrobenzofurane subunit of avermectins and milbemycins, as summarized in Scheme 11.[33]

In the first case, after oxidation of the C-5 hydroxyl group and protection of the tertiary hydroxyl group as the corresponding silyl derivative, the required two-carbon side chain was introduced via a modified Wittig reaction involving treatment of acetaldehyde-*tert*-butylimine with LDA in THF at −78°C and then with diethyl chlorophosphate at −10°C to generate the anion which reacted with the



Scheme 11.

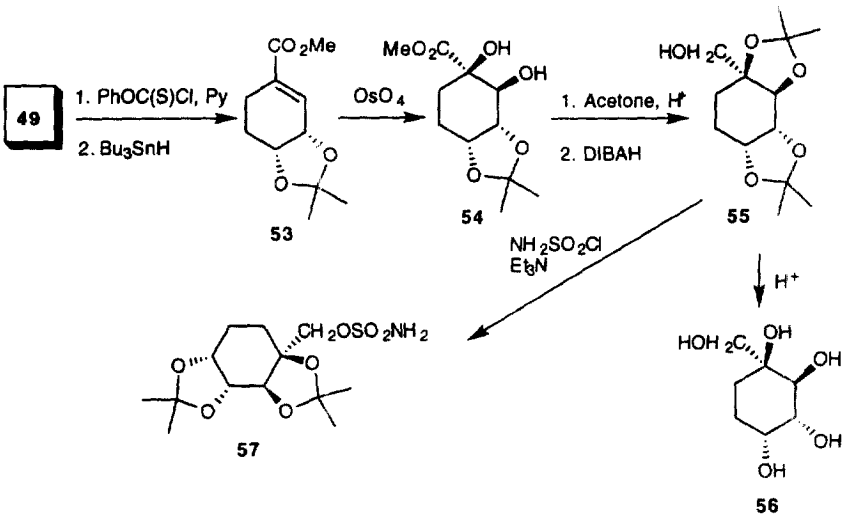
carbonyl group to give after work-up a mixture of α,β-unsaturated aldehydes **46**, which were separated and further elaborated to the intended target in a three-step sequence involving reduction (9-BBN), hydroboration/oxidation (BH_3, H_2O_2, NaOAc) and eventually deprotection (pyridinium tosylate in ethanol).

On the other hand, transformation of **35** into the triol **51** was required for the construction in enantiomerically pure form of the oxahydrindene subunit **52** related to avermectins and milbemycins. In order to avoid the formation of a mixture of olefin isomers, a suitable adaptation of the procedure originally developed by Lesuisse and Berchtold[23] on the corresponding acetal quinide **32**, involving prior Swern oxidation of the free secondary alcohol to the corresponding ketone followed by dehydration with phosphorus oxychloride in pyridine, was successfully used to obtain **48**. Reduction of the ketone from the less hindered β-face to the α-alcohol, followed by thermodynamically controlled isopropylidenation to the more stable acetonide **49** and subsequent oxidation (PCC) produced the β,γ-unsaturated ketone **50**, which reacted with methyl magnesium bromide to furnish after removal of the protecting group the optically active precursor **51** of the subunit **52**.

McComsey and Maryanoff[34] found that the α,β-unsaturated ketoester **49** could be readily deoxygenated by radical-based methodology to give **53** in good yield in contrast to the results reported in the literature (Scheme 12).

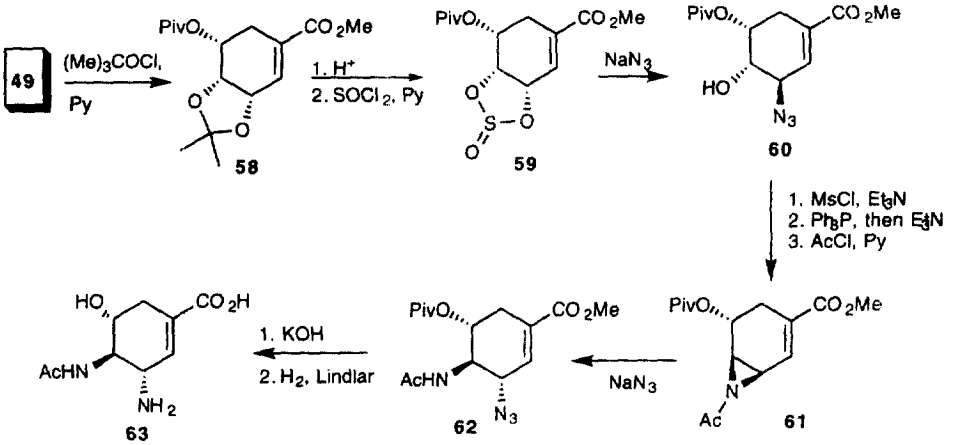
These findings paved the way to more convenient access to both pseudo-β-D-fructopyranose **56** and to the branched-chain cyclitol derivative **57**, a carba isostere of topiramate, a clinically useful antiepileptic drug, involving as common steps, osmylation to give the diol **54**, then protection as isopropylidene ketal and reduction to afford **55**.

The same cyclohexene intermediate **49** and the chiral synthon **35** have been recently utilized to gain access to the interesting carbocyclic sialic acid analogues **63** and **70** with potent anti-influenza activity.[35] Interestingly, although shikimic acid would have been a more convenient chiral starting material, its high cost and low availability in large quantities made it impracticable for scale-up of candidates for drug development, forcing the authors to choose quinic acid instead. The synthetic sequences outlined in Schemes 13 and 14 present several interesting transformations including a regiospecific cyclic sulfite ring opening by azide ion at the allylic C-3 position of **59** to produce the β-hydroxy azide **60**, which was converted in a three-step sequence into the aziridine **61**, which in



Scheme 12.

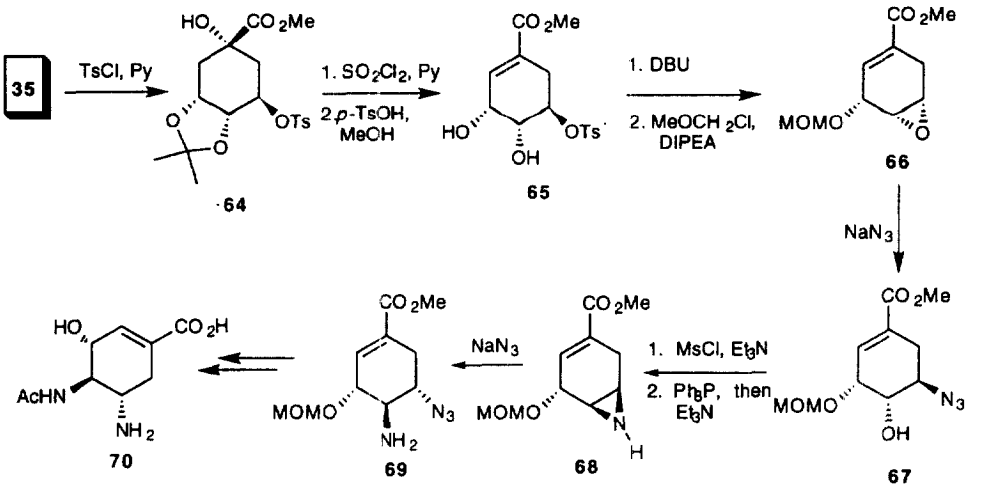
turn regiospecifically opened to give the azide **62** as the sole product. Saponification and reduction complete the synthesis of the planned analogue **63**.



Scheme 13.

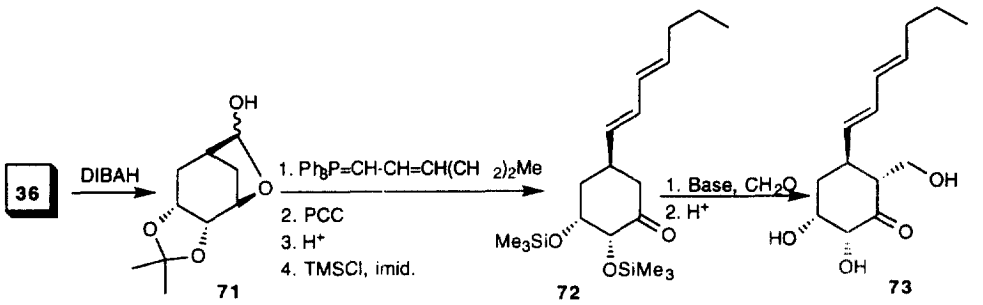
The preparation of the isomeric analogue **70** called for the selective dehydration of the C-1 hydroxyl of **35**. This operation was accomplished by treatment with sulfuryl chloride in pyridine of the tosylate **64**, followed by acetonide cleavage in refluxing methanol to afford **65**, which directly crystallized out of the reaction mixture in 54% overall yield, the other regioisomer aromatizing in these conditions and being easily separated by crystallization. Quantitative conversion of **65** to the key epoxide intermediate **66**, originally prepared from shikimic acid, was obtained by treatment with DBU and MOM-protection of the hydroxyl group.

Regio- and stereospecific epoxide ring opening by sodium azide furnished the azido alcohol **67**, which was further converted to the aziridine **68**, which underwent exclusive attack by azide ion at the C-5 position to give the intermediate **69**. This was easily converted to the analogue **70** by standard chemistry.



Scheme 14.

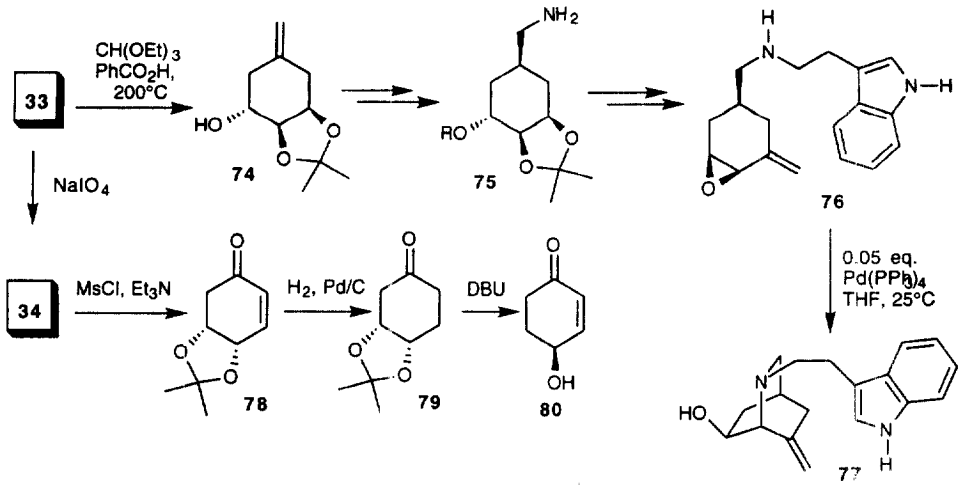
The C-1 deoxygenated product **36**, easily prepared as described in Scheme 8 by treatment with tributyltin hydride of the xantate derived by treatment of **29** with potassium hydride, carbon disulfide and methyl iodide, represents a very convenient building block for an elegant synthesis of (+)-palitantin **73**, an antifungal antibiotic isolated from *Penicillium palitans*, described by Hanessian,[29] as summarized in Scheme 15. Reduction of the lactone moiety with DIBAH produced the lactol **71**, which was chain extended via Wittig reaction, oxidized and, after a deprotection/protection step, the separated pure *trans* isomer **72** underwent site selective hydroxymethylation to give the intended target.



Scheme 15.

As already depicted in Scheme 8, the γ-lactone functionality of **29** can be efficiently reduced by means of $LiAlH_4$ or $NaBH_4$ to produce the triol derivative **33**, the two geminal functions at C-1 may be seen as synthons of either an exocyclic methylene group or of a carbonyl group. In the first case, a very clean thermolysis of the cyclic *ortho* ester obtained by benzoic acid-catalyzed reaction of **33** with triethyl orthoformate generated **74**, which was subsequently converted into the amine **75**, a precursor of the optically active isoquinuclidine derivative **77** through a palladium mediated cyclization via isomerization of the vinyl epoxide **76**.[26] On the other hand, sodium metaperiodate oxidation of the 1,3-diol moiety of **33** led to the formation of the ketone **34**, which was easily dehydrated in a one-pot elimination process promoted by methansulfonyl/triethyl amine system to **78**, a precursor of the enantiomeric pure (*S*)-4-hydroxy-2-cyclohexenone **80** via the intermediacy of **79** (Scheme 16).[27]

Recently, a very facile dehydration of the β-hydroxy moiety of **34** by acetylation followed by *in situ* treatment with diisopropylethylamine has been described as an improved procedure to obtain the



Scheme 16.

enone **78** in essentially quantitative yield.[36] Interestingly, the ease with which the elimination occurs has been accounted for by the boat conformation of the cyclohexane ring which is imposed by the isopropylidene acetal ring.

Compound **78** has been utilized as the starting material for an enantioselective approach to the enone **87**, the tricyclic central core of (+)-manzamine A,[37] a member of a family of complex β-carboline alkaloids displaying antitumor and antibacterial activities, as well as for an enantioselective total synthesis of (+)-eutypoxide B **92**,[36] a metabolite isolated from the culture medium of the fungus *Eutypa lata*. Both approaches capitalized upon the high stereoselectivity of 1,4-additions to α,β-unsaturated ketones derived from quinic acid to introduce the required configuration at the key position of the cyclohexane ring.

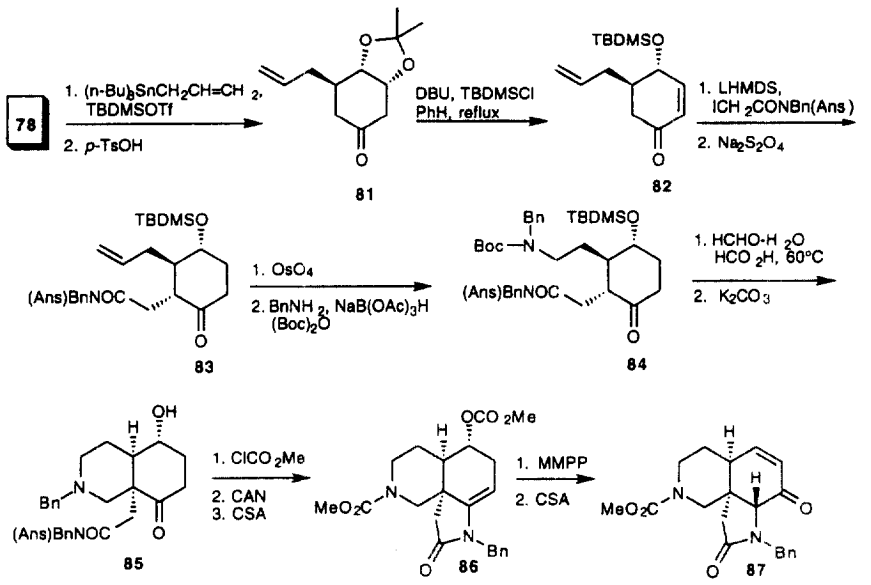
Thus, stereoselective conjugate addition of tri-*n*-butylallylstannane in the presence of one equivalent of TBDMSOTf followed by cleavage of the resulting enoxysilane during acidic work-up produced the saturated ketone **81**,[37] which on treatment with DBU and TBDMSCl in refluxing benzene was converted into the enone **82**. Alkylation of the kinetic anion with *N*-(*p*-methoxybenzyl)-*N*-(benzyl)iodoacetamide and direct reduction produced the trisubstituted cyclohexanone **83**.

Oxidative transformation of the allyl group into an acetaldehyde side chain, followed by reductive amination with benzylamine and BOC-protection afforded the intermediate **84**, required for the crucial intramolecular Mannich cyclization to **85** formed as a single stereoisomer. Removal of benzyl- and *p*-methoxybenzyl protecting groups and camphorsulfonic acid (CSA)-catalyzed dehydration afforded the tricyclic enamide **86**, which was eventually converted into **87** by magnesium monoperoxyperphthalic acid (MMPP) oxidation followed by acid-promoted rearrangement of the derived epoxide and subsequent β-elimination (Scheme 17).

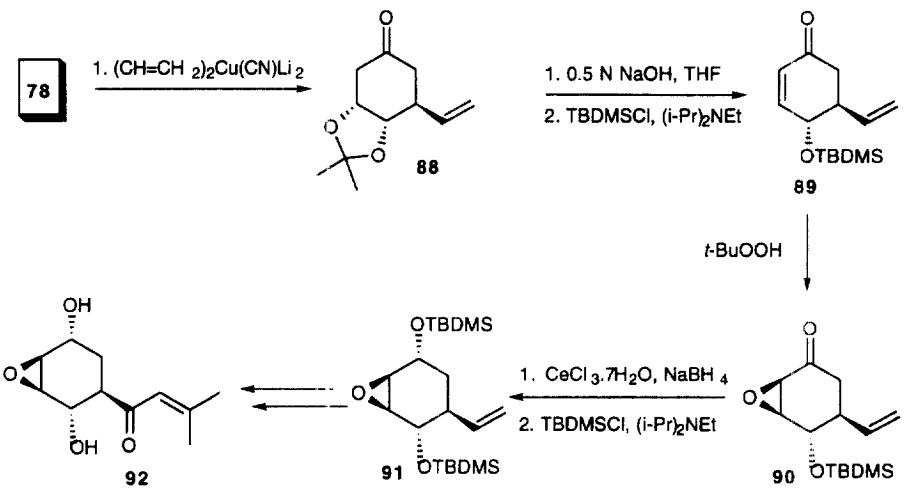
On the other hand, the conjugate addition of a high-order cyanocuprate to **78** afforded the ketone **88**[36] which was easily transformed in virtually quantitative yield by base-induced elimination into the corresponding enone, already partially formed in the addition step, being immediately protected as the silyl ether **89**.

Treatment of the latter with *t*-BuOOH and a catalytic amount of Triton B provided exclusively the epoxide **90**, which was subsequently reduced with sodium borohydride in the presence of cerium(III) chloride to give a mixture of diastereoisomeric alcohols which were separated by chromatography and the required α-isomer was fully protected as **91**, before proceeding to build up the side chain of the target **92**, the vinyl group acting as an aldehyde synthon (Scheme 18).

Interestingly, the intermediate **82** has also been utilized as the starting point for a stereoselective



Scheme 17.

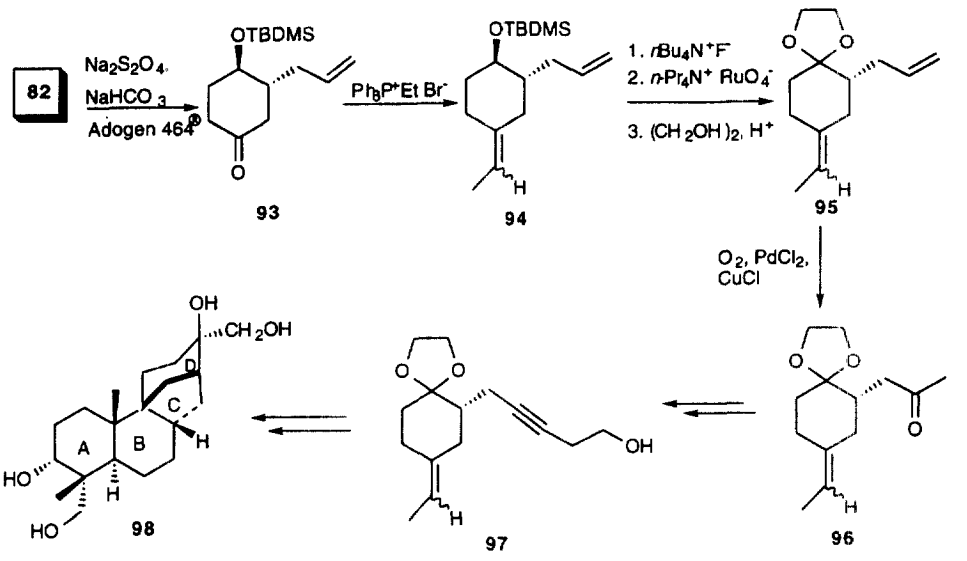


Scheme 18.

formal synthesis of the diterpene tetraol (+)-aphidicolin **98**,[38] a potent antiviral and antimitotic agent isolated from *Cephalosporium aphidicola* possessing an interesting arrangement of fused, spiro and bridged rings.

The first step of the preparation of the enyne precursor **97** required for the key palladium catalyzed cycloisomerization to form the C and D rings of **98** consisted of a chemoselective reduction of **82** to furnish the saturated ketone **93**, which was then transformed by Wittig reaction into the ethylidene derivative **94**. Functional group manipulation produced **95**, which was transformed to the ketone **96** through a regioselective Wacker oxidation as outlined in Scheme 19.

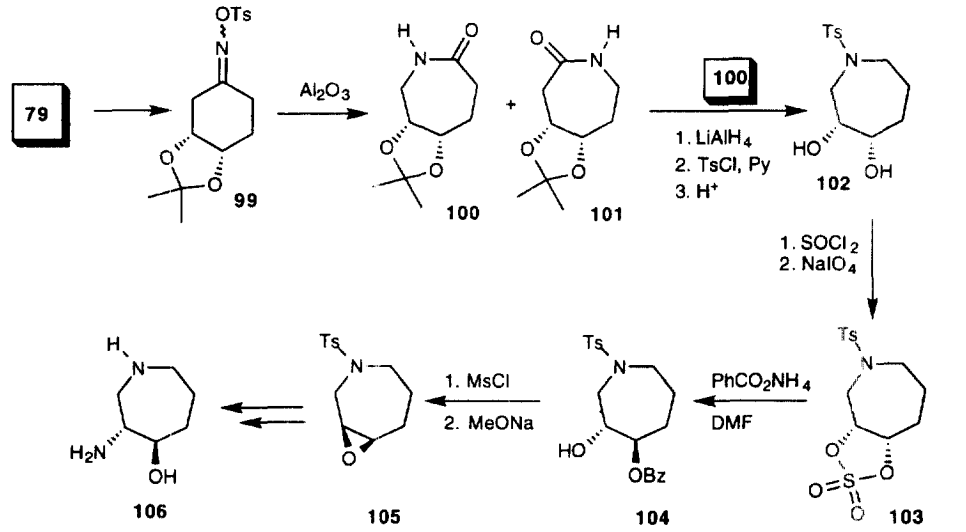
Incorporation of a nitrogen atom into the quinic acid skeleton has been successfully used as a means to prepare chiral hexahydroazepines. Thus, 3-amino-4-hydroxyhexahydroazepine **106**, the central core



Scheme 19.

of balanol, an unusual metabolite isolated from the fungus *Verticillum balanoides*, has been obtained using **79**[39,41] as a chiral source.

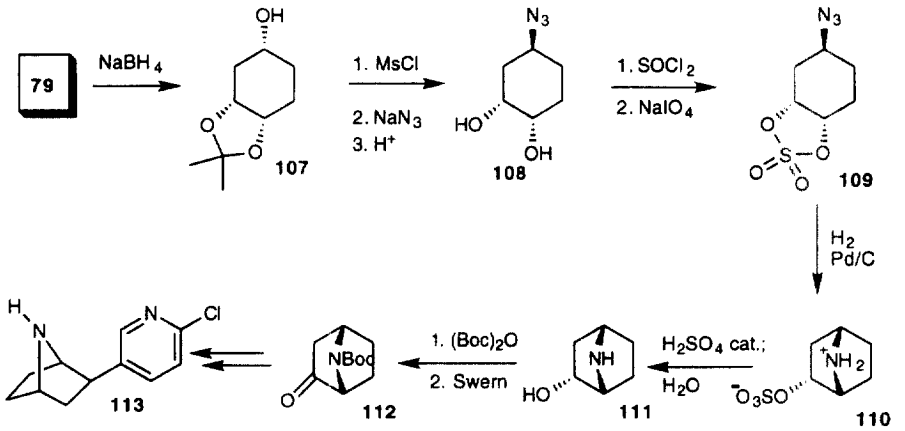
The crucial step entailed a Beckmann rearrangement promoted by basic alumina on the corresponding oxime tosylates **99**, producing a mixture of regioisomeric amides **100** and **101**, easily separated by simple crystallization. Lithium aluminum hydride reduction of **100**, followed by tosylation and removal of the acetonide protecting group furnished the intermediate **102**. The 1,2-diol moiety of **102** was transformed into the cyclic sulfate **103**, which underwent regio- and stereoselective ring opening by means of benzoate ion to provide the hydroxybenzoate **104**, which, after suitable activation, was easily converted into the *N*-tosylhexahydroazepine epoxide **105**, a precursor of **106**, already converted into balanol (Scheme 20).



Scheme 20.

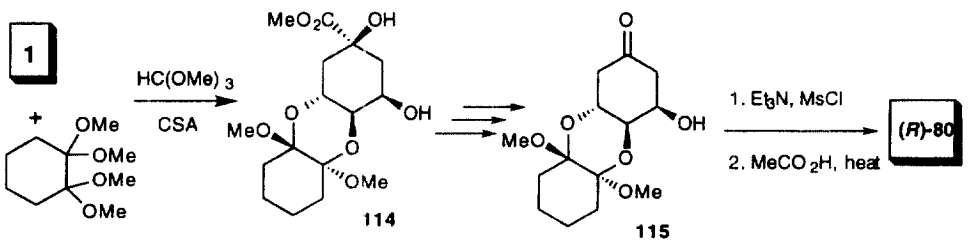
The saturated ketone **79**, available from quinic acid in multigram quantities in five simple steps,[27] has been successfully used as a convenient chiral template for an enantioselective formal synthesis of (+)-epibatidine **113**,[40,41] a simple alkaloid isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolor*, which was reported to be a remarkable non-opiod analgesic and nicotinic acethylcholine receptor agonist. The structural novelty coupled with scarcity in nature and intriguing pharmacological properties have made **113** a popular target for synthesis.

Our own approach begins with sodium borohydride reduction of **79** to give an unseparable 11:1 mixture of **107** and its epimer which were easily separated as the corresponding mesylates, submitted to azide displacement and removal of the acetonide to give **108** as a white solid. After transformation into the key cyclic sulfate **109** by standard methodology, hydrogenation over 10% Pd/C in THF:H_2O proceeded smoothly with concomitant internal displacement forming the inner salt **110**. Hydrolysis of the sulfate group gave the secondary alcohol **111**, which was protected as the Boc-derivative and submitted to Swern oxidation to yield the corresponding ketone **112**, already transformed into the natural target and thus completing its enantioselective formal synthesis (Scheme 21).



Scheme 21.

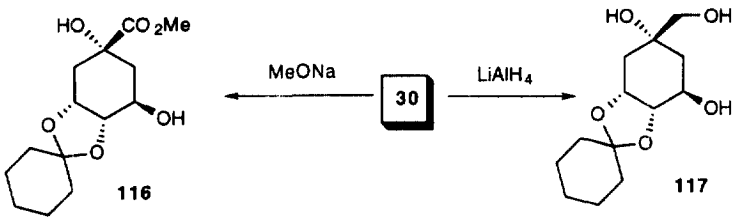
Recently, (*R*)-4-hydroxy-2-cyclohexenone **80** has been conveniently prepared[42] taking advantage of the ability of the reagent developed by Ley *et al.*[43] to protect the *trans* vicinal hydroxyl groups of quinic acid. Thus, CSA-catalyzed transketalization of **1** with cyclohexanedione tetramethyl ketal in methanol afforded **114**. Lithium aluminum hydride ester reduction followed by sodium periodate oxidation converted the C-1 functionalities into a carbonyl group to give **115**, which underwent dehydration via mesylation/elimination to give (*R*)-**80** on heating in acetic acid (Scheme 22).



Scheme 22.

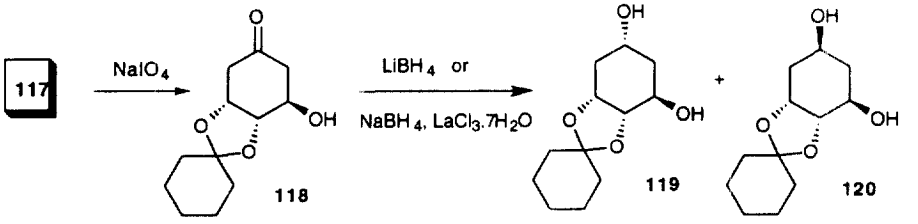
4.2. *Cyclohexylidene quinide ketal 30*

The C-1 elaboration of **30** has been accomplished in a similar manner as that of the corresponding derivative **29**. Thus, the lactone ring could be opened by treatment with sodium methoxide to produce the methyl ester **116**[44–46] as well as being reduced with $LiAlH_4$ to give the triol **117** (Scheme 23).



Scheme 23.

Recently, the reduction step from **30** to **117** has been greatly improved by Schulz and Gani[47] who found that this operation could be much more conveniently performed using sodium borohydride in ethanol rather than lithium aluminum hydride, then submitting the crude **117** directly to sodium metaperiodate oxidation of the geminal C-1 functions leading to **118** in 95% overall yield. The reduction of the carbonyl group of **118** with $LiBH_4$ has been reported by Gero *et al.*[48] to produce a 1:1 mixture of the epimeric secondary alcohols **119** and **120** from which the 4-equatorial alcohol **119** could be easily separated by fractional crystallization (Scheme 24).



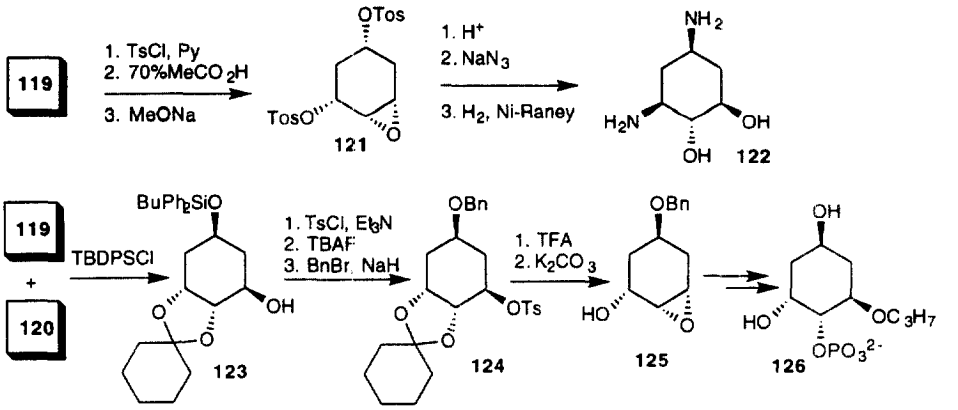
Scheme 24.

The availability of the intermediate **119** allowed the same authors to develop a strategy leading to the synthesis of D-(+)-2,6-dideoxystreptamine **122** along the steps indicated in the following Scheme 25. After conversion of **119** to **121** by standard steps, a regioselective acid-promoted epoxide ring opening, followed by azidolysis of both tosyloxy groups and final reduction of the intermediate diazide by Raney nickel completed the elegant sequence leading to **122**.

Even more interestingly, a detailed investigation of the reduction step led Schulz and Gani[47] to discover that La^{3+} or Ce^{3+} assisted borohydride reduction of the cyclohexanone **118** induces a reversal of diastereoselectivity producing a 6:1 to 9:1 mixture of epimers in favour of **120**, the 4-*re*-face of **118** being better exposed to the reductant, thus forcing the carbonyl *O*-atom and the OH group to occupy axial positions through chelation to a highly charged metal ion. Working on a 20 g scale, the authors found that the required equatorial alcohol **120** could be more conveniently separated from the axial-epimer as the corresponding 4-silyl ether **123** rather than directly.

These findings have enabled the authors to obtain via the intermediate **124**, (−)-(1*R*,2*R*,4*R*,6*S*)-1,6-epoxy-4-benzyloxycyclohexan-2-ol **125**, a key precursor to (−)-(1*R*,2*R*,4*R*,6*S*)-6-propyloxycyclohexan-1,2,4-triol 1-phosphate **126**, predicted to be a submicromolar inhibitor of inositol monophosphatase, along the steps summarized in Scheme 25.

On the other hand, the intermediate **116** could be converted into different unsaturated esters through functional group manipulation. Thus, **127** could be formed from **116** through a two-step sequence

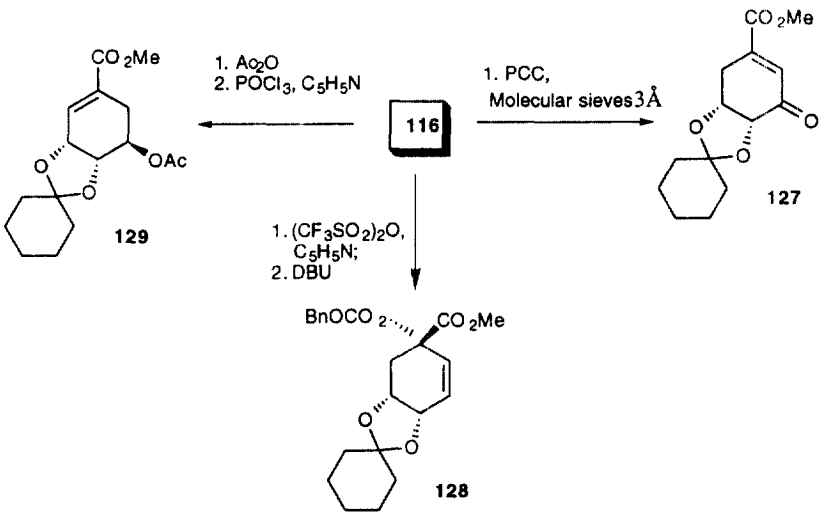


Scheme 25.

involving initial Swern oxidation of the secondary alcoholic function followed by dehydration by action of phosphorus oxychloride in the presence of pyridine.[23,44,45]

Later, it has been demonstrated that this operation could be conveniently accomplished in a one-step procedure using PCC as the oxidant in the presence of 3 Å molecular sieves, although this protocol cannot be scaled up to 25 g, probably for the problematic purification of **127**.[46,49] The best yield (81%) was obtained performing the oxidation of **116** with the PCC/Al_2O_3 system, followed by acetylation of the crude product with acetic anhydride in the presence of catalytic amounts of DMAP.[21]

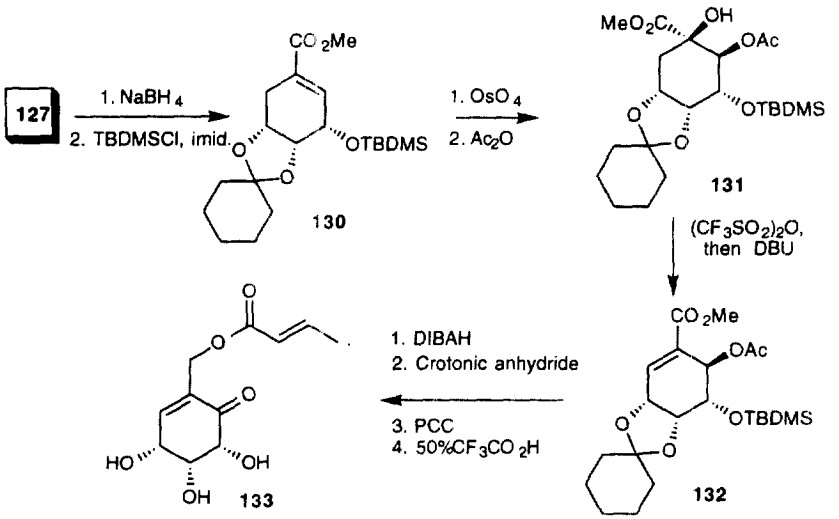
Moreover, the olefinic ester **128** has been prepared by treatment of the carbonate corresponding to **116** with triflic anhydride in the presence of pyridine followed by triflic acid elimination by means of DBU,[50] while the conjugated ester **129** has been derived from **116** through a selective protection of the secondary alcohol as the corresponding acetate followed by dehydration of the free tertiary hydroxyl group by treatment with phosphorus oxychloride. The elimination occurred solely in the direction of the ketalized diol to give the more stable flattened half chair ring system.[21] These transformations are summarized in Scheme 26.



Scheme 26.

In a series of papers, Shing *et al.* (see later for details) described a number of applications of

quinic acid as the chiral educt to the enantioselective synthesis of natural products and related analogues. Their extensive efforts in this area led to the preparation of many useful quinic acid derived compounds, later widely utilized as intermediates for a variety of natural targets. Thus, the silyl-ether **130** of the α-alcohol obtained by sodium borohydride stereospecific reduction of **127**, the hydride attack proceeding from the less hindered β-face, has been successfully elaborated to 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone **133**,[44,45] a glyoxalase inhibitor from cultures of *Streptomyces griseosporeus* following the steps summarized in Scheme 27. The sequence commenced with a stereoselective dihydroxylation to the corresponding diol followed by selective acetylation to give the monoacetate **131**. Esterification of the tertiary alcohol with triflic anhydride set the stage for a DBU-mediated β-elimination to install the crucial double bond in the required position producing the enoate **132** which underwent subsequent DIBAH reduction to afford the corresponding diol.



Scheme 27.

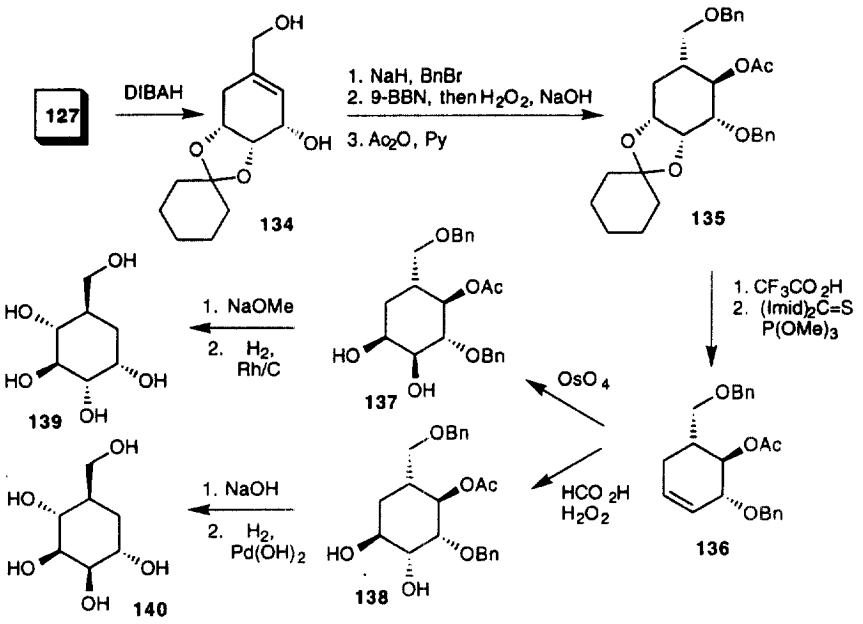
Selective esterification of the primary alcohol with crotonic anhydride, followed by PCC oxidation of the free secondary alcohol to the corresponding ketone and removal of the protective group complete the synthesis of **133** in an overall yield of 80%.

Soon after, the same authors found that DIBAH reduction of **127** furnished the corresponding diol **134**,[46] a very effective common precursor to approach the synthesis of targets featuring cyclohexane ring systems bearing different oxygenated and amino functionalities.

As an example, Scheme 28 outlines the common pathway from **134** to both pseudo-α-D-glucopyranose **139** and pseudo-α-D-mannopyranose **140**,[51,52] carbocyclic analogs of monosaccharides with the ring oxygen atom substituted for by a methylene group, through the cyclohexene intermediate **136**.

Thus, after protection of the two hydroxyl groups as benzyl ethers, a stereocontrolled hydroboration–oxidation sequence gave exclusively the α-alcohol, which was subsequently protected as its acetyl derivative **135**. Removal of the ketal protecting group by acid treatment, followed by Corey–Winter deoxygenation provides the crucial intermediate **136**, a suitable substrate for both *cis*- or *trans* dihydroxylation to afford **137** and **138** respectively, which are then easily taken to the required targets **139** and **140** after removal of the protecting groups (17 and 13% overall yields, after 12 or 11 steps respectively from quinic acid).

The structure of quinic acid has been revealed to be particularly suitable for the synthesis of many



Scheme 28.

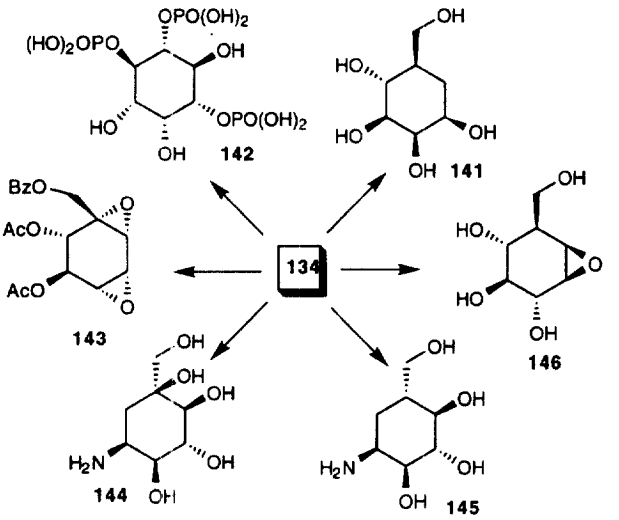


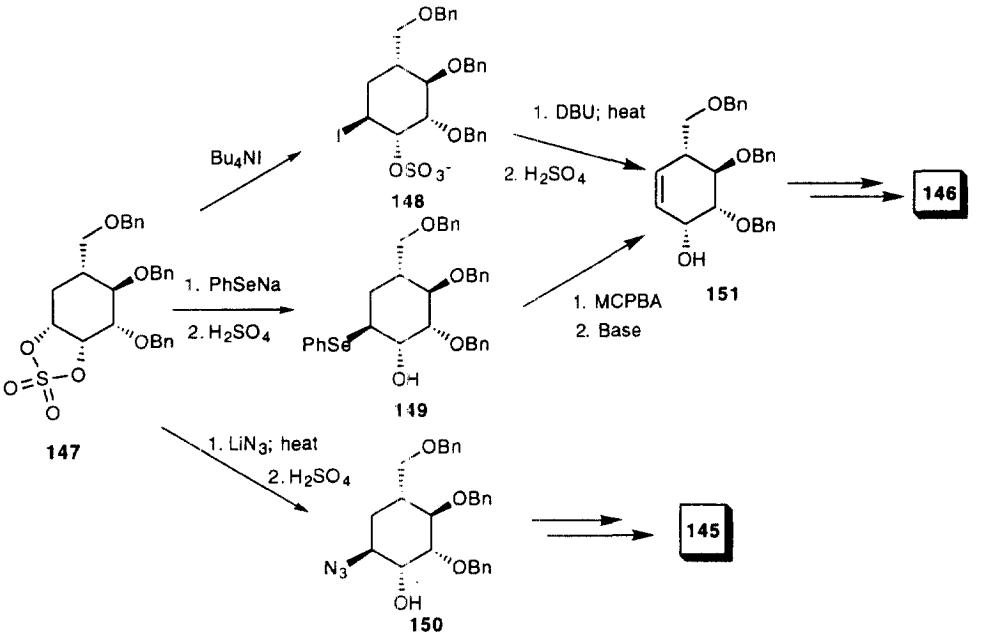
Figure 2.

other pseudosugars, besides the already mentioned pseudo-β-D-fructopyranose **56**,[34,46,49] pseudo-α-D-glucopyranose **139** and pseudo-α-D-mannopyranose **140**.[51,52]

Thus, **134** has been the starting point for the synthesis of a number of related compounds including pseudo-β-D-mannopyranose **141**,[46,49] cyclophellitol **146** and its diastereomers,[53–55] D-*myo*-inositol 1,4,5-triphosphate **142**,[56] (+)-crotoepoxide **143** and the corresponding iso-diastereomer,[57] pseudo amino sugars such as validamine **145** and its C-2 epimer,[58] valiolamine **133** and diastereomers,[59,60] which are collected in Figure 2.

The epoxide-like reactivity of cyclic sulphates has been advantageously applied to the construction

of the pseudoaminosugars validamine **145**[58] and valiolamine **144**,[59,60] isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneous* IFO12703, as well as to open a new way to cyclophellitol **146**,[53,55] a unique pseudopyranose isolated from the culture filtrates of the mushroom *Phellinus* sp. possessing a β-epoxide moiety (Scheme 29).



Scheme 29.

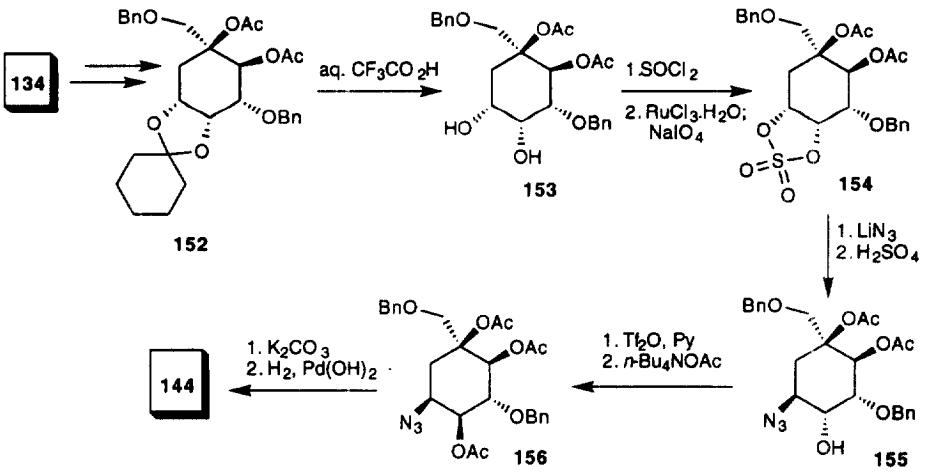
Thus, the cyclic sulphate **147** has been regioselectively opened by different nucleophiles, the degree of regioselectivity being strictly connected with the size of the nucleophile, to provide the key intermediates **148**, **149** and **150** successfully utilized as the precursors for a convenient entry to **146** via **151** and to **145** respectively, as summarized in Scheme 29.

Alternatively, the cyclic sulfate **154**, easily prepared from **134**, was the key intermediate for a nice synthesis of valiolamine **144**, the most potent α-glucosidase inhibitor among carbasugars, following the steps summarized in Scheme 30. Interestingly, the configuration of the carbon atoms of the cyclic sulfate had to be inverted.

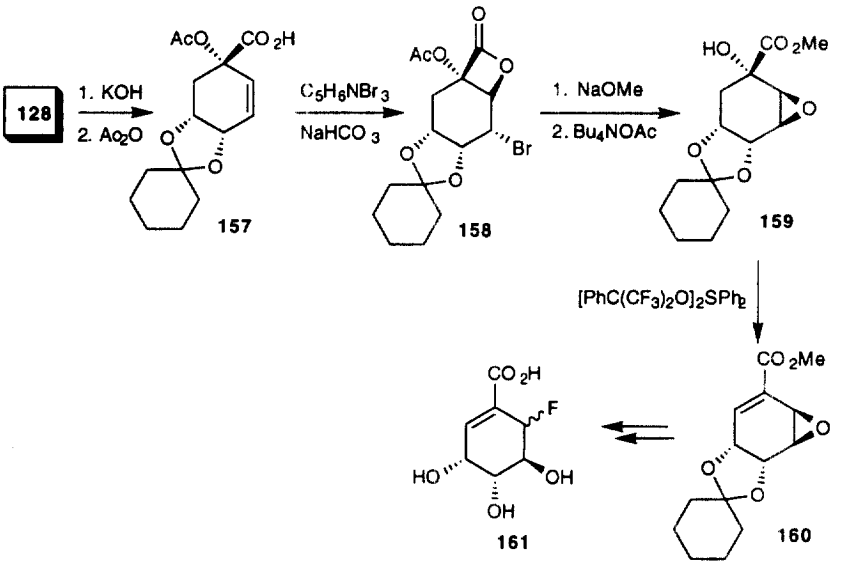
The nitrogen functionality was introduced employing the azide anion to regioselectively open the cyclic sulfate moiety to give **155**, before inverting the adjacent stereogenic center by trifluoromethanesulfonylation and subsequent displacement with tetrabutylammonium acetate to give the azidotriacetate **156**.

Deacetylation and hydrogenolysis allowed completion of the synthesis of valiolamine **144** in 14 steps from quinic acid with an overall yield of 8.4%.

A further application of the cyclohexylidene quinide **30** has been proposed by Sutherland *et al.*[50] who used the substituted cyclohexene derivative **128** as the key intermediate for the preparation of 6-fluoroshikimic acid **161**. As summarized in Scheme 31, the stereospecific formation of the epoxide **159** was achieved through the β-lactone intermediate **158**, in turn derived by bromolactonization of the unsaturated acid **157**. The subsequent dehydration of **159** has proven to be a very difficult process and could be accomplished only by using the Martin sulfurane dehydrating agent $[PhC(CF_3)_2O]_2SPh_2$. The fluoride–pyridine promoted ring opening of the epoxide **160** followed by saponification and removal of the ketal protecting group completed the preparation of **161**, obtained as a mixture of epimeric α- and β-fluoroderivatives.



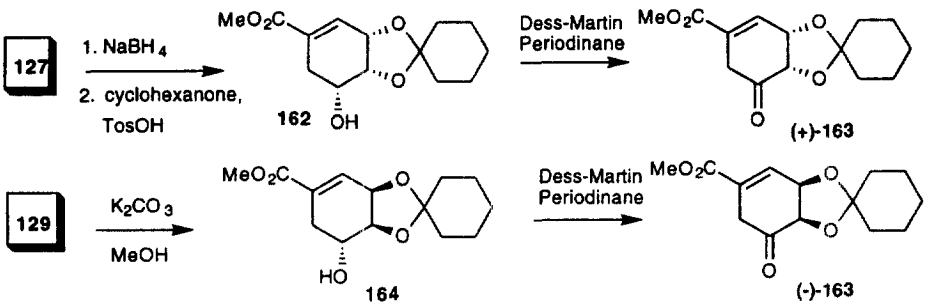
Scheme 30.



Scheme 31.

Finally, the successful transformation of **30** into the β,γ-unsaturated ketone **163**, subsequently incorporated into the bicyclic core structure of the enediyne antibiotic esperamycin-A_1, is one more reason to appreciate the versatility of D-(−)-quinic acid as a chiral starting material in natural product synthesis. Interestingly, the β,γ-unsaturated ketone **163** has been prepared in both enantiomeric forms.[21]

Thus, (+)-**163** was obtained by transketalization of **127** to the more thermodynamically stable ketal adjacent to the double bond, followed by oxidation of the derived homoallylic alcohol **162** with Dess–Martin periodinane reagent, the choice of which being crucial to avoid concomitant undesired double bond isomerization. Alternatively, (−)-**163** was prepared from the already described **129** through deacetylation to **164** followed by periodinane oxidation as summarized in Scheme 32.



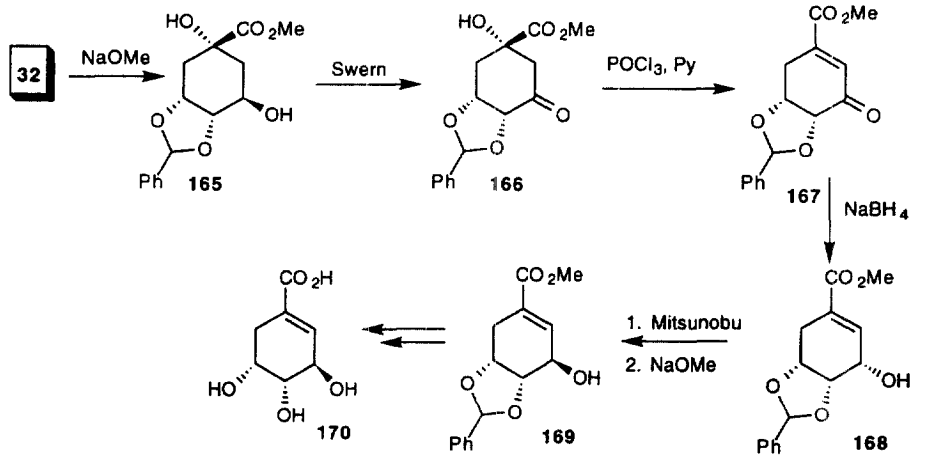
Scheme 32.

4.3. *Cyclopentylidene quinide 31*

This compound has been described in 1995 by White *et al.*[22] by a procedure analogous to that used to obtain **30** during their exploratory investigations directed at the asymmetric synthesis of the fungal metabolites Mycosporin I and Mycosporin–gly. After initial unsuccessful attempts to utilize intermediates derived from **31** by the same chemistry already described for **30**, they were forced to search for alternative solutions which were found starting from the benzylidene acetal **32** and will be discussed in the next section.

4.4. *Benzylidene quinide 32*

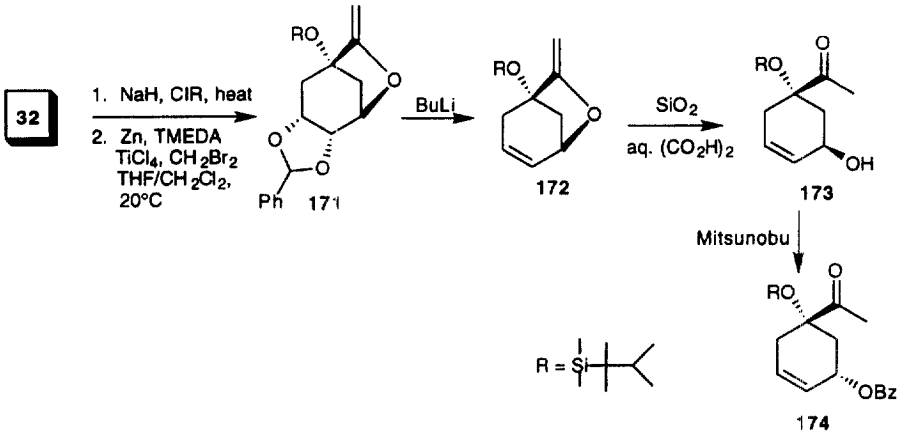
The benzylidene quinide **32** was prepared more than ten years ago by Berchtold *et al.*[23] by acid-catalyzed reaction of quinic acid and benzaldehyde with removal of water. A mixture of diastereomers at the newly introduced stereogenic center is formed but, fortunately, the major diastereomer can be easily separated by crystallization. The same chemistry described for the other ketals **29** and **30** allowed its conversion into the α,β-unsaturated ketoester **167**. Reduction of the ketone group of **167** with sodium borohydride followed by inversion at the carbon bearing the secondary hydroxyl group by the Mitsunobu reaction and saponification of the intermediate benzoate provided the benzylidene acetal of (−)-methyl-4-*epi*-shikimate **169**, which has been used as a convenient precursor of (−)-4-*epi*-shikimic acid **170** as outlined in Scheme 33.



Scheme 33.

As depicted in Scheme 34, the six step synthesis of the enantiomerically pure synthon **174** for

the A-ring of daunomycinone in an overall yield of 17% from D-(−)-quinic acid, represents a very intriguing application of this chemistry.[61]

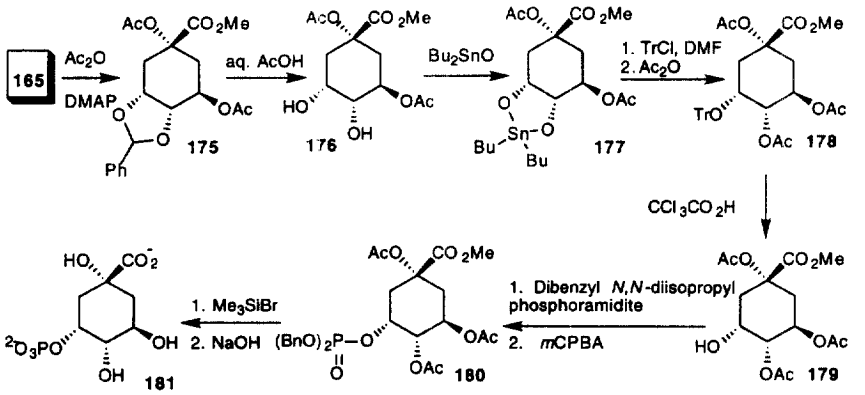


Scheme 34.

After protection of the tertiary hydroxyl function as dimethyl(1,1,2-trimethylpropyl)silyl ether, chosen to withstand treatment with alkyl lithium reagents even better than the more usual tert-butyldimethylsilylether, methylenation of the lactone by treatment with a mixture of zinc, titanium chloride, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and dibromomethane gave rise to the enol ether **171** in 74% yield.

Its transformation to the cyclohexene derivative **173** was achieved in 53% yield through a retro[4+2] cycloaddition of the anion resulting by deprotonation (BuLi) of the acetal carbon at low temperatures (−25° to −10°C). Mild acid treatment served to promote the enol ether hydrolysis to give **173**. The inversion of the configuration of the resulting allylic alcohol was then easily obtained under Mitsunobu conditions to give the benzoate **174**.

A selective functionalization of adjacent hydroxyl groups was required for the synthesis of (−)-shikimate and (−)-quinate-3-phosphates. As exemplified in Scheme 35 for the preparation of (−)-quinate 3-phosphate **181**, this operation has been successfully accomplished by Tisnés *et al.*[62] employing a methodology widely applied in carbohydrate and nucleoside chemistry, entailing the dimeric structure of *O*-stannylene acetals which allows a differentiation of the nucleophilic character of the two oxygen atoms.



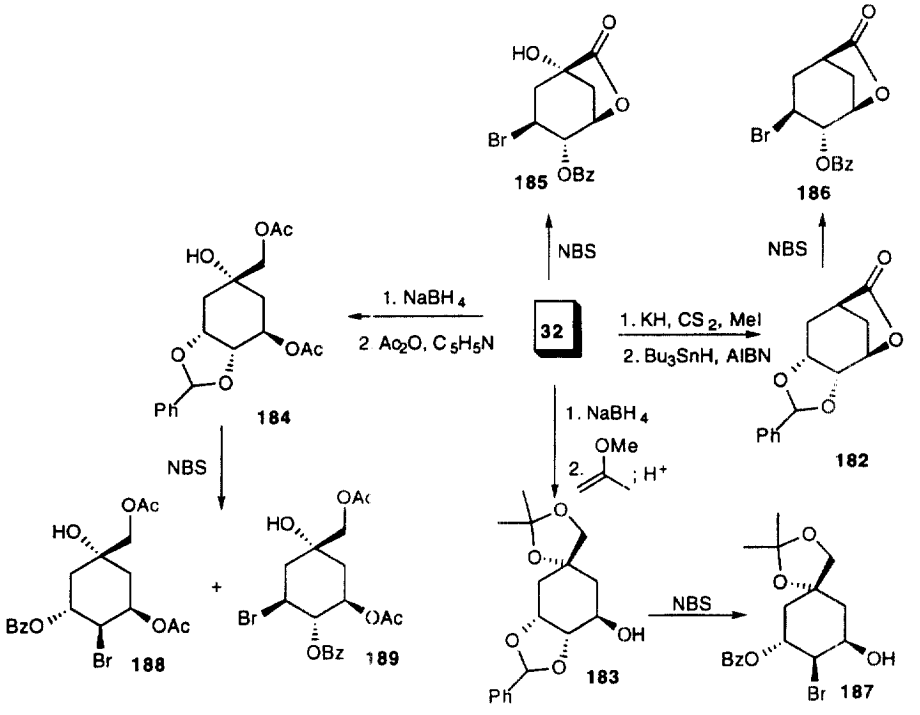
Scheme 35.

This noteworthy regioselective activation of the hydroxyl groups of **176**, obtained by cleavage of the acetal protection of **175**, in turn derived by acetylation of **165**, was achieved as the stannylene derivative **177**. Its treatment with trityl chloride in DMF produced the trityl derivative **178** in 65% overall yield after acetylation of the remaining hydroxyl group.

Cleavage of the trityl group by action of trichloroacetic acid gave **179** which was then phosphorylated in a two-step procedure using dibenzyl *N,N*-diisopropylphosphoramidite electrophile and oxidized at the phosphorus atom to afford **180**. Careful removal of the protecting groups (debenzylation had to be effected before saponification in order to avoid possible phosphate migration) gave **181** isolated as a triethylammonium salt in 20% yield from quinic acid.

Separation of the reactivity of functional group as the benzylidene acetal **32** presents additional advantages in comparison to the parent ketals. In fact, the benzylidene ring system could be opened not only under standard aqueous acid conditions but also either reductively[16] or by applying the interesting protocol introduced by Hanessian,[63] who demonstrated that benzylidene acetals underwent regioselective cleavage on treatment with NBS to afford the corresponding bromobenzoates.

Accordingly, submitting the benzylidene acetal quinide derivatives **32**, **182**, **183** and **184** to Hanessian's protocol, the corresponding bromobenzoates **185**, **186**, **187**, and the mixture of **188** and **189** are produced with high stereospecificity, while the regiospecificity of the process is highly dependent on the rigidity of the substrates (Scheme 36).



Scheme 36.

A variety of successful applications of this methodology to natural product synthesis can be found in the literature, including the synthesis of mycosporin I **190**, a fungal metabolite possessing regulatory effect on spore formation, and related derivatives starting from **185**,[22] iso-5-enolpyruvylshikimate-3-phosphate **191** via **185**,[64] the entire top-half **192** and the C-20–C-34 segment of the immunosuppressant agent FK-506 from **186** and **185** respectively,[65,25] and the carbaphosphonate **193**, a potent inhibitor of 3-dehydroquinate synthase via **187**,[66] which are collected in Figure 3.

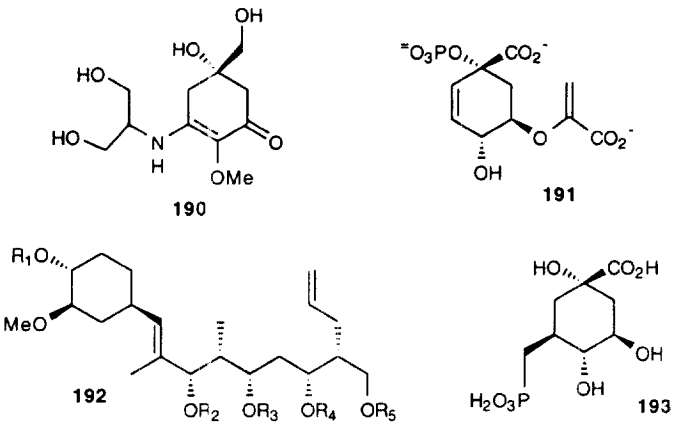


Figure 3.

Recently, the benzylidene quinide **32** has been used for an experimentally preferable two-step procedure for the preparation of the quinide **4**, the benzylidene protecting group being removed by catalytic hydrogenation over 10% palladium on charcoal in 93% yield.[16]

5. Natural product synthesis through quinic acid ring opening

Quinic acid is a very versatile starting material for natural product synthesis: its choice from the chiral pool, initially invoked almost exclusively for the preparation of cyclohexane featuring natural compounds, has been soon after addressed to the preparation of open chain functionalized building blocks, which could be further transformed in optically active cyclopentane substituted skeletons. The required C–C bond breaking of the cyclohexane ring system could be easily operated taking advantage of the presence of hydroxyl groups on adjacent carbons. Therefore, quinic acid acts as a convenient bis-aldehyde chiron.

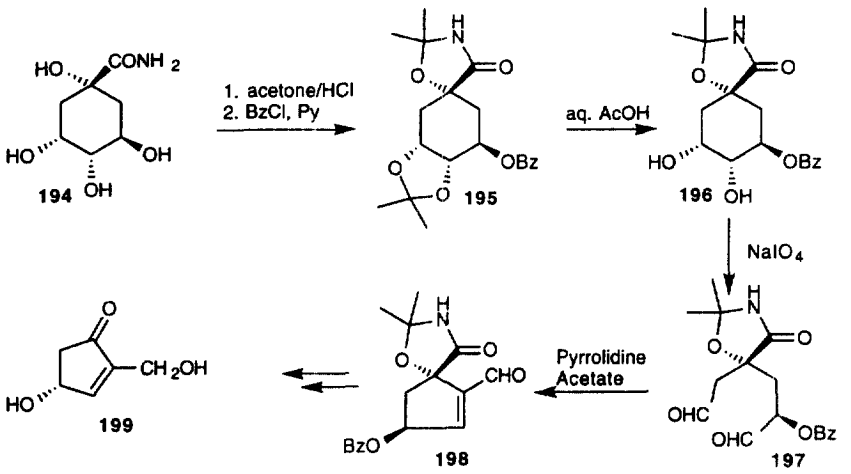
5.1. *Cyclopentanoids*

Stoodley *et al.*[67,68] demonstrated, for the first time, the feasibility of utilising quinic acid as a forerunner of functionally substituted cyclopentenones. They were able to obtain a series of cyclopentanoid natural products using quinamide **194** as the starting point as illustrated in Scheme 37.

Thus **194**, easily prepared by treatment of methyl quinate with methanolic ammonia, was treated with acetone in the presence of hydrogen chloride as described by Fischer and Dangschat in their work[3] defining the structure of quinic acid. The mixture of products formed in this reaction was separated by silica-gel chromatography and benzoylated at the remaining hydroxyl group to give the fully protected di-isopropylidene quinamide **195**.

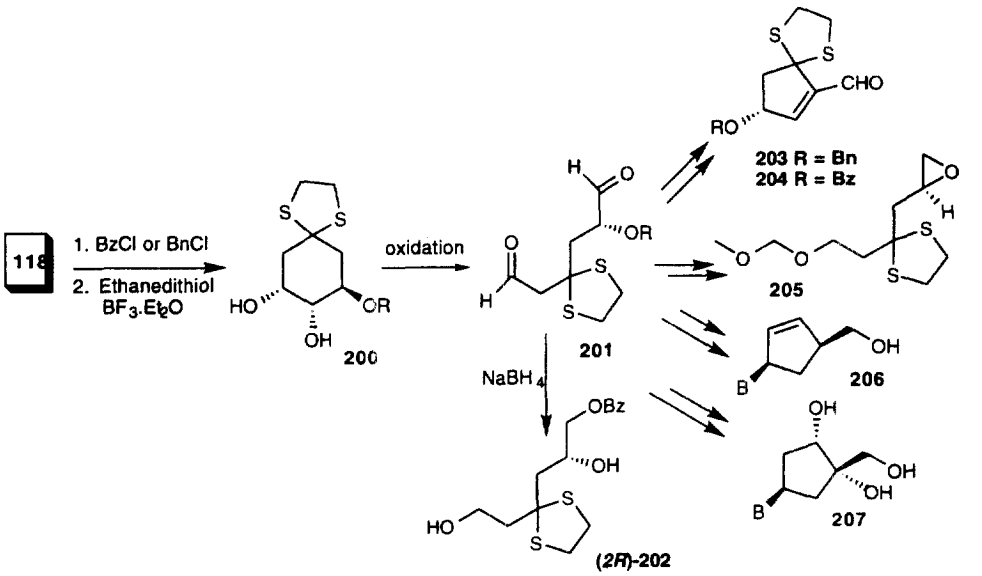
The same authors[67,68] had shown that the dioxolan ring of **195** could be selectively demasked by mild acid treatment to give **196** which was oxidized with sodium periodate to afford the crude dialdehyde **197**. The latter was directly submitted to the aldolization step in the presence of pyrrolidine acetate which smoothly promoted the intramolecular cyclization to the cyclopentene aldehyde **198**, a useful precursor of (4*R*)-4-hydroxy-2-hydroxymethylcyclopent-2-en-1-one **199**, a widely utilized intermediate in cyclopentanoid synthesis (i.e. prostanoids, pentenomycins).

Analogously, the oxidative ring opening of the cyclohexanonetriol **200**, in turn prepared starting from **118**,[68] was the key operation for producing **201**, a very useful intermediate for a variety of natural targets. A suitable protection of the carbonyl group to survive a sequence of reactions was found as the corresponding thioketal **200** which was formed by reaction of the benzoate of **118** with ethane-1,2-dithiol in the presence of boron trifluoride etherate with the additional bonus of a simultaneous deprotection of the vicinal diol. The oxidation step of the oxidative ring-contraction of a cyclohexane



Scheme 37.

diol into a cyclopentene carbaldehyde has been accomplished both with lead tetraacetate[68,69] or with triphenylbismuth carbonate[70] as in the case shown in Scheme 38, in order to avoid sulphoxide formation.

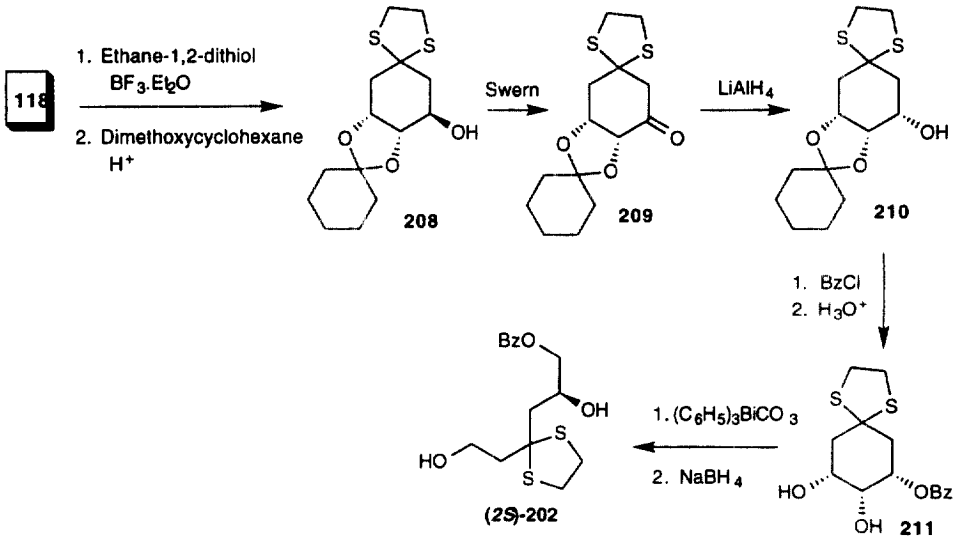


Scheme 38.

The intermediate **201** bearing a residual hydroxyl group protected both as the corresponding benzyl ether or benzoate ester, could be easily cyclized in the presence of catalytic amounts of pyrrolidine acetate to produce the substituted cyclopentene aldehydes **203**[68,69] and **204**,[68,71] classical prostanoid precursors.

Interestingly, the dialdehyde **201** has been also transformed into the epoxide **205**, destined to become a portion of the macrocyclic carbon skeleton of maytansinoids.[72] Compound **204** has been also utilized as the chiral precursor for the preparation of interesting carbocyclic nucleosides such as **206** and **207** having guanine as the base.[73]

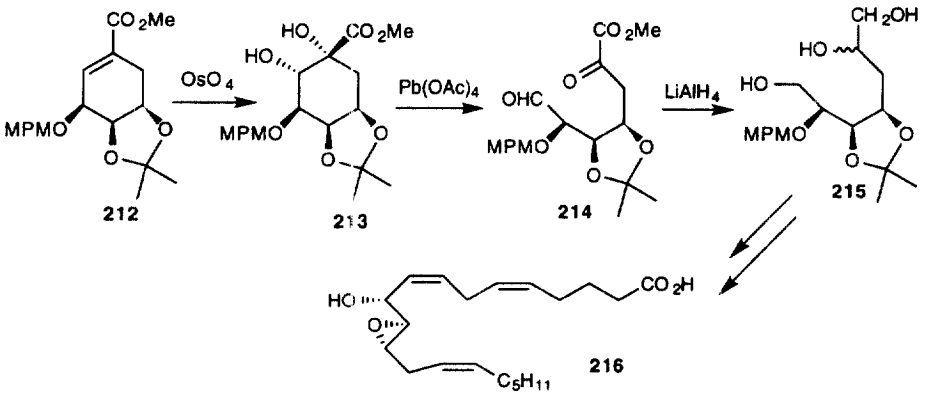
As indicated in Scheme 38 the reduction of **201** with sodium borohydride[70] gave the diol benzoate **202** resulting from a benzoyl migration. Interestingly, the enantiomer of **202** could be obtained from **118**[70] following the sequence outlined in Scheme 39, involving treatment with ethane-1,2-dithiol in the presence of boron trifluoride etherate followed by reketalization with dimethoxycyclohexane to give **208**. Swern oxidation produced the corresponding ketone **209**, which underwent stereoselective reduction with lithium aluminum hydride to give the alcohol **210**, which was benzoylated and then treated with acid to afford the vicinal diol **211**, which was easily converted to (2*S*)-**202** by the sequence previously described.[70]



Scheme 39.

5.2. *Open chain compounds*

Quinic acid has recently become of interest as the chiral starting material for the synthesis of homochiral linear natural compounds. As for cyclopentanoids, the strategy entails an oxidative ring cleavage of a vicinal diol moiety. These concepts have been applied to a very nice synthesis of hepoxilin B_3 **216** and its diastereomers, as summarized in Scheme 40.[74]

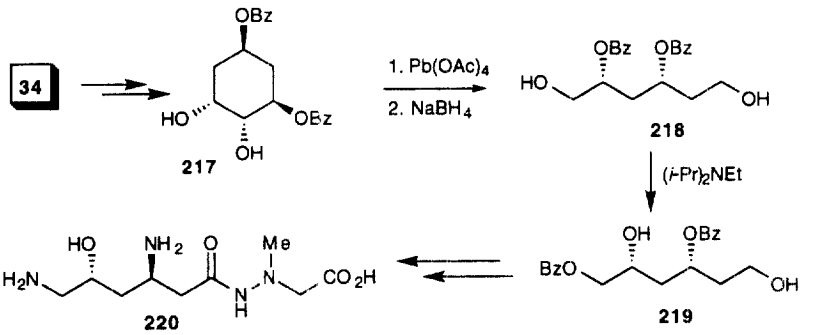


Scheme 40.

Thus, dihydroxylation of **212**, obtained by trityl cation assisted protection with 4-methoxybenzylchloroimidate of the corresponding allylic alcohol, in turn easily available in four steps from quinic acid as for **162**,[56] was followed by lead tetraacetate oxidation of the derived diol **213** giving rise to the dicarbonyl intermediate **214** which was immediately reduced by means of lithium aluminum hydride to the chiral triol **215**. The newly generated *vic*-diol acted as a precursor of a required aldehyde group to submit to a Wittig olefination for the installation of the lower chain. The basic skeleton was then completed by homologating a new aldehyde group obtained by Swern oxidation of the corresponding primary alcohol (Scheme 40).

A further example of oxidative ring cleavage of quinic acid derivatives for the construction of the carbon skeleton of a linear natural compound is offered by the synthesis of negamycin (+)-**220**,[75] an antibiotic first isolated from the culture filtrates of three species of *Streptomyces purpeofuscus*.

As depicted in Scheme 41, the lead tetraacetate oxidation of the diol moiety of **217**, in turn derived from **34** by a combination of methods available in the literature, led to the formation of the corresponding dialdehyde, immediately reduced to the corresponding diol **218**, which was further elaborated to the natural target after an interesting intramolecular differentiation promoted by diisopropylethylamine, the reagent of choice to favour the required 1,4-migration of the benzoyl group to afford **219**.



Scheme 41.

6. Concluding remarks

The use of quinic acid in natural product synthesis continues to inspire synthetic chemists around the world. It should come as no surprise that its applications have been burgeoning over recent years allowing a concise and flexible approach to a growing number of important synthetic targets. In fact, quinic acid affords the possibility to create new bonds on all the carbon atoms of the cycle taking advantage of the versatility of the functional groups of quinic acid and to introduce regio- and stereoselectively a variety of new functionalities. Moreover, the cleavage of the cyclohexane at a chosen position allows quinic acid to serve as a versatile precursor for acyclic structures directly and, after subsequent cyclization, for cyclopentane derivatives. All the possible transformations are summarized in Figure 4.

The future must surely hold further development of new chiral materials thus broadening the scope of quinic acid as a chiral template for the synthesis of structurally complex natural products and related compounds.

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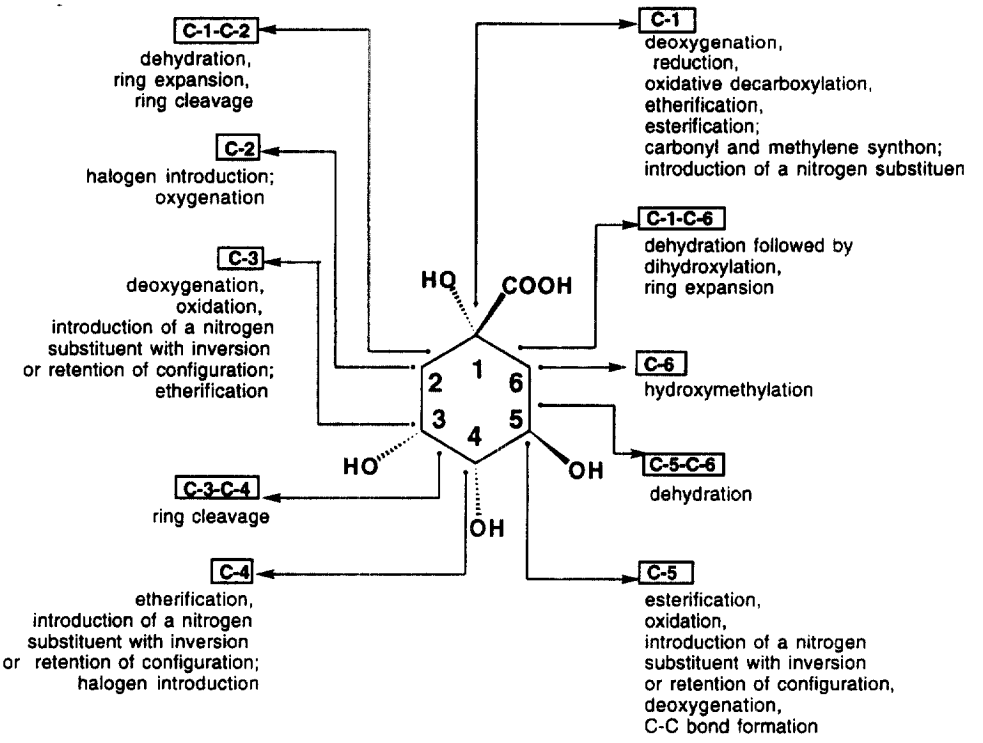

Figure 4.

References

1. Draths, K. M.; Ward, T. L.; Frost, J. W., *J. Am. Chem. Soc.*, **1992**, *114*, 9275–9276.
2. Haslam, E., "*Shikimic Acid Metabolism and Metabolites*", Wiley-Interscience: New York, 1993.
3. Fisher, H. O. L.; Dangschat, G., *Chem. Ber.* **1932**, *65*, 1009–1031.
4. Wollf, W. J. in "*Kirk–Othmer Encyclopedia of Chemical Technology*", Wiley, New York, 1983, Vol. 21, p. 423.
5. Delfourne, E.; Despeyroux, P.; Gorrichon, L.; Veronique, J., *J. Chem. Res. (S)*, **1991**, 56–57
6. Scholz-Böttcher, B. M.; Ernst, L.; Maier, H. G., *Liebigs Ann.*, **1991**, 1029–1036.
7. Fisher, M.; Friedrichsen, W.; Grewe, R.; Haendler, H., *Chem. Ber.*, **1968**, *101*, 3313–3325.
8. Guenin, R., Schneider, C. H., *Helv. Chim. Acta*, **1983**, *66*, 1101–1109.
9. Grewe, R.; Vangermain, E., *Chem. Ber.*, **1965**, *98*, 104–110.
10. Snyder, C. D.; Rapoport, H., *J. Am. Chem. Soc.*, **1973**, *95*, 7821–7828.
11. Fisher, H. O. L., *Chem. Ber.*, **1921**, *54*, 775–785.
12. Philippe, M.; Sepulchre, A. M; Gero, S. D.; Loibner, H.; Streicher, W.; Stutz, P., *J. Antibiotics*, **1982**, *25*, 1507–1512.
13. Huang, P. Q.; Sabbe, K.; Pottie, M., Vandewalle, M., *Tetrahedron Lett.*, **1995**, *36*, 8299–8302.
14. Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L., *J. Org. Chem.*, **1997**, *62*, 465–473.
15. Manthey, M. K.; Gonzalez-Bello, C.; Abell, C., *J. Chem. Soc., Perkin Trans. 1*, **1997**, 625–628.
16. Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I., *Tetrahedron Lett.*, **1988**, *29*, 281–284.
17. Su, Z.; Paquette, L. A., *J. Org. Chem.*, **1995**, *60*, 764–766.
18. Paquette, L. A.; Bailey, S., *J. Org. Chem.*, **1995**, *60*, 7849–7856.
19. Eberle, M.; Arigoni, D., *Helv. Chim. Acta*, **1960**, *43*, 1508–1513.
20. Grewe, R.; Nolte, E., *Liebigs Ann.*, **1952**, *575*, 1–17.

21. Ulibarri, G.; Nadler, W.; Skrydstrup, T.; Audrain, H.; Chiaroni, A.; Riche, C.; Grierson, D. S., *J. Org. Chem.*, **1995**, *60*, 2753–2761.
22. White, J. D.; Cammack, J. H.; Sakuma, K., Rewcastle, G. W.; Widener, R. K., *J. Org Chem.*, **1995**, *60*, 3600–3611.
23. Lesuisse, D.; Berchtold, G. A., *J. Org. Chem.*, **1985**, *50*, 888–890.
24. White, J. D.; Cammack, J. H.; Sakuma, K., *J. Am. Chem. Soc.*, **1989**, *111*, 8970–8972.
25. White, J. D.; Toske, S. G.; Yakura, T., *Synlett*, **1994**, 591–593.
26. Trost, B. M.; Romero, A. G., *J. Org. Chem.*, **1986**, *51*, 2332–2342.
27. Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J., *J. Org. Chem.*, **1989**, *54*, 3738–3740.
28. Molin, H.; Pring, B. G., *Tetrahedron Lett.*, **1985**, *26*, 677–680.
29. Hanessian, S.; Sakito, Y.; Dhanoa, D.; Baptistella, L., *Tetrahedron*, **1989**, *45*, 6623–6630.
30. Dyong, I.; Hermann, R.; Mattes, R., *Chem. Ber.*, **1980**, *113*, 1931–1944.
31. Dyong, I.; Hermann, R., *Tetrahedron Lett.*, **1981**, *22*, 4225–4226.
32. Gill, M; Steglich, W. in "*Progress in the Chemistry of Organic Natural Products*", Vol. 51, pp. 1–317, W. Herz, H. Grisbach, G. W. Kirby, Ch. Tamm, Eds, 1987.
33. Hanessian, S.; Beaulieu, P.; Dubé, D., *Tetrahedron Lett.*, **1986**, *27*, 5071–5074.
34. McComsey, D. F.; Maryanoff, B. E., *J. Org. Chem.*, **1994**, *59*, 2652–2654.
35. Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Graeme Laver, W.; Stevens, R. C., *J. Am. Chem. Soc.*, **1997**, *119*, 681–690.
36. Barros, M. T.; Maycock, C. D.; Ventura, M. R., *J. Org. Chem.*, **1997**, *62*, 3984–3988.
37. Kameneka, T. M.; Overman, L. E., *Tetrahedron Lett.*, **1994**, *35*, 4279–4282.
38. Toyota, M.; Nishikawa, Y.; Fukumoto, K., *Tetrahedron*, **1996**, *52*, 10347–10362.
39. Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V., *Synlett*, **1996**, 29–30.
40. Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V., *Tetrahedron Lett.*, **1997**, *38*, 681–684.
41. Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V., *Tetrahedron*, in press.
42. Gebauer, O.; Brückner, R., *Liebigs Ann.*, **1996**, 1559–156.
43. Ley, S. V.; Priepke, H. W. M., *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 2290–2292.
44. Shing, T. K. M.; Tang, Y., *J. Chem. Soc., Chem. Commun.*, **1990**, 312.
45. Shing, T. K. M.; Tang, Y., *Tetrahedron*, **1990**, *46*, 6575–6584.
46. Shing, T. K. M.; Tang, Y., *J. Chem. Soc., Chem. Commun.*, **1990**, 748–749.
47. Schulz, J.; Gani, D., *Tetrahedron Lett.*, **1997**, *38*, 111–114.
48. Cleophax, J.; Gero, S. D.; Leboul, J.; Akhtar, M.; Barnett, J. E. G.; Pearce, C. J., *J. Am. Chem. Soc.*, **1976**, *98*, 7110–7112.
49. Shing, T. K. M.; Tang, Y., *Tetrahedron*, **1991**, *47*, 4571–4578.
50. Sutherland, J. K.; Watkins, W. J.; Bailey, J. P.; Chapman, A. K.; Davies, G. M., *J. Chem. Soc., Chem. Commun.*, **1989**, 1386–1387.
51. Shing, T. K. M.; Cui, Yu-xin; Tang, Y., *J. Chem. Soc., Chem. Commun.*, **1991**, 756–757.
52. Shing, T. K. M.; Cui, Yu-xin; Tang, Y., *Tetrahedron*, **1992**, *48*, 2349–2358.
53. Shing, T. K. M.; Tai, V. W.-F., *J. Chem. Soc. Perkin Trans. I*, **1994**, 2017–2025.
54. Tai, V. W.-F.; Fung, P.-H.; Wong, Y.-S.; Shing, T. K. M., *Tetrahedron: Asymmetry*, **1994**, *5*, 1353–1362.
55. Shing, T. K. M.; Tai, V. W.-F., *J. Chem. Soc., Chem. Commun.*, **1993**, 995–996.
56. Falck, J. R.; Yadagiri, P., *J. Org. Chem* , **1989**, *54*, 5851–5852.
57. Shing, T. K. M.; Tam, E. K. W., *Tetrahedron Lett.*, **1996**, *37*, 353–356.
58. Shing, T. K. M.; Tai, V. W.-F., *J. Org. Chem.*, **1995**, *60*, 5332–5334.
59. Shing, T. K. M.; Wan, L. H., *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 1643–1645.
60. Shing, T. K. M.; Wan, L. H., *J. Org. Chem.*, **1996**, *61*, 8468–8479.

61. Johnson, B. M.; Vollhardt, K. P. C., *Synlett*, **1990**, 209–210.
62. Chahoua, L.; Baltas, M.; Gorrichon, L.; Tisnès, P.; Zedde, C., *J. Org. Chem.*, **1992**, *57*, 5798–5801.
63. Hanessian, S.; Plessas, N. R., *J. Org. Chem.*, **1969**, *34*, 1035–1044.
64. Bartlett, P. A.; Maitra, U.; Chouinard, P. M., *J. Am. Chem. Soc.*, **1986**, *108*, 8068–8071.
65. Rama Rao, A. V.; Chakraborthy, T. K.; Sankaranayanan, D.; Purandare, A. V., *Tetrahedron Lett.*, **1991**, *32*, 547–550.
66. Montchamp, J.-L.; Piehler, L. T.; Frost, J. W., *J. Am. Chem. Soc.*, **1992**, *114*, 4453–4459.
67. Elliott, J. D.; Hetmanski, M; Stoodley, R. J.; Palfreyman, M. N., *J. Chem. Soc. Perkin Trans. I*, **1981**, 1782–1789.
68. Elliott, J. D.; Kelson, A. B.; Purcell, N.; Stoodley, R. J.; Palfreyman, M. N., *J. Chem. Soc. Perkin Trans. I*, **1983**, 2441–2449.
69. Barrière, J.-C.; Chiaroni, A.; Cléophax, J.; Gero, S. D.; Riche, C.; Vuilhorgne, M., *Helv. Chim. Acta*, **1981**, *64*, 1140–1144.
70. Barton, D. H. R.; Géro, S. D.; Maycock, C. D, *J. Chem. Soc. Perkin Trans. I*, **1982**, 1541–1551.
71. Barros, M. T.; Santos, A. G.; Godinho, L. S.; Maycock, C. D., *Tetrahedron Lett.*, **1994**, *35*, 3999–4002.
72. Barton, D. H. R.; Géro, S. D.; Maycock, C. D., *J. Chem. Soc., Chem. Commun.*, **1980**, 1089–1091.
73. Maycock, C. D.; Barros, M. T.; Santos, A. G.; Godinho, L. S., *Tetrahedron Lett.*, **1993**, *34*, 7985–7988.
74. Belosludtsev, Y. Y.; Kollah, R. O.; Falck, *Tetrahedron Lett.*, **1994**, *35*, 5327–5330
75. Maycock, C. D.; Barros, M. T.; Santos, A. G.; Godinho, *Tetrahedron Lett.*, **1992**, *33*, 4633–4636.

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