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Novel and Efficient Syntheses of (−)-Methyl 4-*epi*-Shikimate and 4,5-Epoxy-Quinic and -Shikimic Acid Derivatives as Key Precursors to Prepare New Analogues

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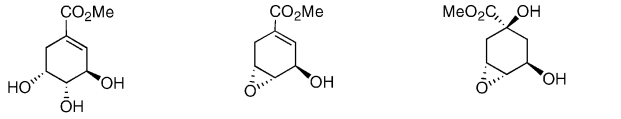


(−)-Methyl 4-*epi*-shikimate (−)-Methyl 4,5-epoxyshikimate (−)-Methyl 4,5-epoxyquinate

We have developed simple methods that provide a rapid entry into the synthesis of a series of quinate and shikimate analogues, including (−)-methyl 4-*epi*-shikimate and the 4,5-epoxy analogues of the parent acids. Epoxy derivatives of quinic and shikimic acids were converted into methyl *scyllo*-quinate and (+)-methyl 3-*epi*-shikimate, respectively, by processes involving a regio- and stereoselective epoxide ring opening. The strategies described take place through short, high-yield reaction sequences.

The shikimate pathway is the biosynthetic sequence that links the metabolism of carbohydrates to the biosynthesis of aromatic amino acids, folate coenzymes, and various isoprenoid quinones.[1] Additionally, all the intermediates can also be considered branch point compounds that may serve as substrates for other metabolic pathways. This route is exclusively present in plants, fungi, and microorganisms.[2] The complete absence in mammals makes shikimate-pathway enzymes potential targets for nontoxic herbicides, antimicrobial agents, and antifungal agents.[3] Another relevant fact is the evidence of this pathway in *apicomplexa* parasites (malaria, pneumonia, tuberculosis), opening a new field in the design of new antiparasite compounds.[4]

The syntheses of quinic and shikimic acids (**1** and **2**, respectively, Chart 1) as well as their analogues, have been an active area of research with a view to the study of enzymatic mechanisms and to the design and synthesis of inhibitors.[5] Potent and selective inhibitors of influenza neuraminidase, such as oseltamivir (**3**) and GS-4071 (**4**),[6] the glyoxalase I inhibitor COCT (**5**),[7] or the potent α-glycosidase inhibitor valiolamine (**6**),[8] are some key examples of such analogues (Chart 2).

CHART 1

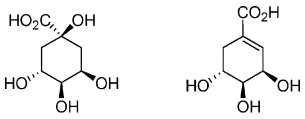
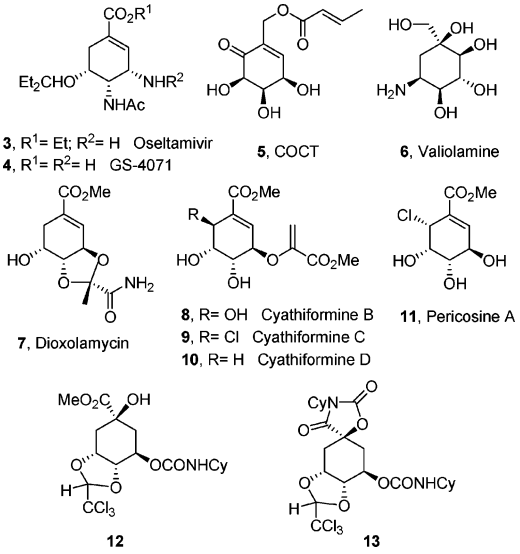


CHART 2



In addition, quinic and shikimic acid epimers are important derivatives. Improved syntheses of 3-*epi*-[9] and 5-*epi*-[10] analogues of both acids have been reported. However, only a limited number of syntheses of the 4-*epi* isomer have been reported in the literature, although the 4-*epi*-shikimic acid skeleton is a constituent of several natural products such as dioxolamycin (**7**),[11] cythiaformines B, C, and D (**8**, **9**, and **10**, respectively),[12] and pericosine A (**11**;[13] Chart 2). There are two published asymmetric syntheses of 4-*epi*-shikimic acid derivatives based on a Diels-Ader reaction. In 1986, Posner and Wettlaufer

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reported the synthesis of methyl 3,4,5-tri-*O*-acetyl-4-*epi*-shikimate through a 15-step procedure,[14] and more recently, Stoodley and co-workers have described the synthesis of 4-*epi*-shikimic acid in eight steps and 17% overall yield.[15] Additionally, syntheses of (−)-4-*epi*-shikimic acid from natural quinic acid have also been developed by Rapoport and Snyder[16] and Berchtold and Lesuisse[17] in 12 and 17% estimated yields, respectively.

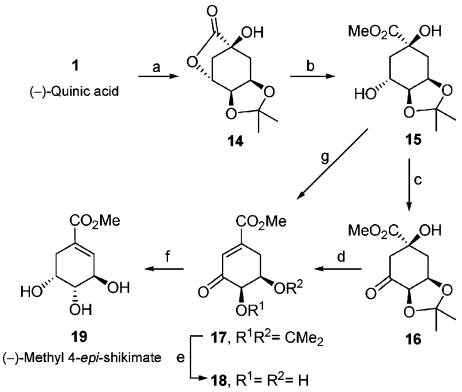
Similarly, two syntheses of 4-*epi*-quinic acid analogues have been described. Snyder and Rapoport[16] have reported the synthesis of (−)-methyl 4-*epi*-quinate via HF epimerization of 1,3,4,5-tetraacetylquinate in 10% yield. In another report, Frank and Miethchen[18] have shown the conversion of (−)-methyl quinate into its 4-*epi* derivative **12**, which contains a carbamoyl function in 3-position and trichloroethylidene acetal group in 4,5-position, in addition to a spiro byproduct **13** (10%). This convenient acetalation reaction is accompanied by inversion of the configuration at the middle chiral carbon atom of the triol unit. Despite the short, simple procedure, in our experience, this reaction sequence leads to a tedious workup and chromatographic steps.

In this context, both 4-*epi*-shikimic and 4-*epi*-quinic acids can be regarded as important chirons that should have manifold uses as starting materials in the chemical synthesis of a wide range of target molecules. Our interest in the chemistry of quinic and shikimic acid derivatives prompted us to report here our own studies on a more efficient synthesis of methyl 4-*epi*-shikimate and on approaches to the preparation of methyl 4-*epi*-quinate.

Starting with relatively inexpensive, commercially available quinic acid (**1**), Scheme 1 illustrates the synthetic pathway toward the (−)-methyl 4-*epi*-shikimate (**19**).

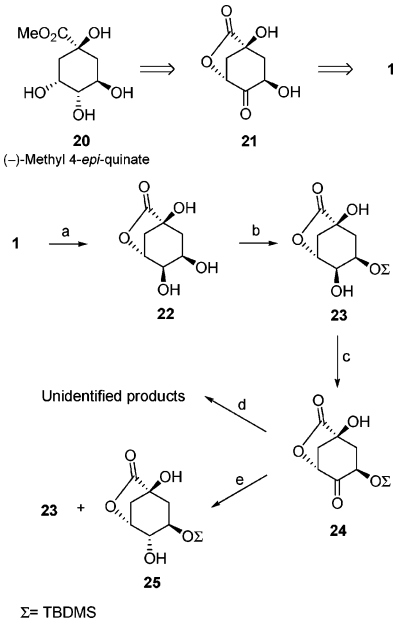
The acid-catalyzed reaction of **1** with acetone, according to Stoodley and co-workers,[19] led to isopropylidene acetal **14** in high yield. In the presence of sodium methoxide in methanol, ring-opening of the lactone was performed to give diol **15**. The secondary alcohol in **15** was oxidized into the corresponding ketone **16**, which was followed by dehydration of the tertiary alcohol with $POCl_3$ in pyridine, giving the enone **17** in high yield. The formation of **17** from **15** via an oxidation followed by a β-elimination has been reported by Shing and Tang[20] as a high yielding process; however, in our hands, we were only able to obtain a yield of 45% for this process. As a result, we utilized a two-step procedure to obtain **17**. Then hydrolysis of the acetal group in **17** with aqueous trifluoroacetic acid gave keto diol **18**. Selective reduction of the carbonyl group in **18** was accomplished with $NaBH(OAc)_3$, giving exclusively the allylic alcohol **19** in good yield. It is noteworthy that the synthesis of (−)-methyl 4-*epi*-shikimate (**19**) from (−)-quinic acid was achieved in six steps with an overall yield of 30% using cheap and commercially available starting material. As a result of the latter and of the simplicity of all the reactions involved in this synthesis, the scale-up of the process has been carried out easily up to 10 g.

SCHEME 1[a]



[a] Reagents and conditions: (a) Na_2SO_4, H_2SO_4, acetone, reflux, 24 h, 85%; (b) NaOMe, MeOH, 0 °C to room temperature, 5 h, 82%; (c) PCC, CH_2Cl_2, rt, 8 h, 80%; (d) 1.3 equiv $POCl_3$, Py, 0 °C to room temperature, 8 h, 85%; (e) $CF_3CO_2H-H_2O$ (1:1), 0 °C, 45 min, 90%; (f) $NaBH(OAc)_3$, CH_2Cl_2, rt, 2 h, 70%; (g) PCC, Py, CH_2Cl_2, 4 Å molecular sieves, rt, 24 h, 45%.

SCHEME 2[a]



[a] Reagents and conditions: (a) *p*-TsOH, toluene, reflux, 24 h, 100%; (b) TBDMSCl, DMAP, imidazole, DMF, 0 °C, 2 h and then rt, 3 h, 70%; (c) Dess−Martin, CH_2Cl_2, rt, overnight, 100%; (d) TBAF, AcOH, THF, rt, 2 h; (e) reduction: see Table 1.

Having established a route for the preparation of (−)-methyl 4-*epi*-shikimate, we embarked on the synthesis of (−)-methyl 4-*epi*-quinate (**20**, Scheme 2).

It was envisaged that (−)-methyl 4-*epi*-quinate (**20**) would be accessible from lactone **21**; the retrosynthesis from quinic acid (**1**) is outlined in the upper part of Scheme 2. To have access to keto lactone **21**, the first step involves the double protection of quinic acid (**1**) in the toluene−*p*-sulfonic acid catalyzed reaction, to quantitatively yield lactone **22**. The selective protection of the C-3 hydroxyl group of **22** was achieved in 70% yield using *tert*-butyldimethylsilyl chloride

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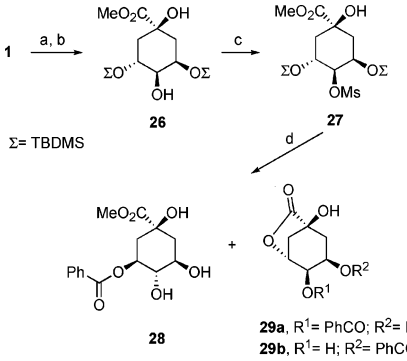
TABLE 1. Reaction Conditions for the Reduction of Ketone 24

entry	reduction agent	equiv	*T* (°C)	*t* (h)	ratio[a] **23**:**25**
1	$NaBH(OAc)_3$	2	25	24	100:0
2	$LiAlH(t\text{-}BuO)_3$	2	0	24	100:0
3	L-selectride	1.1	−70	16	75:25
4	K-selectride	1.1	−70	16	80:20

[a] Calculated by ^1H NMR.

SCHEME 3[a]



[a] Reagents and conditions: (a) MeOH, HCl, 60 °C, 6 h, 100%; (b) TBDMSCl, Et_3N, DMF, 0 °C, 2 h and then 0 °C to room temperature, 16 h, 75%; (c) MsCl, Py, rt, 8 h, 85%; (d) $PhCO_2H$, CsF, DMF, 90 °C, 24 h, 55% of **28** and 30% of **29**.

(TBDMSCl). Then, the secondary alcohol in **23** was oxidized by reaction with Dess−Martin reagent in methylene chloride at room temperature to give ketone **24**. The next step was the deprotection of the silyl group in **24** to get **21**. The reaction was carried out in the presence of TBAF−AcOH−THF, which gave a mixture of unidentified products. Several other standard desilylation methods also failed. At this point, we decided to use the crude mixture from the oxidation step to reduce the ketone directly. The reaction conditions are given in Table 1.

The synthesis of the key intermediate, 4-*epi*-diol **25**, was first tried using $NaBH(OAc)_3$ at room temperature. In these conditions, we isolated exclusively diol **23** after 24 h (entry 1, Table 1). A similar result was obtained when the reaction was performed with $LiAlH(t\text{-}BuO)_3$, a milder reducing agent, at 0 °C (entry 2, Table 1). Entries 3 and 4 of Table 1 show the results when the reduction of the keto compound **24** was carried out with L- and K-selectride, which provided diastereoisomers **23** and **25** in ratios 75:25 and 80:20, respectively. However, the moderate ratio toward compound **25** in these processes prompted us to search for a more efficient route. A Mitsunobu[21] reaction ($p\text{-}NO_2-C_6H_4CO_2H$, Ph_3P, DEAD, toluene or THF) of the free secondary alcohol in compound **23** did not give positive results, and a complex mixture of compounds was obtained.

An alternative approach is an inversion of the disilyl-protected derivative of methyl quinate **26** (Scheme 3). When the latter was treated under Mitsunobu conditions ($p\text{-}NO_2-C_6H_4CO_2H$, Ph_3P, DEAD, toluene or THF), the reaction led to the recovery of the starting material. Thus, the conversion of diol **26** (prepared from quinic acid in two steps: esterification followed by hydroxyl protection[22]) to the inverted hydroxyl derivative at C-4 would be best achieved by activation of the hydroxyl group as mesylate (compound **27**), followed by a reaction with benzoic acid−cesium fluoride in DMF at 90 °C. Surprisingly, this approach provides the benzoate derivatives **28** and **29** (the latter as an inseparable mixture of products) in isolated yields of 55 and 30%, respectively.

SCHEME 4

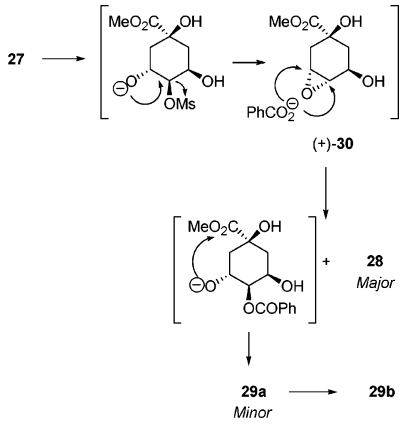
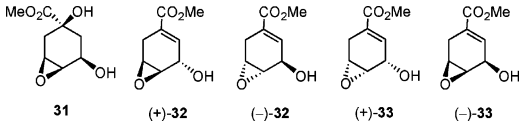


CHART 3



The formation of these compounds can be explained by the mechanism shown in Scheme 4, which involves initial removal of the TBDMS groups from **27** by means of fluoride ions present in the reagent CsF, followed by displacement of the mesyl group with the oxyanion located at the 5-position. The subsequent opening of the epoxide intermediate **30** with the benzoate anion afforded **28** as the major compound and **29a**, which can undergo a migration of the benzoate group from O-4 to O-3, giving rise to **29b**.

To confirm the mechanism, the reaction was carried out in the absence of benzoic acid. As expected, epoxide **30** was obtained, although under these conditions, **30** was isolated in low yield.

The proposed epoxy alcohol (+)-**30** is not reported in the literature. However, we have found that its diastereomer **31** (Chart 3) is a useful key intermediate in the synthesis of neuraminidase enzyme inhibitors.[23] On the other hand, the corresponding shikimate epoxide (−)-**32**[24] is a versatile chiral building block for the synthesis of chorismate-type analogues. Other isomers of this derivative, such as (+)-**32**,[24b] (−)-**33**,[24b,25] and (+)-**33**,[24b,26] have also proven to be important precursors of biologically active compounds, because they contain several stereocenters and a high diversity of functionality. Given the importance of these derivatives, we have explored the synthesis of epoxides (+)-**30** and (−)-**32** through a strategy that allows easy access to these synthons.

The analogue (+)-**30** was prepared from mesylate **27**, according to Scheme 5. Desilylation of **27** with HCl in MeOH

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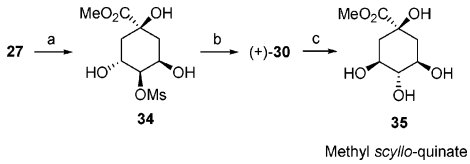
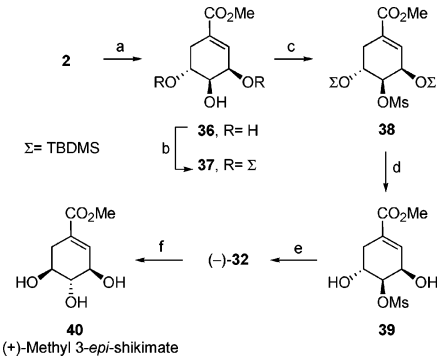
SCHEME 5[a]



[a] Reagents and conditions: (a) HCl concd, MeOH, rt, 4 h, 95%; (b) K_2CO_3, MeOH, 0 °C, 5 h, 77%; (c) CF_3CO_2H, H_2O, rt, 36 h, 100%.

SCHEME 6[a]



[a] Reagents and conditions: (a) HCl concd, MeOH, 60 °C, 6 h, 100%; (b) TBDMSCl, Et_3N, DMAP, DMF, rt, 1 h, 75%; (c) MsCl, Py, 0 °C to rt, 2 h, 84%; (d) HCl concd, MeOH, rt, 3 h, 96%; (e) DBU, toluene, rt, overnight, 78%; (f) $CF_3CO_2H-H_2O$ (1:1), rt, 36 h, 100%.

furnished the triol **34**. The latter was converted to epoxide (+)-**30** by treatment with potassium carbonate in MeOH at 0 °C for 5 h. Alternatively, (+)-**30** can be obtained with NaOMe in MeOH or DBU in THF. However, these procedures proved to be inefficient because longer reaction times are required and lower yields are achieved. Thus, quinic acid was transformed into epoxide (+)-**30** in five steps with an overall yield of 47%.

We next investigated various reaction conditions for nucleophilic ring opening of the epoxide. The opening was efficiently accomplished both regio- and stereoselectively with aqueous trifluoroacetic acid, with methyl *scyllo*-quinate (**35**) being isolated exclusively in quantitative yield. This attractive route allows, for the first time, an efficient synthesis of the *scyllo*-derivative of quinic acid, which could have manifold uses as a chiron starting material in the synthesis of a wide range of target molecules. Previously, this isomer was isolated, along with other derivatives, by random isomerization of quinic acid.[27]

The corresponding methyl shikimate epoxide (−)-**32** was prepared from shikimic acid in a similar manner, as outlined in Scheme 6. Commercial shikimic acid (**2**) was transformed into methyl shikimate **36** by refluxing with HCl in MeOH, and the latter was selectively protected at OH-3 and OH-5 with TBDMSCl to afford **37** in 75% yield. Treatment of **37** with mesyl chloride gave the mesylate **38**, which was silyl deprotected in HCl/MeOH. To prepare epoxide (−)-**32** bases such as NaOMe, DBU, or K_2CO_3 were employed. Best results were achieved with DBU in toluene, resulting in the formation of the epoxide **32** in 47% overall yield and in five steps from shikimic acid.

Selective opening of the epoxide under identical conditions to those mentioned above for the quinate derivative, gives rise exclusively to (+)-methyl 3-*epi*-shikimate (**40**) in quantitative yield. It is noteworthy that only one synthesis is reported in the literature for this isomer.[28] This takes place with lower yield (22%) and in nine steps using tedious chromatographic columns to separate the mixture of isomers obtained in various reactions.

In summary, we have shown that the synthesis of (−)-methyl 4-*epi*-shikimate from quinic acid has been efficiently achieved in six steps with a 30% overall yield. The approach detailed here is a significant improvement over previously reported protocols, thus providing easy access to this chiron for other synthetic applications. Additionally, we have prepared the 4,5-epoxy derivatives of quinic and shikimic acids and have highlighted the synthetic utility of these metabolites by describing an efficient synthesis of methyl *scyllo*-quinate and (+)-methyl 3-*epi*-shikimate.

Experimental Section

(−)-Methyl 4-*epi*-Shikimate (19). $NaBH(OAc)_3$ (1.14 g, 5.38 mmol) was added to a solution of **18** (500 mg, 2.69 mmol) in 34 mL of anhydrous CH_2Cl_2. After stirring for 2 h at room temperature, the reaction was quenched with solid $NaHCO_3$ and filtered, and the filtrate was then extracted with water. The aqueous layer was concentrated, and the crude residue was purified by flash chromatography using silica gel 60 Å (32−63 μm) at pH 7 (gradient eluent 15−50% MeOH/EtOAc) to give **19** as a white hygroscopic solid in 70% yield.

(+)-Methyl (1*S*,3*R*,4*S*,5*R*)-4,5-Epoxy-1,3-dihydroxycyclohexane-1-carboxylate (30). To a solution of **34** (80 mg, 0.28 mmol) in anhydrous MeOH (4.6 mL) at 0 °C was added K_2CO_3 (39 mg, 0.28 mmol). The reaction was stirred for 5 h at 0 °C, and then the solvent was evaporated. The residue was poured into water and extracted with $CHCl_3$. Subsequent purification by flash chromatography, using silica gel 60 Å (32−63 μm) at pH 7 and with EtOAc as eluent, afforded **30** as a white solid in 83% yield.

(−)-Methyl (3*R*,4*S*,5*R*)-4,5-Epoxy-3-hydroxy-1-cyclohexene-1-carboxylate (32).[23a] To a stirred solution of **39** (115 mg, 0.46 mmol) in anhydrous toluene (2.3 mL) at 0 °C was added dropwise DBU (0.103 mL, 0.69 mmol). After stirring the mixture at room temperature overnight, the solvent was evaporated. The crude material was purified by flash chromatography, using silica gel 60 Å (32−63 μm) at pH 7 and with Et_2O/hexane as eluent, to afford (−)-**32** as a white solid in 80% yield.

Methyl *scyllo*-Quinate (35). To a stirred solution of **30** (71 mg, 0.38 mmol) in water (2 mL) was added trifluoroacetic acid (0.006 mL, 0.075 mmol). The reaction was stirred at room temperature for 36 h. Two additional portions of trifluroacetic acid (0.006 mL) were added after 12 and 24 h. The mixture was extracted with CH_2Cl_2, and the aqueous fraction was concentrated to afford **35** as a colorless oil in quantitative yield.

(+)-Methyl 3-*epi*-Shikimate (40).[27] A similar procedure to that described for **35** afforded **40** as a white solid in quantitative yield.

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Supporting Information Available: Complete experimental procedures, ^1H and ^{13}C NMR spectral data, and some two-dimensional NMR experiments are shown in addition to mp, IR, optical rotation, microanalysis, and MS data. The level of purity is indicated by the inclusion of copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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