Stereochemistry of Quinate–Shikimate Conversions. Synthesis of (−)-4-*epi*-Shikimic Acid

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Abstract: Addition of hydrogen cyanide to (3*R*,5*R*)-3,4,5-triacetoxycyclohexanone (**2**) proceeded nonstereospecifically to yield a 40:60 mixture of the two cyanohydrin epimers (1*RS*,3*R*,4*S*,5*R*)-1-hydroxy-5/3,4-triacetoxycyclohexane-1-carbonitrile (**4**), characterized as tetraacetates **5** and **6**. Dehydration of cyanohydrins **4** under various conditions gave in equal proportions nitriles **9** and **10**, arising from the two possible modes of elimination. The corresponding (−)-shikimic acid (**11**) and (−)-4-*epi*-shikimic acid (**12**) were then obtained from nitriles **9** and **10**, respectively, by hydrolysis. (−)-4-*epi*-Shikimic acid [**12**,(3*R*,4*R*,5*R*)-3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid] was completely characterized and compared with racemic **12** prepared by hydrogen fluoride epimerization of methyl (−)-triacetylshikimate (**15**). Also, the shikimate and 4-*epi*-shikimate methyl esters (**15** and **16**) were shown to yield the same dihydro product, methyl (1*R*,3*R*,4*S*,5*R*)-3,4,5-triacetoxycyclohexane-1-carboxylate (**18**), thereby verifying the functional stereochemistry assigned to **12**. Similarly, dehydration of methyl 3,4,5-tribenzoyl- and 3,4,5-triacetylquinate (**20a,b**) proceeded nonstereospecifically but predominately to shikimate esters. On the other hand, methyl 3,4,5-triacetyl-*epi*-quinate (**22**), prepared *via* HF epimerization of methyl 1,3,4,5-tetraacetylquinate (**19**), yielded as the major product upon dehydration the 4-*epi*-shikimate ester **16**. The implications of these interconversions for quinate–shikimate chemistry are discussed.

In the course of the preparation of [7-^{14}C]shikimic acid,[1,2] a useful precursor for studying aromatic biosynthesis, it became obvious that, contrary to literature reports, several of the required intermediates were obtained as stereoisomeric mixtures. Because of the unexpected nature of these results and the potential biological interest in the isomers obtained, we have completed a detailed study of the reactions involved and report our results herein.

The synthesis of shikimic and quinic acid derivatives by cyanide addition to (3*R*,5*R*)-3,4,5-triacetoxycyclohexanone (**2**) followed by dehydration and/or hydrolysis (Scheme I) has been available for some time and is reported to proceed stereospecifically to shikimic acid (**11**) and quinic acid (**7a** *via* **5**).[3] Conveniently, ketone **2** is obtained stereochemically intact by a Hunsdiecker degradation of the tetraacetate of quinic acid (**1**).[3a] Both cyanohydrin acetate **5** and nitrile **9** were reported to be formed free of the corresponding isomers, **6** and **10**,[4] the evidence in both cases being the isolation of crystalline material identical with that authentically derived from the parent natural products.[3a] Overall then, the route would seem to offer an ideal approach for the synthesis of optically active, carboxy-labeled shikimic and quinic acids.

In our hands, however, application of these procedures soon revealed a number of inconsistencies. Cyclohexanone **2** could be prepared in high yield (70–100%) after minor modification of the original procedure.[3a] For example, the use of carbon tetrachloride as solvent avoided contamination of the product ketone with ethyl tetraacetylquinate which was obtained as an impurity when this reaction was performed in ethyl bromide as recommended. It was also determined that the bicarbonate wash suggested to remove acetyl bromide, formed concurrently, catalyzed a variable amount of elimination to 4,5-diacetoxy-2-cyclohexenone (**3**).[4] On the other hand, acetyl bromide could be effectively removed *in vacuo* at 40° without concomitant elimination, and a stable product could then be obtained by crystallization from ether. Attempted chromatographic purification on silica gel also resulted in quantitative elimination of a molecule of acetic acid to give again the interesting enone **3**. Since either the 3- or 5-acetate may be eliminated, **3** must be assumed to be a mixture of the two possible 4-epimers although this was not revealed by the criteria applied (tlc, gc, and nmr).

Conversion of ketone **2** to cyanohydrin **4** proceeded as described in 87% yield.[3a] The apparent homogeneity of the product on tlc and instability to gc precluded any investigation of the cyanohydrin epimer question at this point. Furthermore, silylation of the tertiary alcohol function of **4** led to a mixture of ethers which could not be resolved by gc but whose nature could be easily discerned upon nmr examination of the trimethylsilyloxy signals at δ 0.29 (40%) and 0.31 (60%). Acetylation, however, gave a preparation which was separated by gc into two difficultly resolvable components. The nonhomogeneous nature of the crude cyanohydrin acetates was also shown by careful column chromatography which allowed resolution into these two components. Material obtained first from the

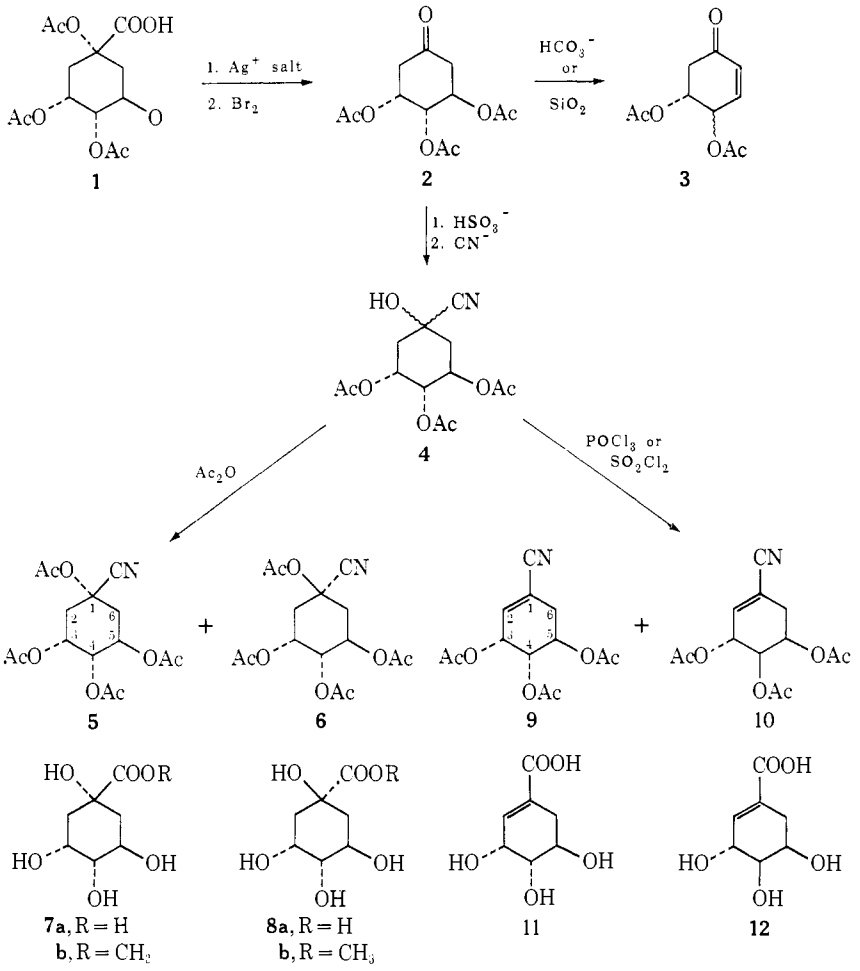
(1) Details will be forthcoming: R. M. Baldwin, C. D. Snyder, and H. Rapoport, manuscript in preparation. A preliminary report has appeared: R. M. Baldwin, C. D. Snyder, and H. Rapoport, *J. Amer. Chem. Soc.*, **95**, 276 (1973).

(2) All compounds unless otherwise specified are optically active and possess the stereochemistry shown. Where necessary the sequence rule (*R*/*S*) convention [R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 13, 81 (1956); R. S. Cahn, *J. Chem. Educ.*, 41, 116 (1964)] has been used to define stereochemistry unambiguously although for clarity trivial names are utilized whereever possible. Numbering follows IUPAC-IUB Nomenclature rules for Cyclitols [*Eur. J. Biochem.* **5**, 1 (1968)]; *i.e.*, the same numbering system is used for shikimate and quinate systems and numbering proceeds through the shikimate double bond.

(3) (a) R. Grewe and E. Vangermain, *Chem. Ber.*, **98**, 104 (1965); (b) H. J. Bestmann and H. A. Heid, *Angew. Chem., Int. Ed. Engl.* **10**, 336 (1971); (c) J. Corse and R. E. Lundin, *J. Org Chem.*, **35**, 1904 (1970).

(4) In this series the symmetrical translocation of a double bond from one side of the C-1/C-4 axis to the other is formally equivalent to 4 epimerization and will be shown as such in the structural formulas. The mechanism of origin, therefore, should not be deduced from the formulas.

Scheme I



column crystallized spontaneously and corresponded to the more volatile constituent by gc. Recrystallization gave a product which by melting point (167°, lit.[3a] mp 162°), mass spectrum, and rotation was identical with the quinate-type epimer **5**. Conversely, the final fraction was an oil corresponding to the less volatile constituent and by mass spectrum and elemental analysis was isomeric with **5**. On the basis of nmr spectra the two compounds differed only in subtle placement of the acetate methyl signals. The assumption then must be that we have isolated the *epi*-quinate isomer **6** which appears, also by gc, to be predominant (60:40). It follows that utilization of cyanohydrin **4** as an intermediate to quinic acid will require an epimeric separation at some point in the sequence. On the other hand, this approach could lead efficiently to optically active carboxy-labeled *epi*-quinic acid (**8a**, or its γ-lactone[3c]) if that were desired.

Dehydration of the epimeric mixture of cyanohydrins **4** with either phosphorus oxychloride or sulfuryl chloride in pyridine led, after chromatographic purification, to a 1-cyclohexene-1-carbonitrile fraction which by gc could be clearly resolved into two components. Although both dehydrating reagents gave the same product ratio, sulfuryl chloride was significantly more reactive and more efficient. Perhaps this reagent should be considered more often for dehydrations where chlorine-sensitive functionalities are not present.

Preparative gc allowed identification of the less

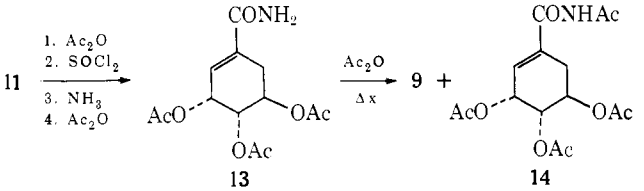
Table I. Ratios of Isomeric Olefins Obtained by $POCl_3$ and SO_2Cl_2 Dehydration of Various Tertiary Alcohols

Tertiary alcohol	Dehydrating reagent (in pyridine)	Isomeric olefin pair	Ratio[a]
4	$POCl_3$	**9:10**	47:53
	SO_2Cl_2	**9:10**	47:53
20a	$POCl_3$	**11:12**	84:16[b]
	SO_2Cl_2	**11:12**	82:18[b]
20b	SO_2Cl_2	**15:16**	79:21
22	SO_2Cl_2	**15:16**	14:86

[a] Determined by quantitative gc; for column conditions, see Experimental Section. [b] Determined by ultraviolet extinction after separation on a borate column; see Experimental Section.

volatile nitrile component as **9** by comparison with authentic material derived from shikimic acid (Scheme II), while the other component was assigned isomeric

Scheme II



structure **10** on the basis of mass (M^+, *m/e* 281) and nmr spectra and a compatible elemental analysis. In

spite of numerous attempts, nitrile **10** could not be crystallized, this property probably being responsible for its initial omission[3a] since in our hands nitrile **9** frequently crystallized spontaneously from the crude reaction mixture. The independent synthesis of **9** deserves comment in that the unexpected by-product **14** was obtained in addition to the desired nitrile upon treatment of triacetylshikimic acid amide (**13**) with acetic anhydride. Easily resolvable by chromatography, **14** was demonstrated by nmr (four methyl singlets) to be a tetraacetyl derivative of **13**, most probably the *N*-acetylamide.[5] The possiblity of a bicyclic structure involving a cyclol acetate cannot be unambiguously ruled out but models of the various possibilities appear strained. The similarity of the proton absorptions at C-3, -4, -5 to those of analogous protons in other shikimates provides evidence against such distortion. That **14** is not an intermediate in the dehydration was shown by recovery without a trace of nitrile formation after resubmission to the reaction conditions.

Both nitriles **9** and **10** were hydrolyzed separately to shikimic acid (**11**) and 4-*epi*-shikimic acid (**12**). Freed of sodium salts by ion exchange, the acids could be purified by kieselgel chromatography. Alternatively, the nitriles could be hydrolyzed as a mixture and separated as free acids by column chromatography on cellulose employing a 1-butanol–ethanol–borate buffer eluent[6] which proved unique among many solvent systems tested in its capacity to resolve **11** and **12**. Column fractions were deborated by first passage through a cation exchange column and then treatment with methanol, removing *in vacuo* the volatile methyl borate so formed.

Further purification of the *epi*-acid **12** by crystallization proved impossible in contradistinction to the racemic form[7] which was reported to be easily crystallized from methanol–water (mp 198–199°). Solvent systems successful with shikimic acid were ineffectual in this case although precipitation as the cyclohexylamine salt did allow further purification. However, the salt proved extremely hygroscopic and sensitive to disproportionation upon drying so that it was unsuitable for characterization. Reconversion then to the free acid gave a similarly hygroscopic oil from which the crystalline acid **12** (mp 60–64°) could be obtained only by high vacuum sublimation and thereafter handled only in an anhydrous atmosphere.

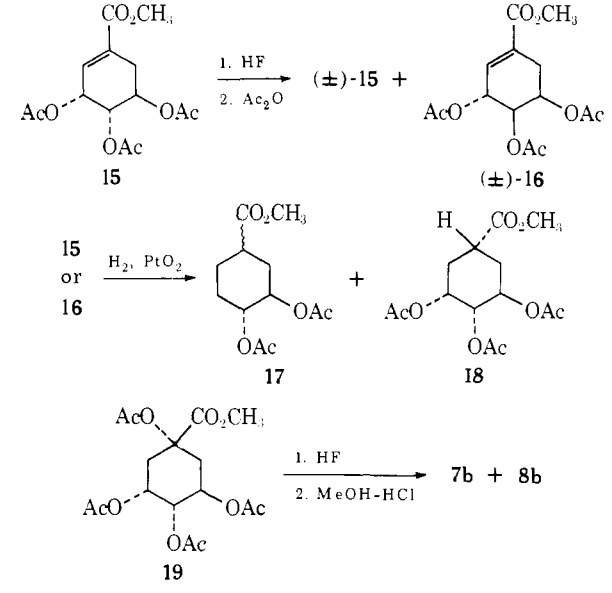
The disparity in crystalline properties between the (−) and (±) forms of 4-*epi*-shikimic acid is dramatic. Since shikimic acid itself does not show such a difference [mp (−) 190–191°, (±) 191–192°][8] it was important to the overall argument that a direct comparison with racemic **12** be made. Therefore methyl triacetylshikimate (**15**) was subjected to hydrogen fluoride rearrangement conditions[7] and after reacetylation methyl (±)-triacetyl-4-*epi*-shikimate (**16**) was obtained by preparative gc. As reported,[7] epimerization results in an 84:16 mixture favoring the shikimate ester. We also found that this equilibrium is established in less than 2 hr at room temperature, although racemization proceeds at a considerably slower rate ($t_{1/2}$ = 2.6 hr) which is consistent with the mechanism postulated for this reaction. Hydrolysis of racemic ester **16** gave after ion exchange the free acid which crystallized easily (mp 200–201°). Chromatographically and spectrally the (−) and (±) forms of **12** are identical as can be seen in Table II.

Table II. Properties of Shikimic (**11**), 4-*epi*-Shikimic (**12**) and (±)-4-*epi*-shikimic (±)-(**12**) Acids

Property	**11**	Compd **12**	(±)**12**
Melting point	190–191°	60–64° (hygroscopic)	200–201°
Tlc, R_f			
Cellulose-*n*-BuOH–EtOH–borate buffer (1:1:1)	0.36	0.51	0.51
Silica gel-*n*-BuOH–AcOH–H_2O (100:6:25)	0.60	0.60	0.60
Uv absorption (95% EtOH)	212 nm (ε 8860)	213 nm (ε 8270)	212 nm (ε 8670)
$[\alpha]^{22}D$ (H_2O)	−157° (*c* 1)	−93° (*c* 0.9)	0

Finally, in order to verify the hydroxyl orientations of **12** (and correspondingly of (±)-**12** as obtained by HF epimerization), *epi*-ester **16** (Scheme III) was re-

Scheme III



duced catalytically and the products were compared to the analogous reduction of shikimate ester **15**. If the structure of **12** is as proposed, then the same two dihydro products are realizable from both **15** and **16** and the only difference might arise in the relative amounts of C-1 epimers. Any other structure, *e.g.*, 3-*epi*-shikimic acid, would lead to distinctly different dihydro products in the two series.

Thus reduction of **15** afforded two products in a 2:3 ratio; one was the deacetoxydihydro ester **17** and the other was one of the possible dihydro esters, **18**. A trace of acetic acid added as suggested[9] to suppress

(5) An analogous structure has been postulated for a similarly obtained pentaacetate of quinic acid amide: R. Grewe, A. Bokranz, and H. W. Herberg, *Chem. Ber.*, **88**, 1367 (1955).
(6) C. B. Coulson and W. C. Evans, *J. Chromatogr.*, 1, 374 (1958)
(7) R. Grewe and S. Kersten, *Chem. Ber.*, **100**, 2546 (1967).
(8) R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960).
(9) C. W. Shoppee, B. D. Agashe, and G. H. R. Summers, *J. Chem. Soc.*, 3107 (1957).

hydrogenolysis had only a marginal effect. Although ester **17** was composed of a mixture of C-1 epimers (two methyl ester nmr signals), dihydro ester **18** was homogeneous (gc, tlc, nmr) and by analogy with the reduction of shikimic acid[10] has the configuration shown. The same products were also formed by reduction of the ester **16**, although in somewhat different proportions, and the dihydroshikimate ester so obtained was identical in all respects with ester **18**, thereby confirming structural assignment **12**. Both reductions apparently proceed with the same stereo-bias although one might have predicted that in the case of ester **16**, 4 epimerization would make approach of catalyst to either face more nearly equivalent.

Having established the structure of **12**, an interesting comparison between the two shikimic acids lies in the interpretation of their nmr spectra, particularly since an analysis of shikimic acid has already been performed.[11] The tabulated spectral parameters are shown for comparison in Table III. Decoupling experiments allowed

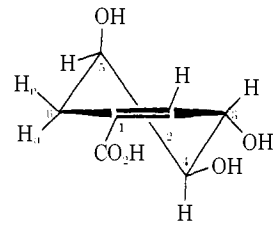
Table III. Nmr Absorption of Shikimic Acid (**11**)[a] and 4-*epi*-Shikimic Acid (**12**)[b]

Compd	Chemical shifts (δ values)					
	C-2-H	C-3-H	C-4-H	C-5-H	C-6-H_{ax}	C-6-H_{eq}
11	6.88	4.41	3.69	4.00	2.14	2.77
12	6.80	4.40	3.73	4.17	2.54	2.54
	Coupling constants (Hz)					
	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$	$J_{6a,6e}$
11	4.0	3.9	8.4	6.2	5.0	18.5
12	3.0	7.4	2.4	4	4	0

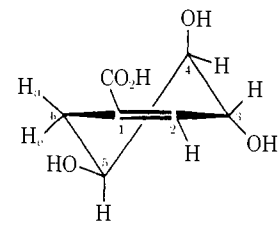
[a] *Cf.* ref 11. 60-MHz spectrum (D_2O), acetonitrile internal standard. [b] 100-MHz spectrum (D_2O), δ values relative to DSS.

definitive assignment of the major coupling constants although exact interpretation was sometimes complicated by minor cross-ring coupling. Also, the proximity of the various absorptions precluded a simple first-order analysis for some of the protons. The most noticeable difference between the two is that the 6a and 6e hydrogens of the *epi* acid have very similar chemical shifts centered in a complex multiplet at δ 2.54 instead of the widely split (J_{6a-6e} = 18.5 Hz) AB pattern observed for the corresponding protons in shikimic acid. Irradiation of the C-5 proton separated this absorption slightly so that the C-6 protons are not exactly chemically equivalent. Similar irradiation of the C-4 proton quartet ($J_{3,4}$ = 7 Hz, $J_{4,5}$ = 2 Hz) resulted in collapse of the C-5 proton signal into a triplet ($J_{5,6}$ = 4 Hz), further illustrating the rough equivalence of the coupled C-6 protons. Finally, irradiation of the C-6 protons suppressed cross-ring coupling ($J_{2,6}$ = 2 Hz) and allowed the coupling between the C-2 and C-3 protons (3 Hz) to become clearly visible.

Given the coupling constants so determined, can a meaningful conformational analysis, similar to that of shikimic acid,[11] be performed? If, of the four classical half-chair and half-boat conformations of cyclohexene, the two half-chair forms (**12a,b**) are assumed energetically most favorable,[12] then consideration of coupling



12a



12b

constants might allow some distinction between the two. Using values calculated from an electron diffraction study of cyclohexene[13] the various dihedral angles between adjacent hydrogens for the two conformations are shown in Table IV in comparison with those de-

Table IV. Theoretical[a] and Experimental[b] Dihedral Angles between Adjacent Hydrogens of the Two Half-Chair Forms, **12a** and **12b**, of 4-*epi*-Shikimic Acid (**12**)

	Dihedral angle, deg				
	H-2, H-3	H-3, H-4	H-4, H-5	H-5, H-6a	H-5, H-6e
Theoretical, **12a**	73	165	61	43	73
Theoretical, **12b**	48	73	61	165	47
Experimental	*c*	150	57	~47	~47

[a] Calculated; *cf.* ref 13. [b] Calculated; *cf.* ref 14. [c] Cannot be determined since Karplus equation is valid only for hydrogens attached to sp^3 hybridized carbon; *cf.* ref 14.

duced by application of the modified Karplus equation[14] to the coupling constants involved. The correlation is not exact but conformation **12a** is favored. Interestingly, the opposite conformation was analogously assigned to shikimic acid.[11] Although one could have arrived at the same conclusion by the simple approximation of minimizing nonbonded interactions (one 1,3 H–OH diaxial interaction in **12a** *vs.* two in **12b**), the correlation with coupling constants is attractive in that the conclusion rests on a more quantitative basis.

During the progress of our study an additional report of a relevant stereospecific dehydration appeared,[15] in this case that of methyl 3,4,5-tribenzoylquinate (**20a**) to methyl 3,4,5-tribenzoylshikimate (**21**). In view of our experience such a result was surprising. Although the evidence for exclusive isomer formation seemed unimpeachable, a series of recrystallizations had been used to obtain the final product upon which the stereochemical analysis had been performed. During any of these steps unsuspected isomer separation could have occurred.

To investigate this reaction tribenzoate **20a** was prepared (65% from quinic acid) and dehydrated with

(10) H. O. L. Fischer and G. Dangschat, *Helv. Chim. Acta*, **18**, 1206 (1935); J. Csaszar and V. Bruckner, *Acta Chim. (Budapest)*, **75**, 411 (1973).

(11) L. D. Hall, *J. Org. Chem.*, **29**, 297 (1964).

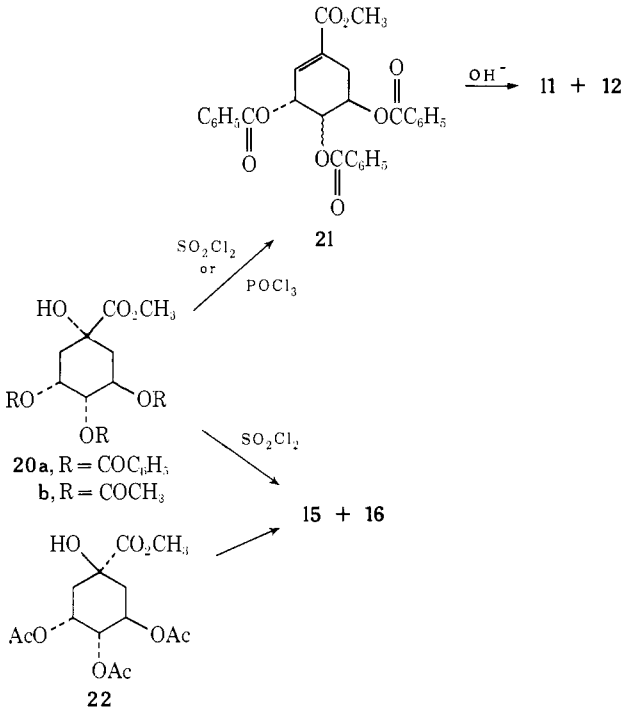
(12) Theorectial as well as experimental estimates suggest that the half-chair conformation of cyclohexane is significantly (3–17 kcal/mol) more stable than the half-boat (*cf.* ref 14 and references therein). Although substituents could in theory effect some change we have assumed that only the half-chair conformations of 4-*epi*-shikimic acid need be considered.

(13) J. F. Chiang and S. H. Bauer, *J. Amer. Chem. Soc.*, **91**, 1898 (1969).

(14) $J = J_0 \cos^2 \phi - 0.3$ where ϕ is the dihedral angle between two adjacent hydrogens and for $0 \leq \phi \leq 90°$, J_0 = 9.3 Hz and for $90 \leq \phi \leq 180°$, J_0 = 10.4 Hz: M. Karplus, *J. Chem. Phys.*, 30, 11 (1959); R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *J. Chem. Soc.*, 3699 (1962).

(15) J. Cleophax, D. Mercier, abd S. D. Gero, *Angew. Chem., Int. Ed. Engl.*, **10**, 652 (1971).

Scheme IV

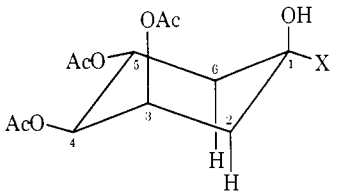


sulfuryl chloride in pyridine–chloroform to yield the shikimate esters **21** (Scheme IV). Although exact conditions for the latter reaction were not reported,[15] a 1:2 ratio of pyridine–chloroform and a limited quantity of sulfuryl chloride (2 equiv) were found to be efficient. Column chromatography allowed purification, with care being taken to collect the entire product band in order to avoid fractionation. As expected from analogous esters, no separation (by tlc) of isomers was detected, and the ester fraction was obtained as a crystalline solid (mp 50–54°, lit.[15] mp 60–62°). Since the material was too nonvolatile for gc analysis, the entire product was hydrolyzed and, after ion exchange and ether extraction to remove benzoic acid, crude shikimic acids were obtained. The presence of *epi*-acid **12** was detected by tlc, and the mixture was resolved on a column to afford an 82:18 ratio of **11** to **12**. A similar dehydration with phosphorus oxychloride in pyridine gave the same result (Table I) in slightly diminished yield.

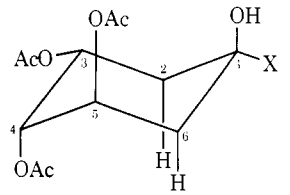
In order to determine whether the steric bulk of the benzoate esters was efficacious in achieving the degree of selectivity observed above, we prepared the analogous triacetate of methyl quinate (**20b**), in which steric bulk is minimized, and subjected this ester to sulfuryl chloride dehydration. Separation by gc allowed the product composition estimate (79:21, **15**:**16**) to be performed at the ester stage. The similarity of these results indicates a rather fundamental degree of stereochemical control related to a structural feature more proximal to the reaction site than the ester termini.

Originally,[3a] the sole formation of nitrile **9** from cyanohydrin **4** (quinate form, X = CN) had been rationalized on the basis that the required[16] *trans*-diaxial proton abstraction was hindered at the 6-axial site by an adjacent 5-equatorial acetate, thereby favoring abstraction of the 2-axial proton. Since we now know

(16) Dehydration of cyanohydrins with phosphorus oxychloride–pyridine has been shown to proceed by abstraction of the trans-diaxial proton: T. Holm, *Acta Chem. Scand.*, 18, 1577 (1964).



quinate form



epi-quinate form

that nitrile **9** is not the only product of this reaction and that cyanohydrin **4** is a mixture of C-1 epimers, such a rationalization is inappropriately derived although the stereoselectivity observed upon quinate (X = CO_2CH_3) dehydration does follow the original suggestion. Likewise, dehydration of an *epi*-quinate form might be expected to proceed conversely since, except for a uniform 1,3-diaxial interaction at both hydrogens posed by the 4-acetate, the environment of the 6-axial proton in the *epi* series is identical with that of the 2-axial proton of the quinate series. Since quinate dehydration favors shikimate formation, *epi*-quinate dehydration should yield predominantly 4-*epi*-shikimate.

To test this hypothesis in the cyanohydrin series (X = CN) proved impossible because we were unable to effect an epimer separation either of cyanohydrin **4** or the trimethylsilyl ether of **4**. We therefore turned to the quinate ester series for the definitive data.

Methyl *epi*-quinate (**8b**) was prepared directly by HF epimerization of methyl tetraacetylquinate (**19**) followed by HCl–methanol treatment to complete the deacetylation. The crystalline **7b**/**8b** mixture so obtained, inseparable by silica gel chromatography, upon conversion to trimethylsilyl ethers was easily resolved by either column chromatography or preparative gc (**7b**:**8b**, 79:21). Exposure to 10^{-3} *M* HCl–methanol quantitatively regenerated the pure esters without epimerization (as shown by resilylation and gc analysis). Also, optical activity was totally retained in the overall process.

That **8b** had indeed been obtained was demonstrated by the coincidence (plus a methyl ester absorption) of its nmr spectrum with that reported[3c] for *epi*-quinic acid (**8a**). Selective acetylation then yielded methyl 3,4,5-triacetyl-*epi*-quinate (**22**). Finally, when triacetate **22** was subjected to sulfuryl chloride dehydration the 4-*epi*-shikimate **16** was formed predominately (**15**:**16**, 14:86) and in high yield (95%).

Clearly both in the quinate and *epi*-quinate series an axial hydrogen–equatorial ester interaction is sufficient to effect significant although not complete stereochemical control in the mode of dehydration. Presumably, the same results would be obtained from the purified cyanohydrin epimers if they could be obtained and in fact using the above data a 40:60 ratio of **9**:**10** would be predicted, in reasonably close agreement with the 47:53 ratio observed.

In conclusion then, cyanohydrin and quinate dehydrations are nonstereospecific although with improved purification the various isomers now can be obtained. Likewise, cyanide addition is nonstereospecific so that both quinic and *epi*-quinic acid derivatives are available. Both of these results are of import for quinate–shikimate chemistry in that they correct some previous misconceptions and allow entry into a series of compounds of biological importance.

Experimental Section[17]

(3*R*,5*R*)-3,4,5-Triacetoxycyclohexanone (2). Silver tetraacetylquinate[3a] (1.50 g, 3.21 mmol) and silver acetate (6.60 g, 39.6 mmol) were mixed and dried at 90° *in vacuo* overnight. Carbon tetrachloride (75 ml) was distilled from P_2O_5 through dried apparatus into the flask containing the dried silver salt mixture, a reflux condenser capped with a drying tube was attached, bromine (2.00 ml, 39.0 mmol) was added to the vigorously stirred solution, and after about 1 min reaction began. After the vigorous effervescence had ceased, the solution was filtered to remove AgBr, the precipitate was washed with CCl_4, and the combined filtrate and washings were evaporated *in vacuo* until acetyl bromide was completely removed. The product was triturated with ether and recrystallized from ether at −50°, giving ketone **2**; 615 mg, 77%: mp 77–78° (lit.[3a] mp 78°); nmr δ 2.07 (2), 2.10 (1, s, OAc), 2.6–2.9 (br m, $-CH_2-$), 5.2–5.7 (br m, C*H*OAc); $[\alpha]^{22}D$ −74.7° (*c* 1.6, benzene) (lit.[3a] $[\alpha]^{23}D$ −73.9°); mass spectrum *m/e* 273 ($M^+ + 1$, 0.3%), 255 (0.3), 244 (0.5), 212 ($M^+ - 60$, 6), 170 (32), 152 (28), 128 (41), 110 (86), 84 (34), 43 (100).

(4*RS*,5*R*)-4,5-Diacetoxy-2-cyclohexenone (3). Ketone **2** (50 mg, 0.184 mmol) was chromatographed on kieselgel (eluent, 2% methanol–chloroform) to yield **3** as a colorless oil (37 mg, 95%): nmr δ 2.07, 2.14 (s, OAc), 2.6–2.9 [m, $-CH_2-$), 5.2–5.9 (m, CHOAc), 6.15, 6.75 (d, J = 11 Hz, $-CH{=}CH-$); uv 218 nm (ε 8880); $[\alpha]^{22}D$ −70.8° (*c* 1.7, benzene); mass spectrum *m/e* 212 (M^+, 9%), 170 (42), 152 (7), 128 (48), 110 (40), 84 (70), 43 (100).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.6; H, 5.7. Found: C, 57.0; H, 5.9.

(1*RS*,3*R*,4*S*,5*R*)-1-Hydroxy-5/3,4-triacetoxycyclohexane-1-carbonitrile (4). Cyanohydrin **4** was prepared as reported[3a] and obtained as a colorless oil (87%): tlc R_f 0.53 (5% methanol–chloroform); nmr δ 2.07 (2, OAc), 2.10 (1, OAc), 2.2–2.5 (br m, CH_2), 5.0–5.6 (br m, C*H*OAc).

Trimethylsilyl Ether of 4. Cyanohydrin **4** (92 mg, 0.31 mmol) was treated with chlorotrimethylsilane–hexamethyldisilazane–pyridine reagent[18] (1.8 ml) at room temperature overnight. Solvents were then removed *in vacuo* and the crude silyl ether, obtained by extraction of the residue with ether, was chromatographed (20% ether–benzene) to obtain the purified ether as an oil (75 mg, 65%): tlc R_f 0.66 (20% ether–benzene); gc R_T 7.8 min (column b, *t* = 225°), R_T 10 min (column d, *t* = 230°), R_T 12 min (column e, *t* = 220°), R_T 29.5 min (column f, *t* = 215°), R_T 24.5 min (column g, *t* = 200°); nmr δ 0.294 (3.6), 0.313 (5.4, s, $(CH_3)_3Si$), 2.085 (1), 2.065 (2), 2.105 (1), 2.122 (1), 2.132 (1, s, OAc), 4.9–5.6 (br m, C*H*OAc).

(1*R*,3*R*,4*S*,5*R*)-5/1,3,4-Tetraacetoxycyclohexane-1-carbonitrile (5) and (1*S*,3*R*,4*S*,5*R*)-5/1,3,4-Tetraacetoxycyclohexane-1-carbonitrile (6). Crude cyanohydrin **4** (113 mg, 0.38 mmol) was dissolved in a mixture of pyridine (0.25 ml) and acetic anhydride (0.25 ml). After standing overnight at room temperature the reaction was partitioned between ether (10 ml) and 2 *N* H_2SO_4 (2 ml), and the ether layer was washed with saturated bicarbonate, dried over saturated NaCl solution, and evaporated. The crude product was chromatographed (20% ether–benzene) to obtain a mixture of **5** and **6** (107 mg, 83%). Isomer **5** was obtained pure (12 mg) by recrystallization from ether at −20° of fractions 1 and 2 from the above chromatography: mp 167° (lit.[5] mp 161°); gc R_T 19.0 min (column b, *t* 210°); nmr δ 2.03 (1), 2.05 (1), 2.13 (2, s, OAc), 2.35–2.65 (br d, $-CH_2-$), 5.1–5.6 (br m, C*H*OAc); $[\alpha]^{22}D$ −29° (*c* 0.6, 95% ethanol) (lit.[5] $[\alpha]^{20}D$ −31°); mass spectrum *m/e* 341 (M^+, 0.4%), 281 ($M^+ - 60$, 1.2), 2.55 (9), 239 (15), 222 (9), 213 (8), 197 (15), 179 (15), 137 (26), 119 (50), 109 (29), 103 (25), 43 (100).

Isomer **6** was obtained pure as an oil (17 mg) from the last two fractions of the above chromatography: gc R_T 20.5 min (column b, *t* = 210°); nmr δ 2.05 (1, OAc), 2.10 (2, OAc), 2.13 (1, OAc), 2.3–2.7 (br d, $-CH_2-$), 5.1–5.5 (m, C*H*OAc); $[\alpha]^{22}D$ −29° (*c* 0.7, 95% ethanol); mass spectrum same as **5**.

Anal. Calcd for $C_{15}H_{19}O_8N$: C, 52.8; H, 5.6; N, 4.1. Found: C, 52.9; H, 5.6; N, 4.0.

Dehydration Reactions. $POCl_3$. Substrate (1 mmol) was dissolved in pyridine (1.5 ml) and freshly distilled $POCl_3$ (0.200 ml, 2.2 mmol) added at room temperature. After 2 hr the reaction was treated with ice and extracted with ether. The ether extracts were washed with 2 *N* HCl, dried over saturated NaCl, and evaporated to yield crude product which was purified by chromatography.

SO_2Cl_2. Substrate (1 mmol) was dissolved in pyridine (1.5 ml) and ethanol-free chloroform (3 ml) added. The reaction was then cooled to −78°, freshly distilled SO_2Cl_2 (0.178 ml, 2.2 mmol) was added, and the solution was allowed to slowly (1.5 hr) warm to −10° where the temperature was held for an additional 0.5 hr. Isolation and purification then proceeded as with $POCl_3$.

(3*R*,4*S*,5*R*)-3,4,5-Triacetoxy-1-cyclohexene-1-carbonitrile (9) and (3*R*,4*R*,5*R*)-3,4,5-Triacetoxy-1-cyclohexene-1-carbonitrile (10). Cyanohydrin **4** was subjected to dehydration ($POCl_3$) as described and chromatography (20% ether–benzene) gave a mixture of nitriles **9** and **10** in 83% yield. The two were separated by preparative gc (**9**, R_T 36 min; **10**, R_T 30 min, column c, *t* = 210°) and nitrile **9** was further purified by crystallization from ether: mp 109–110° (lit.[3a] mp 110°); gc R_T 21.5 min (column b, *t* = 1 97°); tlc R_f 0.36 (15% acetonitrile–benzene); nmr δ 2.08 (s, OAc), 2.4–2.7 (m, $-CH_2-$), 5.1–5.8 (br m, C*H*OAc), 6.45 (m, $-CH{=}$); uv 207 nm (ε 14,150); $[\alpha]^{22}D$ −210° (*c* 1.0, benzene), (lit.[3a] $[\alpha]^{20}D$ −215°); mass spectrum *m/e* 281 (M^+, 1%), 239 (4), 222 (1), 197 (3), 179 (7), 137 (7), 119 (8), 43 (100).

Nitrile **10** was obtained as an oil: gc R_T 17.5 min (column b, *t* = 197°); tlc R_f 0.36 (15% acetonitrile–benzene); nmr δ 2.06 (1, OAc), 2.10 (2, OAc), 2.5–2.7 (m, $-CH_2-$), 5.0–5.7 (m, C*H*OAc), 6.5 (m, $-CH{=}$); uv 207 nm (ε 13,300); $[\alpha]^{22}D$ −152° (*c* 1.6, benzene); mass spectrum 281 (M^+, 2%), 239 (17), 222 (2), 197 (17), 179 (29), 137 (22), 119 (29), 43 (100).

Anal. Calcd for $C_{13}H_{15}O_6N$: C, 55.5; H, 5.4; N, 5.0. Found: C, 55.7; H, 5.2; N, 4.8.

Cyanohydrin **4** also was dehydrated with SO_2Cl_2 as above and a mixture of nitriles **9** and **10** was obtained in 85% yield after chromatography. Isomer ratios are shown in Table I.

***N*-Acetyltri-*O*-acetylshikimic Acid Amide (14).** 3,4,5-Triacetylshikimic acid amide[3a] (**13**) 1.27 g, 4.25 mmol) was dissolved in acetic anhydride (30 ml) and refluxed for 6 hr. Tlc (40% acetonitrile–benzene) indicated two products: nitrile **9**, R_f 0.69, and tetraacetate **14**, R_f 0.46; no amide **13**, R_f 0.24, remained. The sample was chromatographed to yield crystalline nitrile **9** (504 mg, 42%), mp 110°. Crystalline tetraacetate **14** (543 mg, 41%) was also obtained from the chromatography. A portion of this product was refluxed again for 6 hr in acetic anhydride and recovered intact. A sample of **14** was recrystallized from ether–hexane (3:1): mp 107–108°; nmr δ 2.07, 2.08, 2.09, 2.47 (s, OAc), 2.5–3.0 (br m, $-CH_2-$), 5.3 (2), 5.75 (1, br m, C*H*OAc), 6.5 (m, $-CH{=}$); uv 217 nm (ε 15,850).

Anal. Calcd for $C_{13}H_{19}NO_8$: C, 52.8; H, 5.6; N, 4.1. Found: C, 52.5; H, 5.3; N, 3.8.

Shikimic Acid (11). Nitrile **9** (from SO_2Cl_2 dehydration, 136 mg, 0.05 mmol) was dissolved in water (5 ml) containing KOH (3.0 mmol). After refluxing for 3 hr, the reaction mixture was passed through a 50-ml column of Dowex AG 50W-X1 (H^+ form) and the eluent (250 ml) was evaporated to dryness. The residue was chromatographed on a kieselgel column (butanol–water–acetic acid, 90:10:2) to yield shikimic acid (**11**) as a crystalline solid (54 mg, 62%). A sample was recrystallized from 95% ethanol–ether (1:5), melting point, tlc, uv, and rotation are in Table II; nmr as in Table III.

4-*epi*-Shikimic Acid (12). Nitrile **10** (from SO_2Cl_2 dehydration, 162 mg, 0.58 mmol) was hydrolyzed as nitrile **9** above. The acid obtained after chromatography (76 mg) was dissolved in methanol (0.2 ml) and ethyl acetate (1 ml) was added. The slight precipitate which formed (8 mg) was removed by centrifugation and cyclohexylamine (37 mg, 0.37 mmol) added to form the salt as an oil which was dissolved in water and passed through a 10-ml ion-ex-

(17) Nmr spectra were determined in $CDCl_3$ (δ values relative to internal TMS) or D_2O (δ values relative to internal DSS) with a Varian T-60 instrument; 100-MHz spectra were determined in D_2O on a Varian HA-100 instrument employing a DSS internal lock. Ultraviolet absorption measurements were made in 95% ethanol using a Cary 14 recording spectrophotometer. Melting points are uncorrected. Elemental analyses were performed by the Analytical Laboratory, University of California, Berkeley, Calif. Column chromatographies were carried out on tlc grade Camag kieselgel (or MN-300 cellulose powder) while analytical tlc plates employed a 250 μ layer of kieselgel (or cellulose). Except as noted gc studies were accomplished using 10 ft × 0.25 in. columns packed with 80–100 mesh acid-washed, DMCS treated Chromosorb W containing 5% liquid loadings: column a, QF-1 (5 ft × 0.25 in.); column b, QF-1; column c, QF-1 (15 ft × 0.75 in.); column d, FFAP; column e, XE-60; column f, NPGS; and column g, OV-17. Analytical gc separations were performed using a Varian Aerograph 90-P while preparative scale work utilized a Hewlett-Packard Prepmaster 775. An ETL-NPL automatic polarimeter (Type 143) was used to measure optical rotation. Mass spectra were determined using a CEC-103 instrument. All reactions were performed under a nitrogen atmosphere

(18) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963)

change column, H^+ form. From the eluent (50 ml), *epi*-acid **12** (50 mg, 50%) was obtained by evaporating to dryness, and then further drying at 80° (10^{-3} mm) followed by sublimation at 140° (10^{-3} mm): mp 60–64°; uv 213 nm (ε 8270); mass spectrum *m/e* 156 ($M^+ - 18$, 100%), 138 ($M^+ - 2 \times 18$, 58), 111 (32), 97 (75), 60 (50), 39 (75); tlc and rotation in Table II; nmr in Table III.

Anal. Calcd for $C_7H_{10}O_5$: C, 48.3; H, 5.8. Found: C, 47.9; H, 6.0.

Methyl Triacetylshikimate (15). Methyl shikimate was prepared by treatment at 0° of shikimic acid (Calbiochem, 870 mg, 5 mmol) in methanol (30 ml) with ethereal CH_2N_2. After removal of solvents *in vacuo*, the crude methyl shikimate [tlc R_f 0.84 (30% methanol–chloroform); nmr δ 3.75 (s, CO_2CH_3), rest of spectrum as **11**] was dissolved in pyridine (2 ml)–acetic anhydride (2 ml). After remaining overnight at room temperature, the solvents were removed *in vacuo* and the residue was dissolved in chloroform which was washed with 2 *N* H_2SO_4 and saturated bicarbonate and dried over $MgSO_4$. The yield upon solvent removal was 1.61 g, a portion of which was chromatographed to yield the pure ester **15** as an oil (94%): tlc R_f 0.45 (20% ether–benzene); gc R_T 11.7 min (column a, t = 190°); nmr δ 2.08 (2, OAc), 2.05 (1, OAc), 2.1–2.3 (m, $-CH_2-$), 3.76 (s, CO_2CH_3), 5.2 (2), 5.7 (1, m, C*H*OAc), 6.7 (m, $-CH=$); uv 210 nm (ε 13,300); $[\alpha]^{22}D$ −168° (*c* 0.9, methanol); mass spectrum *m/e* 314 (M^+, 0.2%), 272 (0.3), 254 (0.8), 212 (8), 170 (13), 152 (36), 121 (17), 43 (100).

Anal. Calcd for $C_{14}H_{18}O_8$: C, 53.5; H, 5.8. Found: C, 53.3; H, 5.5.

(±)-Methyl Triacetyl-4-*epi*-shikimate [(±)-16]. Ester **15** (200 mg, 0.64 mmol) was placed in an evacuated HF system[19] and HF (*ca.* 4 ml, dried over CoF_3) was distilled in at −78°. After the mixture was stirred for 2 hr at room temperature, the HF was removed *in vacuo*, and the residue was treated with 3% HCl in methanol for 1 hr at reflux and then, after solvent evaporation, was reacetylated (0.3 ml each of pyridine and acetic anhydride) as above. The product ratio of **15**:**16** was determined by gc (column a). The pure mixture of esters was obtained by column chromatography (50% ether–petroleum ether) to yield 179 mg (90%); $[\alpha]^{22}D$ −98.5° (*c* 0.6, methanol); $t_{1/2}$ for racemization = 2.6 hr.

The rearrangement was repeated on a 4-mmol scale for 16 hr. Purification as above led to a **15**:**16** mixture in 88% yield: $[\alpha]^{22}D$ −2.8° (*c* 0.8, methanol), 98% racemized. Ester (±)-**16** was then obtained pure by preparative gc (column c, t = 205°): tlc R_f 0.45 (20% ether–benzene); gc R_T 9.3 min (column a, t = 190°); nmr δ 2.05, 2.07, 2.10 (s, OAc), 2.6–2.8 (br m, $-CH_2-$), 3.77 (s, CO_2CH_3), 5.13 (q, $J_{H-3,H-4}$ = 7 Hz, $J_{H-4,H-5}$ = 2 Hz, C-4, C*H*OAc), 5.3–5.8 (m, C-3 and 5, C*H*OAc), 6.73 (m, $-CH=$); uv 211 nm (ε 11,900); mass spectrum *m/e* 314 (M^+, 5%), 272 (2), 254 (38), 221 (9), 212 (74), 198 (20), 194 (25), 170 (88), 152 (92), 121 (83), 111 (65), 109 (59), 43 (100).

Anal. Calcd for $C_{14}H_{18}O_8$: C, 53.5; H, 5.8. Found: C, 53.9; H, 5.8.

(±)-4-*epi*-Shikimic Acid [(±)-12]. Ester (±)-**16** (66 mg, 0.21 mmol) was dissolved with heating in water (2 ml) containing KOH (83 mg, 1.25 mmol). After 30 min reflux, the cooled reaction was passed through an H^+ ion exchange column. The residue obtained after solvent removal from the eluent was recrystallized from methanol–acetone–ether (1:1:2) to yield (±)-**12** (22 mg, 59%), properties in Table II.

Reduction Studies. Ester **15** (125 mg, 0.4 mmol) was dissolved in ethyl acetate (6 ml) containing 1.6% acetic acid and platinum oxide (30 mg) was added. The reaction was exposed to hydrogen at 1 atm until uptake ceased (*ca.* 1 hr). Tlc (20% ether–benzene) indicated no starting ester (R_f 0.43) remained and two products (R_f 0.32 and R_f 0.47) were present. These were resolved on a column (15% ether–benzene) to obtain methyl (1*RS*,3*R*,4*R*)-3,4-diacetoxycyclohexane-1-carboxylate (**17**) (27 mg, 26%) first and then methyl (1*R*,3*R*,4*S*,5*R*)-3,4,5-triacetoxycyclohexane-1-carboxylate (**18**) (75 mg, 58%), both as oils.

Ester **17**: nmr δ 1.7–2.1 (br m, $-CH_2-$), 2.02, 2.05 (s, OAc), 2.2–2.7 (b, C*H*CO_2CH_3), 3.67, 3.70 (s, CO_2CH_3), 4.7–5.1 (b, 2, C*H*OAc); mass spectrum *m/e* 258 (M^+, 0.2%), 243 ($M^+ - CH_3$, 0.3), 227 ($M^+ - OCH_3$, 2), 205 (2), 198 (7), 185 (9), 172 (6), 156 (55), 97 (23), 43 (100).

Anal. Calcd for $C_{12}H_8O_6$: C, 55.8; H, 7.0. Found: C, 55.7; H, 6.7.

Ester **18**: nmr δ 1.8–2.2 (br m, $-CH_2-$), 1.98 (1, OAc), 2.07 (2, OAc), 2.4–3.1 (m, C*H*CO_2CH_3), 3.67 (s, CO_2CH_3), 4.9–5.3 (b, 3, C*H*OAc), $[\alpha]^{22}D$ −31.4° (*c* 1.2, methanol); mass spectrum *m/e* 316 (0.1%), 285 ($M^+ - OCH_3$, 3), 274 ($M^+ - COCH_3$, 3), 256 (7), 243 (15), 230 (9), 224 (18), 196 (16), 183 (12), 171 (43), 154 (100), 137 (45), 128 (61), 95 (50).

Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.2; H, 6.4. Found: C, 53.1; H, 6.4.

Ester **16** (60 mg, 0.19 mmol) was reduced as above to obtain ester **17** (6 mg, 12%) and ester **18** (46 mg, 77%), identical with material obtained on reduction of ester **15** above.

Methyl Quinate (7b). Quinic acid (**7a**) (1.92 g, 10 mmol) was dissolved in methanol (60 ml) and cooled to 0°. Diazomethane in ether was added until excess was detectable. Solvents were then removed *in vacuo* to obtain methyl quinate (**7b**) as a viscous oil: tlc R_f 0.55 (37% methanol–chloroform); nmr (D_2O) δ 2.1 (br m, $-CH_2-$), 3.70 (s, CO_2CH_3), 3.4–4.4 (m, CHOH). A crystalline sample was obtained from methanol–ethyl acetate: mp 127–128° (lit.[20] mp 120°); $[\alpha]^{22}D$ −37° (*c* 0.5, methanol).

Methyl 3,4,5-Tribenzoylquinate (20a). Methyl quinate (**7b**, 1.44 g, 7 mmol) was dissolved in pyridine (14 ml) and benzoyl chloride (2.43 ml, 21 mmol) added dropwise with stirring at −30°. The reaction was stored at −10° overnight and then partitioned between equal volumes of chloroform and 2 *N* HCl. The organic layer was washed with bicarbonate solution, dried over $MgSO_4$, and chromatographed (25% ether–benzene) to obtain pure tribenzoate **20**, as a viscous oil (676 mg, 65%): tlc R_f 0.35 (25% ether–benzene); ir 2.90 μ (OH); nmr δ 2.50 (br s, $-CH_2-$), 3.53 (s, CO_2CH_3), 5.5–6.2 (m, C*H*OR), 7.1–8.2 (15, m, ArH); uv (isooctane) 281 nm (ε 2600), 273 (2900), 228 (40,200); $[\alpha]^{22}D$ −117.5° (*c* 1.0, benzene) (lit.[21] $[\alpha]D$ −81°); mass spectrum *m/e* 459 ($M^+ - 59$, 1%), 396 (8), 337 (11), 274 (5), 215 (17), 105 (100).

Anal. Calcd for $C_{29}H_{26}O_9$: C, 67.2; H, 5.1. Found: C, 66.9; H, 4.9.

A trace of methyl 1,3,4,5-tetrabenzoylquinate (122 mg, 10%) was also obtained: mp 74–76°; tlc 0.56 (25% ether–benzene); ir no 2.90 μ; nmr as **19**a, but 20 Ar H's.

Methyl 3,4,5-Tribenzoyl-4-*epi*-shikimate and Methyl 3,4,5-Tribenzoylshikimate (21). Methyl 3,4,5-tribenzoylquinate (**20**a) was dehydrated as above and chromatography (20% ether–benzene) gave ester mixture **21** (72%) as a crystalline solid: mp 50–54° (lit.[15] mp 60–62°); tlc R_f 0.65 (25% ether–benzene); nmr δ 2.78 [d, J_{ax-eq} = 18 Hz, CH_{ax}(H_{eq})], 3.25 [d, J_{ax-eq} = 18 Hz, CH_{ax}(H_{eq})], 3.76 (s, CO_2CH_3), 5.87 (m, C-4,5, C*H*OR), 6.23 (m, C-3, C*H*OR), 7.2–8.2 (m, ArH); uv (isooctane) 282 nm (ε 2650), sh 268 (3000), 229 (44,500).

Anal. Calcd for $C_{29}H_{24}O_8$: C, 69.6; H, 4.8. Found: C, 69.4; H, 5.0.

Ester **20a** also was treated with SO_2Cl_2 as above and shikimates **21** were obtained in 96% yield after chromatography.

Hydrolysis of Methyl Tribenzoylshikimates (21). Samples (155 mg, 0.3 mmol) of ester **21** prepared by the two procedures above (SO_2Cl_2 and $POCl_3$) were hydrolyzed separately by solution in dioxane (2 ml) and adding an aqueous KOH solution (2 ml containing 119 mg, 1.8 mmol of KOH). The mixture became homogeneous after about 30 min of stirring and was allowed to stand for 24 hr at room temperature. After adding 2 *N* HCl (1 ml), solvents were removed *in vacuo* and the residue was washed with ether to remove benzoic acid. Resolution of the residue in water and passage through a 10-ml ion-exchange column (H^- form) gave the salt-free mixture of acids **11** and **12**. These were separated on a cellulose column (borate buffer, 25 mM in $Na_2B_4O_7$–95% ethanol–1-butanol, 25:37:37). Column fractions were again passed through the H^+ ion-exchange column and taken to dryness. Methanol (10 ml) was added to each and evaporated *in vacuo* three times to remove the residual boric acid and the samples were then estimated by uv extinctions; results are in Table I.

Methyl 3,4,5-Triacetylquinate (20b). Methyl quinate (**7b**) (as above, 2.12 g, 10.0 mmol) was dissolved in dry pyridine (20 ml) and acetyl chloride (2.22 ml, 30.0 mmol) was added dropwise with stirring at −30°. After 3 hr at −20 to −30°, the reaction was terminated by partitioning between equal volumes of chloroform and 2 *N* HCl. The chloroform extract was then washed with bicarbonate solution, dried over $MgSO_4$, and evaporated to yield crude product (1.00 g) which was chromatographed (2% methanol–chloroform) giving ester **20b** as a very viscous oil (766 mg, 23%): tlc R_f 0.43 (2% methanol–chloroform); nmr δ 2.02, 2.05, 2.10 (s, OAc), 2.24 (br d, $-CH_2-$), 3.79 (s, CO_2CH_3), 4.9–5.7 (m, C*H*OAc); $[\alpha]^{22}D$

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$-47.5°$ (*c* 1.0, benzene); mass spectrum *m/e* 273 ($M^+ - 59$, 5%), 213 (53), 185 (15), 171 (52), 153 (88), 111 (92), 71 (43), 59 (50), 55 (69), 43 (100).

Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.6; H, 6.1. Found: C, 50.6; H, 6.2.

Dehydration of Ester 20b. Ester **20b** was dehydrated with SO_2Cl_2 as described to give a mixture of esters **15** and **16** in 90% yield after column chromatography (50% ether–petroleum ether). The pure isomers were then obtained as oils by preparative gc (**15**, R_T 82 min; **16**, R_T 65 min; column c, $t = 205°$). Ester **15** was identical with that obtained previously. Ester **16** was identical with ester (±)-**16** obtained above except for rotation, $[\alpha]^{22}D$ $-140°$ (*c* 1.2, methanol) (lit.[7] $[\alpha]^{20}D$ $-140°$).

Methyl 1,3,4,5-Tetraacetylquinate (19.) Tetraacetylquinic acid–isopropyl alcohol (3.60 g, 8.6 mmol)[22] was treated at 0° in ether solution with ethereal CH_2N_2 until the yellow color persisted. Solvent was removed *in vacuo* and the crude product triturated with a small amount of ether to yield a crystalline product (2.90 g, 91%). A sample was recrystallized from ether–petroleum ether: mp 106° (lit.[23] mp 99–101°); nmr δ 1.99, 2.00, 2.04, 2.10 (s, OAc), 3.73 (s, CO_2CH_3), 5.00 (q, $J_{H-3,H-4} = 8$ Hz, $J_{H-4,H-5} = 3$ Hz, C-4, C*H*-OAc), 5.2–5.7 (m, C-3 and 5, C*H*OAc); $[\alpha]^{22}D$ $-22.0°$ (*c* 1.0, methanol) (lit.[23] $[\alpha]^{18}D$ $-21.9°$).

Methyl *epi*-Quinate (8b). Methyl 1,3,4,5-tetraacetylquinate (**19**, 1.86 g, 5 mmol) was treated with anhydrous HF (20 ml) as above for 2 hr at room temperature. After complete removal of HF, 3% HCl–methanol (40 ml) was added and refluxed for 1 hr. The crude product obtained after solvent removal was then chromatographed (20% methanol–chloroform) and a purified mixture of methyl quinate (**7b**) and *epi*-quinate (**8b**) obtained (0.792 g, 77%). The **7b**/**8b** mixture (320 mg, 1.55 mmol) was treated as before with silylating reagent[18] (20 ml) and after 3 hr at room temperature the solvents were removed *in vacuo*. Ether was added, the pyridine–hydrochloride was removed by centrifugation, and the crude product was then subjected to preparative gc (column c, $t = 175°$) to yield the *trimethylsilyl ether of* **7b** (488 mg, 64%): tlc R_f 0.38 (2% ether–petroleum ether); gc R_T 8.0 min (column b, $t = 165°$); nmr δ 0.05 (9), 0.23 (18), 0.28 (9, s, $(CH_3)_3Si$), 1.7–2.5 (m, CH_2), 3.5 (m, C-4, CHOSi), 3.70 (s, CO_2CH_3), 4.1, 4.3 (m, C-3 and -5, CHOSi); mass spectrum *m/e* 494 (M^+, 6%), 479 (76), 435 (96), 404 (51), 389 (25), 361 (29), 345 (100), 331 (29), 314 (89), 299 (86), 288 (67), 276 (85), 255 (96), 230 (41), 225 (83), 217 (81), 204 (92), 201 (45), 191 (94), 147 (84), 143 (54), 133 (67), 89 (61), 73 (89).

Also obtained from the above chromatography was the trimethylsilyl ether of **8b** (127 mg, 17%): tlc R_f 0.32 (2% ether–petroleum ether); gc R_T 11.1 min (column b, $t = 165°$); nmr δ 0.083 (18), 0.15 (9), 0.23 (9, s, $(CH_3)_3Si$), 1.3–2.6 (m, CH_2), 3.34 (q, $J_{H-3,H-4} = 8$ Hz, $J_{H-4,H-5} = 2$ Hz, C-4, CHOSi), 3.67 (s, CO_2CH_3), 3.8–4.1 (m, C-3 and 5, CHOSi); mass spectrum, as above.

Methyl quinate (**7b**) was obtained by solution of the trimethylsilyl ether of **7b** (49 mg) in 10^{-3} *M* HCl–methanol (2 ml). The crystalline product (20 mg, 97%) obtained upon solvent removal was recrystallized from methanol–ethyl acetate: $[\alpha]^{22}D$ $-37.5°$ (*c* 0.5, methanol). Methyl *epi*-quinate (**8b**) was similarly obtained: mp 153–154°, tlc R_f 0.47 (20% methanol–chloroform); nmr (D_2O) δ 1.4–2.6 (m, CH_2), 3.5–4.3 (m, C*H*OH), 3.75 (s, CO_2CH_3); $[\alpha]^{22}D$ $-2.4°$ (*c* 0.5, methanol).

Anal. Calcd for $C_8H_{14}O_6$: C, 46.6; H, 6.8. Found: C, 46.6; H, 6.8.

Methyl 3,4,5-Triacetyl-*epi*-quinate (22). Methyl *epi*-quinate (**8b**) (56 mg, 0.27 mmol) was dissolved in pyridine (0.54 ml) and acetyl chloride (70 mg, 0.89 mmol) added dropwise at $-30°$. The reaction was allowed to slowly warm to room temperature overnight. Ether was added to the reaction mixture, the precipitated pyridine hydrochloride was removed by centrifugation, solvents were then removed *in vacuo*, and the crude product was chromatographed (1% methanol–chloroform) yielding ester **22** as a viscous oil (55 mg, 61%): tlc R_f 0.37 (2% methanol–chloroform); nmr δ 2.00, 2.08, 2.10 (s, OAc), 1.7–2.7 (m, CH_2), 3.84 (s, CO_2CH_3), 5.0–5.7 (m, C*H*OAc); $[\alpha]^{22}D$ $-29°$ (*c* 2.0, benzene); mass spectrum as **20b**.

Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.6; H, 6.1. Found: C, 50.6; H, 6.3.

Dehydration of Ester 22. Ester **22** was dehydrated with SO_2Cl_2 as described and the yield (95%) and isomer ratio (Table I) of ester **15**/**16** were determined by gc (column a).

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