Inversion of an Asymmetric Center in Carbocyclic Inhibitors of 3-Dehydroquinate Synthase: Examining and Exploiting the Mechanism for *syn*-Elimination during Substrate Turnover

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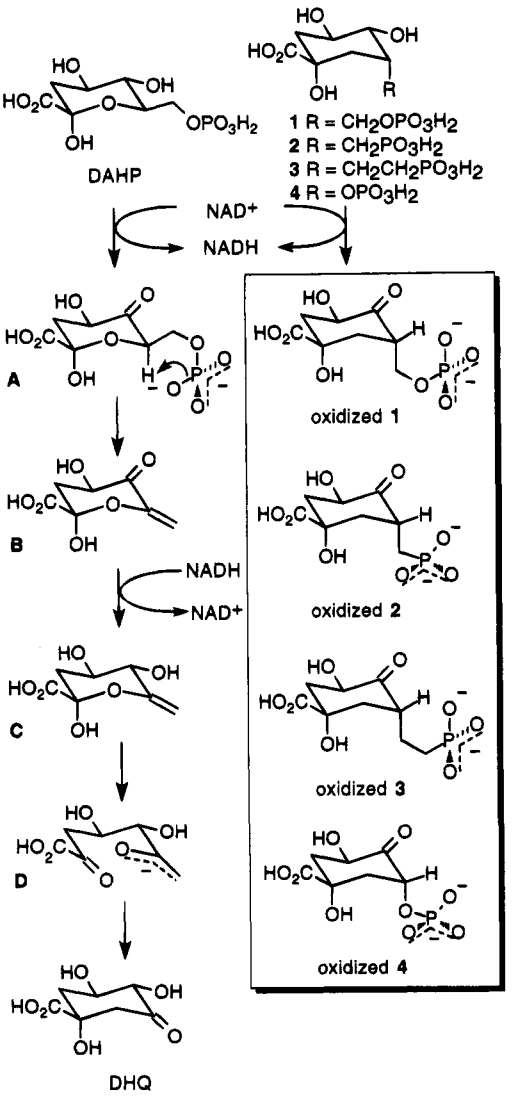
Conversion of 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP) into 3-dehydroquinate (DHQ) by the enzyme DHQ synthase has been proposed to proceed through a step where the phosphate monoester of a reactive intermediate mediates its own elimination. This hypothesis was tested by challenging DHQ synthase with a series of carbocyclic substrate analogues possessing an inverted methine carbon relative to the same asymmetric center in substrate DAHP which loses a proton during elimination of inorganic phosphate. Despite the stereochemical alteration, epicarbocyclic substrate analogues 5-[(phosphonooxy)methyl]-5-deoxyquinate, 5-(phosphonomethyl)-5-deoxyquinate, 5-(phosphonoethyl)-5-deoxyquinate, and 3-(phosphonooxy)quinate inhibited DHQ synthase with respective inhibition constants (K_i) of 30 nM, 55 nM, 30 μM, and 53 μM. These inhibitors were synthesized from quinic acid and with the exception of 3-(phosphonooxy)quinate, were assembled via a strategy employing intramolecular, radical cyclization to establish the stereocenter where the (phosphonooxy)methyl, phosphonomethyl, and phosphonoethyl moieties were attached to the carbocyclic ring. The observed diastereomeric promiscuity in the binding of epicarbocyclic substrate analogues by DHQ synthase is consistent with the hypothesized nonenzymic *syn*-elimination of inorganic phosphate during substrate turnover.

Reactions catalyzed by substrate and reactive intermediate functional groups can be as important as reactions catalyzed by active site residues during enzymatic turnover of substrate into product. Take, for example, the multiple reactions (Scheme 1) which occur during conversion of substrate 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP) into product 3-dehydroquinate (DHQ) catalyzed by DHQ synthase. Various experimental observations have prompted the suggestion that the phosphate monoester of reactive intermediate A (Scheme 1) mediates its own *syn*-elimination.[1] To obtain additional insights into this hypothesis, a new class of epicarbocyclic analogues of substrate DAHP has been synthesized. 5-[(Phosphonooxy)methyl]-5-deoxyquinate **1**, 5-(phosphonomethyl)-5-deoxyquinate **2**, 5-(phosphonoethyl)-5-deoxyquinate **3** and 3-(phosphonooxy)quinate **4** possess an asymmetric carbon atom (Scheme 1) which is inverted relative to the stereochemistry of the same carbon atom in substrate DAHP.

If DHQ synthase employs an active site residue to catalyze the elimination of inorganic phosphate, it is unlikely that the active site would tolerate the drastic repositioning of the phosphoryl and phosphonyl moieties of analogues **1**–**4** (Scheme 1, Table 1) relative to the location of these same moieties in previously synthesized, carbocyclic analogues **5**–**8** (Table 1) of substrate DAHP. Inhibition of DHQ synthase by analogues **1**–**4** would therefore be unlikely. However, if the phosphate monoester of DAHP mediates its own elimination, the active site might be tolerant of the stereochemical modification in analogues **1**–**4**. Inhibition of DHQ synthase by analogues **1-4** would then be possible. The epicarbocyclic analogues of substrate DAHP might even be oxidized to

Scheme 1



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(1) (a) Widlanski, T. S.; Bender, S. L.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 1873. (b) Widlanski, T.; Bender, S. L.; Knowles, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 2299. (c) Bender, S. L.; Widlanski, T.; Knowles, J. R. *Biochemistry* **1989**, *28*, 7560. (d) Widlanski, T.; Bender, S. L.; Knowles, J. R. *Biochemistry* **1989**, *28*, 7572. (e) Nikolaides, N.; Ganem, B. *Tetrahedron Lett.* **1989**, *30*, 1461.

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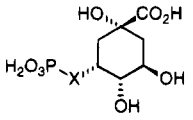
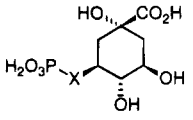
Table 1. Inhibition of 3-Dehydroquinate Synthase by Epicarbocyclic and Carbocyclic Substrate Analogues

Inhibitor	Type of Inhibition	[b]E·NADH Formation	[b]k_{on} ($M^{-1}s^{-1}$)	[b]k_{off} (s^{-1})	K_i (M)
 **1** X = OCH_2	slowly reversible	+	1.4×10^5	4.3×10^{-3}	3.0×10^{-8}
2 X = CH_2	slowly reversible	+	4.4×10^4	2.4×10^{-3}	5.5×10^{-8}
3 X = CH_2CH_2	competitive	+	——	——	3.0×10^{-5}
4 X = O	competitive	-	——	——	5.3×10^{-5}
[a]**5** X = OCH_2	competitive	+	——	——	1.2×10^{-7}
 [b]**6** X = CH_2	slowly reversible	+	1.4×10^5	7.5×10^{-4}	5.4×10^{-9}
[c]**7** X = CH_2CH_2	competitive	+	——	——	1.7×10^{-6}
[c]**8** X = O	competitive	+/-	——	——	1.7×10^{-6}

[a] See ref 1d and 1e. [b] See ref 12a. [c] See ref 1b and 1c.

their C-4 carbonyl forms (Scheme 1) with concomitant formation of enzyme-bound NADH. A mechanistic purpose is thus served by challenging the stereochemical and steric tolerance of DHQ synthase's active site. In addition, an opportunity is provided to further improve the extent DHQ synthase is inhibited by substrate analogues.

Results and Discussion

DHQ synthase has been viewed as a catalytic marvel for most of the thirty-odd years since its existence was conclusively established.[2] An enzyme of only MW 40 000–44 000,[3] DHQ synthase apparently catalyzed (Scheme 1) oxidation of an alcohol, elimination of inorganic phosphate to form an enol, carbonyl reduction, and intramolecular aldol condensation during each conversion of substrate into product. This view of DHQ synthase's catalytic prowess began to crumble under more recent scrutiny of the enzyme. Various results have led to proposals that reactive intermediate C (Scheme 1) undergoes spontaneous cyclization to DHQ without enzymic catalysis[4] and that the phosphate monoester of reactive intermediate A might function as the base required for elimination of inorganic phosphate which leads to formation of the enol of reactive intermediate B.[1b-d] This leaves DHQ synthase as only an oxidoreductase catalyzing the initial oxidation of DAHP and reduction of reactive intermediate B.

Removal of DHQ synthase's role in catalyzing the intramolecular aldol condensation was based on model studies. A precursor was photochemically deprotected to generate reactive intermediate C in solution. Cyclization to DHQ as the only apparent diastereomer was observed.[4a] Later examination of the product mixture did reveal the formation of *epi*-DHQ.[4b,c] These findings are consistent with an enzyme that adopts more than just a spectator role during the intramolecular aldol condensation which converts reactive intermediate C into product.

Proposed phosphate monoester-mediated enolization followed from several lines of evidence. Stereospecifically deuterated 2,6-anhydro-DAHP was used to demonstrate that the enolization involved a *syn*-elimination of inorganic phosphate.[1a,d] In addition, *cis*-vinylhomophosphonate was a much more potent inhibitor of DHQ synthase than *trans*-vinylhomophosphonate.[1b,c] The dependence of deuterium exchange of the proton adjacent to the oxidized carbon on the structure of the DAHP substrate analogue was used as another line of evidence favoring intramolecular enolization.[1b,c]

Our approach to testing whether the phosphate monoester effected its own elimination was to challenge DHQ synthase with a new class of carbocyclic substrate analogues of which 5-[(phosphonooxy)methyl]-5-deoxyquinate **1** is representative. Carba DAHP **5** (Table 1) had already been synthesized and discovered to both inhibit the enzyme and undergo slow, enzyme-catalyzed formation of inorganic phosphate.[1d,e] 5-[(Phosphonooxy)methyl]-5-deoxyquinate **1** and carba DAHP **5** differ only in the stereochemical configuration of the C-5 methine carbon. If the phosphate monoester was catalyzing its own elimination, inhibition of DHQ synthase by 5-[(phosphonooxy)methyl]-5-deoxyquinate **1** seemed a reasonable expectation. Generation of inorganic phosphate might even be observed. On the other hand, active site residue-catalyzed elimination of inorganic phosphate would likely preclude binding of 5-[(phosphonooxy)methyl]-5-deoxyquinate **1**. This diastereomer of carba DAHP **5** would likely overwhelm the steric and stereochemical tolerance of an active site requiring a suitably positioned basic residue to catalyze elimination of inorganic phosphate.

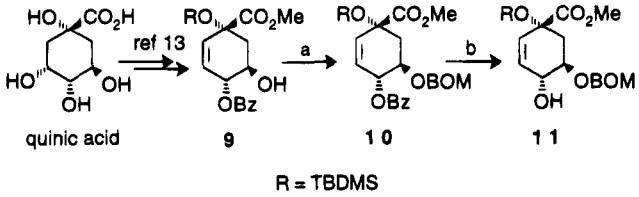
To further challenge the steric and stereochemical tolerance of DHQ synthase's active site, 5-(phosphonomethyl)-5-deoxyquinate **2**, 5-(phosphonoethyl)-5-deoxyquinate **3**, and 3-(phosphonooxy)quinate **4** were synthesized and tested for enzyme inhibition. These carbocyclic substrate analogues, like 5-[(phosphonooxy)methyl]-5-deoxyquinate **1**, are diastereomers of previously reported DHQ synthase inhibitors including, respectively, carbaphosphonate **6** (Table 1), homocarbaphosphonate **7** (Table 1), and carbaphosphate **8** (Table 1).[1c] The difference between these two series is the stereochemistry of the methine to which phosphonomethyl, phosphonoethyl, and phosphoryl moieties are attached. Newly synthesized epicarbocyclic substrate analogues **2**–**4** also provided an

(2) Srinivasan, P. R.; Rothschild, J.; Sprinson, D. B. *J. Biol. Chem.* **1963**, *238*, 3176.

(3) (a) Frost, J. W.; Bender, J. L.; Kadonaga, J. T.; Knowles, J. R. *Biochemistry* **1984**, *23*, 4470. (b) Millar, G.; Coggins, J. R. *FEBS Lett.* **1986**, *200*, 11.

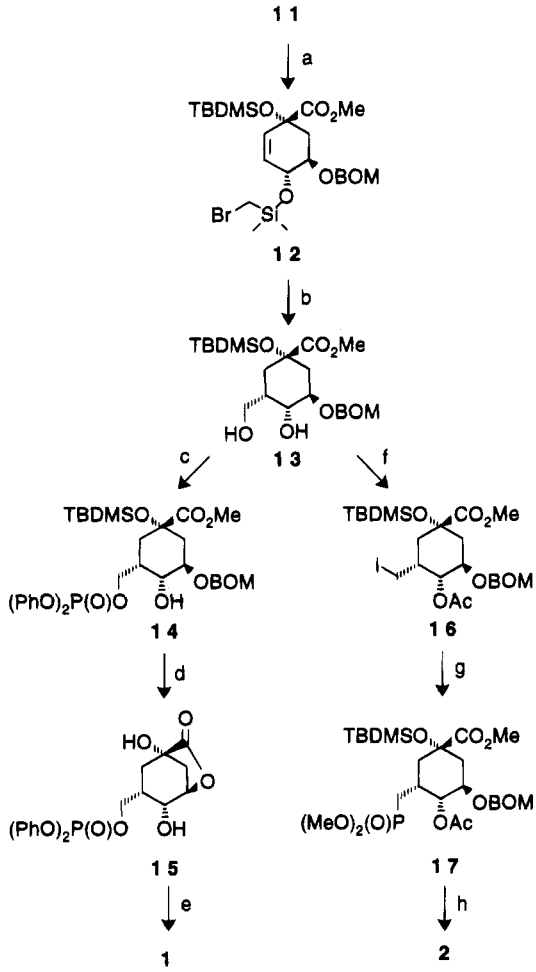
(4) (a) Bartlett, P. A.; Satake, K. *J. Am. Chem. Soc.* **1988**, *110*, 1628. (b) Bartlett, P. A.; McLaren, K. L.; Alberg, D. G.; Fässler, A.; Nyfeler, R.; Lauhon, C. T. Grissom, C. B. *BCPC Monogr.* **1989**, *2*, 155. (c) Bartlett, P. A.; McLaren, K. L.; Marx, M. A. *J. Org. Chem.* **1994**, *59*, 2082.

Scheme 2



[a] BOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 97%; (b) MeONa, THF/MeOH (10:1), 0 °C, 72%.

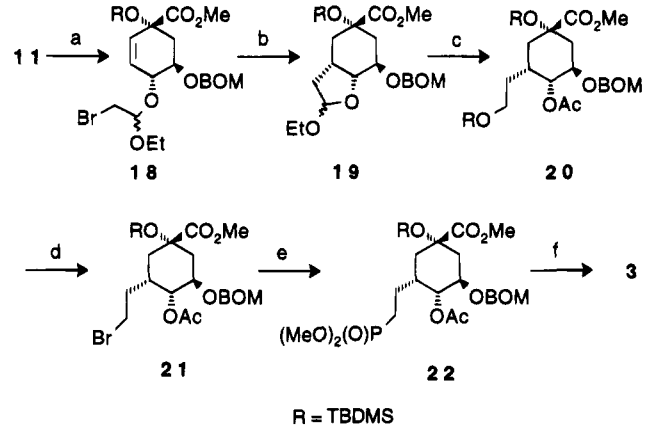
Scheme 3



[a] $BrCH_2SiMe_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 97%; (b) (i) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, (ii) H_2O_2, $NaHCO_3$, MeOH/THF (1:1), reflux, 70%; (c) $(PhO)_2P(O)Cl$, pyr, rt, 85%; (d) aqueous HF, CH_3CN, rt, 75%; (e) (i) H_2, PtO_2, H_2O, (ii) NaOH, H_2O, 61%; (f) (i) *p*-TsCl, pyr, rt, (ii) Ac_2O, rt, 60%, (iii) NaI, acetone, reflux, 100%; (g) $P(OMe)_3$, reflux, 49%; (h) (i) *n*-Bu_4NF, THF, 0 °C, (ii) H_2, 10% Pd–C, MeOH, (iii) TMSBr, Et_3N, CH_2Cl_2, rt, (iv) NaOH, H_2O, 48%.

opportunity to further probe the precedented sensitivity of DHQ synthase inhibition to the positioning[5,1c,d] of phosphoryl and phosphonyl moieties. Replacement of the (phosphonooxy)methyl ($CH_2OPO_3H_2$) moiety of 5-[(phosphonooxy)methyl]-5-deoxyquinate **1** with a phosphonomethyl ($CH_2PO_3H_2$) group makes 5-(phosphonomethyl)-5-deoxyquinate **2** a nonisosteric organophosphonate derivative. By virtue of its phosphonoethyl ($CH_2CH_2PO_3H_2$) group, 5-(phosphonoethyl)-5-deoxyquinate **3** is an isosteric organophosphonate derivative of 5-[(phosphonooxy)methyl]-5-deoxyquinate **1**. Attachment of its phosphoryl group directly to the carbocyclic ring establishes 3-(phosphonooxy)quinate as a nonisosteric organophosphate derivative.

Scheme 4



[a] $BrCH_2CH(OEt)Br$, Et_3N, CH_2Cl_2, −78 °C to rt, 84%; (b) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 78%; (c) (i) aqueous HCl, THF, rt, 74%, (ii) $NaBH_4$, MeOH, 0 °C, 100%, (iii) *t*-$BuMe_2SiCl$, Et_3N, CH_2Cl_2, rt, 84%, (iv) Ac_2O, DMAP, pyr, rt, 87%; (d) (i) *p*-TsOH, MeOH, rt, (ii) CBr_4, PPh_3, THF, rt, 78%; (e) $P(OMe)_3$, reflux, 75%; (f) (i) *n*-Bu_4NF, THF, 0 °C, (ii) H_2, Pd–C, MeOH, (iii) TMSBr, Et_3N, CH_2Cl_2, (iv) NaOH, H_2O, 60%.

Overall Synthetic Strategy. Quinic acid was the starting material for synthesis of all of the epicarbocyclic substrate analogues **1**–**4**. 5-[(Phosphonooxy)methyl]-5-deoxyquinate **1**, 5-(phosphonomethyl)-5-deoxyquinate **2**, and 5-(phosphonoethyl)-5-deoxyquinate **3** were each synthesized from an advanced intermediate (**11**, Scheme 2) which incorporated quinic acid's carbocyclic ring and three of its four stereocenters. Intermediate **11** could routinely be synthesized in 30–40% overall yield from quinic acid. A functionalized C-4 hydroxyl group was then used to intramolecularly deliver (Schemes 3 and 4) a carbon-centered radical to the α face of an appropriately activated carbon at C-5 of the carbocyclic ring. This cyclization employing Nishiyama–Stork methodology[6] (Scheme 3) and a closely related variant[7] (Scheme 4) yielded fused, bicyclic products. The carbon–carbon bonds formed in these reactions provided the C-5 stereochemistry required for subsequent synthetic elaboration into 5-[(phosphonooxy)methyl]-5-deoxyquinate **1**, 5-(phosphonomethyl)-5-deoxyquinate **2**, and 5-(phosphonoethyl)-5-deoxyquinate **3**. Synthesis (Scheme 5) of 3-(phosphonooxy)quinate **4** via phosphorylation of a suitably protected quinic acid differed from assembly of the other epicarbocyclic substrate analogues **1**–**3** by virtue of its incorporation of all four stereocenters in quinic acid.

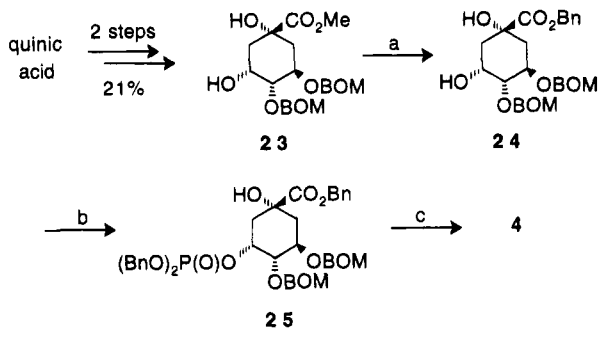
Synthesis of 5-[(phosphonooxy)methyl]-5-deoxyquinate and 5-(phosphonomethyl)-5-deoxyquinate. Cyclization precursor **12** (Scheme 3) was obtained by treatment of allylic alcohol **11** with (bromomethyl)-dimethylsilyl chloride in the presence of NEt_3. Radical cyclization of **12** was then accomplished by slow, syringe-pump addition of a solution of Bu_3SnH in benzene to a refluxing benzene solution of (bromomethyl)silyl ether **12**. The resulting cyclized siloxane was immediately submitted without purification to Tamao oxidation[8] using H_2O_2 and $NaHCO_3$ to provide diol **13**. Although the indicated

(5) (a) Le Maréchal, P.; Froussios, C.; Level, M.; Azerad, R. *Biochem. Biophys. Res. Commun.* **1980**, *92*, 1104. (b) Myrvold, S.; Reimer, L. M.; Pompliano, D. L.; Frost, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1861.

(6) (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (b) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826.

(7) Stork, G.; Mook, Jr., R.; Biller, S. A.; Rychnowsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.

Scheme 5



[a] (i) NaOH, H_2O, THF, rt, 90%, (ii) BnBr, Cs_2CO_3, DMF, rt, 69%; (b) (i) *n*-BuLi, THF, −78 °C, (ii) $[(BnO)_2P(O)]_2O$, THF, −78 °C to 0 °C, 53%; (c) H_2, 10% Pd−C, H_2O, THF, 100%.

structure (Scheme 3) of diol **13** is consistent with literature precedent,[6] an X-ray crystal structure of diol **13** was obtained to unambiguously establish the relative stereochemistry of the C-5 hydroxymethyl group.

Selective phosphorylation of the primary alcohol of diol **13** with diphenyl (phosphonooxy)chloridate afforded protected phosphate **14**. Subsequent removal of the *tert*-butyldimethylsilyl ether upon treatment with aqueous HF in acetonitrile also resulted in hydrolysis of the (benzyloxy)methyl ether and spontaneous lactonization between the C-3 hydroxyl and the C-1 carbomethoxy groups. Lactone **15** was then hydrogenolyzed over Pt to remove the phenyl ester protecting groups. Treatment with base followed by neutralization opened the lactone to afford 5-[(phosphonooxy)methyl]-5-deoxyquinate **1** which was purified by anion-exchange chromatography.

Synthesis (Scheme 3) of 5-(phosphonomethyl)-5-deoxyquinate **2** from diol **13** began with activation of the primary hydroxyl group as a tosylate. Acetylation of the remaining hydroxyl group at C-4 was then followed by prolonged treatment with NaI in refluxing acetone to afford iodide **16**. Arbuzov reaction of **16** with $P(OMe)_3$ yielded fully protected epicarbocyclic substrate analogue **17**. Stepwise deprotection entailed reaction with $Bu_4N^+F^-$ in THF to remove the *tert*-butyldimethylsilyl ether, hydrogenolysis over Pd on C to unmask the C-3 hydroxyl group, and reaction of the phosphonate diester with TMSBr in the presence of NEt_3. Final treatment with aqueous NaOH served to hydrolyze both the bis-trimethylsilylated phosphonate diester and the carbomethoxy group. Although deprotection of **17** proceeded without any intervening purification steps, product 5-(phosphonomethyl)-5-deoxyquinate **2** was purified by anion-exchange chromatography.

Synthesis of 5-(Phosphonoethyl)-5-deoxyquinate. Introduction of an appropriately activated two-carbon fragment with proper stereochemistry at C-5 began (Scheme 4) with reaction of allylic alcohol **11** with 1,2-dibromoethyl ethyl ether to give bromoacetal **18**. The 1,2-dibromoethyl ethyl ether was prepared in situ from vinyl ethyl ether and Br_2. A refluxing benzene solution of bromoacetal **18** underwent cyclization to *cis*-fused, bicyclo **19** upon slow addition of Bu_3SnH and AIBN.[7] Compound **19** was formed as a diastereomeric mixture due to the presence of both epimers at the acetal methine carbon. Although both diastereomers could be easily separated by chromatography on silica gel, the cyclic acetal mixture was routinely hydrolyzed to the corresponding lactol which was immediately reduced with $NaBH_4$ in methanol.

Direct activation of the primary alcohol was problematic because of intramolecular participation of the C-4 hydroxyl with attendant formation of a tetrahydrofuran derivative. A protection−deprotection sequence was therefore adopted where the primary hydroxyl group was selectively protected upon reaction with *tert*-butyldimethylsilyl chloride and NEt_3 followed by acetylation of the C-4 hydroxyl to give intermediate **20**. Hydrolysis of the primary silyl ether and bromination of the resulting alcohol with PPh_3 and CBr_4 provided bromide **21** which underwent Arbuzov condensation with $P(OMe)_3$ yielding fully protected epicarbocyclic substrate analogue **22**. Reaction (Scheme 4) of the bromide **21** with $P(OMe)_3$ gave a higher yield of the phosphonate **22** than the yield of phosphonate obtained from condensation (Scheme 3) of $P(OMe)_3$ with iodide **16**. This apparently indicates that the greater steric accessibility of the bromoethyl group of **21** relative to the iodomethyl group of **16** is a more important determinant of reactivity than the enhanced electrophilic character of a primary iodide relative to a primary bromide. Fully protected phosphonate **22** was sequentially deprotected (Scheme 4) without intervening purification as previously described for phosphonate **17** (Scheme 3). Pure 5-(phosphonoethyl)-5-deoxyquinate **3** was then obtained after anion-exchange chromatography.

Synthesis of 3-(Phosphonooxy)quinate. Although the first synthesis of quinate 3-phosphate **4** has been recently reported,[9] we elaborated a separate, more expeditious approach for its preparation (Scheme 5). The selectively protected diol **23** was obtained in two simple steps from quinic acid as previously described by Knowles.[1c] Despite the low overall yield, these two steps provided an ideally protected intermediate for synthesis of 3-(phosphonooxy)quinate. Phosphorylation of the unprotected hydroxyl group of **23** with diphenyl phosphorochloridate afforded the desired phosphate triester. Unfortunately, the deprotection of this material was problematic. Hydrolysis of the methyl ester also resulted in migration of the phosphate leading to reduced yields and product mixtures which were difficult to purify. A protection strategy (Scheme 5) that circumvented these problems began with hydrolysis of the methyl ester of **23** using NaOH followed by reprotection of the carboxylate by treatment with benzyl bromide and Cs_2CO_3.[10] The resulting benzyl ester **24** was phosphorylated by reaction with *n*-butyllithium and tetrabenzylpyrophosphate. One-step deprotection of **25** was accomplished by hydrogenolysis over Pd on C. Product 3-(phosphonooxy)-quinate **4** was thus obtained in lieu of any problematic phosphate ester migrations.

Enzymology. Incubation of 5-[(phosphonooxy)methyl]-5-deoxyquinate **1** with DHQ synthase did not lead to detectable generation of inorganic phosphate. However, **1** was a slowly-reversible inhibitor[11] with K_i = 30 nM which can be compared (Table 1) to the K_i = 120 nM reported for carba DAHP **5**.[1d,e] This makes 5-[(phosphonooxy)methyl]-5-deoxyquinate **1** the most potent phosphate monoester-containing inhibitor of DHQ synthase. An increase of absorbance at 340 nm indicative of analogue oxidation and formation of enzyme-bound NADH

(8) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694.

(9) Chahoua, L.; Baltas, M.; Gorrichon, L.; Tisnès, P.; Zedde, C. *J. Org. Chem.* **1992**, *57*, 5798.

(10) Wang, S.-S.; Gisin, B. F.; Winter, D. P.; Makofske, R.; Kulesha, I. D.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286.

(11) Morrison, J. F.; Walsh, C. T. *Adv. Enzymol.* **1988**, *61*, 201.

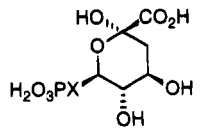
was also observed when 5-[(phosphonooxy)methyl]-5-deoxyquinate **1** was incubated with DHQ synthase. This indicates that **1** is positioned in the active site of DHQ synthase similarly to other carbocyclic substrate analogues which are likewise precedented to undergo oxidation with formation of enzyme-bound NADH.

Carbaphosphonate **6** is a slowly-reversible inhibitor with K_i = 5.4 nM while carbahomophosphonate **7** and carbaphosphate **8** are competitive inhibitors with respective inhibition constants of K_i = 1.7 μM and K_i = 1.7 μM.[1c] For these carbocyclic inhibitors of DHQ synthase, an increase in absorption at 340 nm was measured that was indicative of inhibitor oxidation when bound to the enzyme and formation of enzyme-bound NADH. By comparison, an inhibition constant of K_i = 55 nM was determined (Table 1) for the slowly-reversible inhibition of DHQ synthase by 5-(phosphonomethyl)-5-deoxyquinate **2** and K_i = 30 μM and K_i = 53 μM obtained for the respective inhibition constants of 5-(phosphonoethyl)-5-deoxyquinate **3** and 3-(phosphonooxy)quinate **4**. An increase in absorbance at 340 nm indicative of oxidation of enzyme-bound inhibitor and formation of enzyme-bound NADH was also observed when 5-(phosphonomethyl)-5-deoxyquinate **2** and 5-(phosphonoethyl)-5-deoxyquinate **3** but not when 3-(phosphonooxy)quinate **4** was incubated with DHQ synthase. This can be interpreted as evidence for a similar fit in the enzyme active site for 5-(phosphonomethyl)-5-deoxyquinate **2** and carbaphosphonate **6** as well as for 5-(phosphonoethyl)-5-deoxyquinate **3** and carbahomophosphonate **7**. One explanation for the lack of NADH formation when 3-(phosphonooxy)quinate **4** was incubated with DHQ synthase is that its positioning in the active site of DHQ synthase differs significantly from that of carbaphosphate **8**.

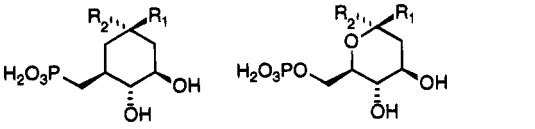
Comparison of enzyme inhibition constants within the newly synthesized series of DHQ synthase inhibitors is also informative. Notably, 5-(phosphonomethyl)-5-deoxyquinate **2**, a nonisosteric derivative of 5-[(phosphonooxy)methyl]-5-deoxyquinate **1**, is 3 orders of magnitude more potent in its inhibition of DHQ synthase than isosteric 5-(phosphonoethyl)-5-deoxyquinate **3**. This is the third series of DHQ synthase inhibitors where a nonisosteric phosphonate derivative of a phosphate monoester leads to vastly improved inhibition relative to an isosteric homophosphonate derivative. For example, carbaphosphonate **6**, which is a nonisosteric derivative of carbaDAHP **5**, is 3 orders of magnitude (Table 1) more potent in its inhibition of DHQ synthase than isosteric carbahomophosphonate **7**.[1c] The trend continues for analogues of DAHP possessing a pyranosyl ring oxygen where nonisosteric DAH phosphonate **26** exhibits 2 orders of magnitude improved inhibition relative to isosteric DAH homophosphonate **27**.[5]

Conclusions

The inhibitors synthesized and evaluated in this account establish another example of diastereomeric promiscuity on the part of DHQ synthase in the binding of substrate analogues. Previously identified pairs of diastereomeric inhibitors include C-1 *epi*-carbaphosphonate[12] **28**/carbaphosphonate **6** and α-2,6-anydro DAHP[5b] **29**/β-2,6-anhydro DAHP **30**. To this list can now be added the diastereomeric pairs including 5-[(phosphonooxy)methyl]-5-deoxyquinate **1**/carba DAHP **5**, 5-(phosphonomethyl)-5-deoxyquinate **2**/carbaphosphonate **6**, 5-(phosphonoethyl)-5-deoxyquinate **3**/carbahomophosphonate **7**, and 3-(phosphonooxy)quinate **4**/carbaphosphate **8**. This establishes two regions of steric and stereochemical tolerance in the active site of DHQ synthase. One site is centered around the methine carbon which is covalently tethered to phosphonic and phosphoryl moieties. The second site is localized at the ring carbon which is attached to the carboxylate functionality of substrate DAHP and its analogues.[12]



26 X = CH_2
27 X = CH_2CH_2



6 R_1 = CO_2H, R_2 = OH **29** R_1 = CO_2H, R_2 = H
28 R_1 = OH, R_2 = CO_2H **30** R_1 = H, R_2 = CO_2H

None of the newly synthesized substrate analogues in this account are better inhibitors than carbaphosphonate **6** and C-1 *epi*carbaphosphonate **28**. However, new insights have been provided into the question of whether the phosphate monoester of DAHP catalyzes its own elimination and the attendant question as to whether DHQ synthase might display diastereomeric promiscuity in the C-5 region of carbocyclic DAHP substrate analogues. Such stereochemical and steric tolerance in active site binding has now been observed with the inhibition of DHQ synthase by 5-[(phosphonooxy)methyl]-5-deoxyquinate **1**, 5-(phosphonomethyl)-5-deoxyquinate **2**, 5-(phosphonoethyl)-5-deoxyquinate **3**, and 3-(phosphonooxy)quinate **4**. These observations, in turn, are consistent with the hypothesis that the phosphate monoester of DAHP mediates its own elimination. Therefore, while DHQ synthase can still be viewed as an aggressive enzyme catalyzing an alcohol oxidation, carbonyl reduction, and intramolecular aldol condensation, it also seems likely that this enzyme is not above recruiting catalytic residues from its own reactive intermediates during turnover of substrate into product.

Experimental Section

General Chemistry. See ref 12b for general experimental information dealing with synthetic manipulations. Organic solutions of products were dried over $MgSO_4$. Combustion analyses were performed by Atlantic Microlab (Norcross, GA). See ref 12a for details concerning enzymological manipulations.

Methyl [1(*R*)-(1α,4α,5β)]-4-(benzoyloxy)-5-[[(benzyloxy)methyl]oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-cyclohexene-1-carboxylate (10). Alcohol **9**[13] (29.3 g, 72.1 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL), and anhydrous diisopropylethylamine (19.0 mL, 108 mmol) was added via syringe under Ar. To the resulting colorless solution was added benzyl chloromethyl ether (90%, 12.0 mL, 79.3 mmol) via syringe at rt. After 13 h, an additional amount of benzyl chloromethyl ether (90%, 3.0 mL, 19.4 mmol) was similarly added. Water was added 2 h later, and the aqueous layer was extracted with ether (3×). The combined organic

(12) (a) Piehler, L. T.; Montchamp, J. -L.; Frost, J. W.; Manly, C. J. *Tetrahedron* **1991**, *47*, 2423. (b) Montchamp, J.-L.; Piehler, L. T.; Frost, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 4453.

(13) Bartlett, P. A.; Maitra, U.; Chouinard, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 8068.

layers were washed successively with dilute aqueous HCl (0.06 M, 2×), aqueous $CuSO_4$ (2×), saturated aqueous $NaHCO_3$ (1×), and brine (1×). The organic layer was dried and concentrated to yield **10** (36.9 g, 97%) as a yellow oil: ^1H NMR ($CDCl_3$) δ 8.00–8.10 (m, 2 H), 7.45–7.60 (m, 1 H), 7.20–7.45 (m, 7 H), 6.00 (d, J = 10 Hz, 1 H), 5.87 (dd, J = 10, 2 Hz, 1 H), 5.70 (dd, J = 8, 2 Hz, 1 H), 4.83 (s, 2 H), 4.56 (s, 2 H), 4.40–4.50 (m, 1 H), 3.77 (s, 3 H), 2.30–2.50 (m, 1 H), 2.18 (dd, J = 12, 12 Hz, 1 H), 0.93 (s, 9 H), 0.15 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.6, 166.2, 137.8, 133.2, 130.8, 130.0, 129.7, 129.0, 128.5, 128.3, 127.6, 127.5, 93.1, 75.0, 73.8, 71.9, 69.1, 52.2, 38.8, 25.5, 18.0, −3.2, −3.5; MS m/z (rel inten) EI 105 (100), 91 (100); CI 395 (100); HRMS (CI) calcd for $C_{29}H_{38}O_7Si$ (M + H^+) 527.2465, found 527.2457.

Methyl [1(*R*)-(1α,4α,5β)]-5-[[(Benzyloxy)methyl]oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-2-cyclohexene-1-carboxylate (11). A solution of $NaOCH_3$ (3.75 g, 70.0 mmol) in CH_3OH (10 mL) was added to a solution of benzoate ester **10** (36.9 g, 70.1 mmol) in THF (100 mL) at rt under N_2. After 15 min, the reaction mixture was cooled to 0 °C and quenched with 1 N aqueous HCl. The aqueous layer was extracted with ether (1×) and the combined organic layers were successively washed with saturated aqueous $NaHCO_3$ (1×), water (1×), and brine (1×). The organic phase was dried and concentrated to a colorless oil. Purification by flash chromatography (hexane, 1:5 EtOAc/hexane, v/v) afforded allylic alcohol **11** (21.4 g, 72%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 5.75–5.85 (m, 2 H), 4.92 (d, J = 7 Hz, 1 H), 4.83 (d, J = 7 Hz, 1 H), 4.75 (d, J = 12 Hz, 1 H), 4.60 (d, J = 12 Hz, 1 H), 4.05–4.15 (m, 1 H), 3.70–3.90 (m, 1 H), 3.72 (s, 3 H), 2.22 (ddd, J = 13, 4, 1 Hz, 1 H), 1.98 (dd, J = 13, 12 Hz, 1 H), 0.85 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.1, 137.1, 132.4, 128.6, 128.1, 128.0, 95.2, 79.9, 75.6, 71.8, 70.0, 52.2, 39.2, 25.5, 18.0, −3.2, −3.6; IR (film, NaCl) 3448 (br), 1742 (s); MS m/z (rel inten) EI 91 (100); CI 316 (19), 315 (100); HRMS (CI) calcd for $C_{22}H_{34}O_6Si$ (M + H^+) 423.2203, found 423.2198. Anal. Calcd for $C_{22}H_{34}O_6Si$: C, 62.58; H, 8.12. Found: C, 62.61; H, 8.08.

Methyl [1(*R*)-(1α,4α,5β)]-5-[[(Benzyloxy)methyl]oxy]-4-[[(bromomethyl) dimethylsilyl]oxy]-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-cyclohexene-1-carboxylate (12). Allylic alcohol **11** (10.8 g, 25.6 mmol) was dissolved in anhydrous CH_2Cl_2 (150 mL) under Ar, and the solution was cooled to 0 °C. Anhydrous Et_3N (4.30 mL, 30.7 mmol) was added via syringe followed by (bromomethyl)dimethylchlorosilane (3.50 mL, 25.6 mmol). After 1 h at 0 °C, saturated aqueous $NaHCO_3$ was added and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with cold water (1×), dried, and concentrated to an oil. Purification by flash chromatography (1:5 EtOAc/hexane, v/v) yielded the silyl ether **12** (14.3 g, 97%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 5.70–5.85 (m, 2 H), 4.86 (s, 2 H), 4.68 (d, J = 12 Hz, 1 H), 4.60 (d, J = 12 Hz, 1 H), 4.20–4.30 (m, 1 H), 3.99 (ddd, J = 11, 8, 4 Hz, 1 H), 3.72 (s, 3 H), 2.50 (s, 2 H), 2.25–2.40 (m, 1 H), 1.97 (dd, J = 12, 11 Hz, 1 H), 0.87 (s, 9 H), 0.32 (s, 3 H), 0.30 (s, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 137.9, 133.3, 128.4, 128.3, 127.8, 127.6, 94.0, 75.4, 72.8, 69.1, 52.1, 38.9, 25.4, 18.0, 15.9, −2.8, −3.0, −3.3, −3.6; IR (film, NaCl) 1743 (m); MS m/z (rel inten) EI 91 (100); CI 413 (100), 412 (20), 411 (96); HRMS (CI) calcd for $C_{25}H_{41}O_6Si_2Br$ (M + H^+) 573.1703, found 573.1692.

Methyl [1(*S*)-(1α,3β,4α,5α)]-3-[[(Benzyloxy)methyl]oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-5-(hydroxymethyl)-cyclohexane-1-carboxylate (13). (Bromomethyl)silyl ether **12** (7.52 g, 13.1 mmol) was dissolved in distilled benzene (100 mL) and Ar was bubbled through the solution for 15 min. The solution was heated to reflux under Ar, and a solution of AIBN (0.10 g) and tributyltin hydride (Bu_3SnH, 4.60 mL, 15.7 mmol) in benzene (45 mL) was added over 15 h via syringe pump (1.05 mmol Bu_3SnH/h) through the top of the reflux condenser. Once the addition was complete, the reaction mixture was refluxed for an additional 2 h. Heating was stopped and the solvent removed under reduced pressure. The resulting colorless oil was dissolved in CH_3OH/THF (1:1, v/v, 80 mL), and aqueous H_2O_2 (30%, 16 mL) was added via syringe. $NaHCO_3$ (2.21 g, 26.2 mmol) was then added as a solid, and the solution was heated to reflux under Ar. After 5 h at reflux, heating was stopped and 20% aqueous $Na_2S_2O_3$ was carefully added. The aqueous layer was saturated with solid $Na_2S_2O_3$ and then extracted with ether (3×). The combined organic layers were dried and concentrated to a yellow oil. This was taken up in technical grade (moist) ether, and I_2 was added until a brown color persisted. DBU (2.5 mL, 1.2–1.5 equiv, relative to the amount of tin hydride employed) was then added dropwise with a pipet until no more precipitate formed. The suspension was then rapidly filtered through a short pad of silica gel under reduced pressure. The filtrate was washed with 10% $Na_2S_2O_3$ to destroy excess I_2. Purification by radial chromatography (4 mm plate, hexane, 1:5 EtOAc/hexane, 1:1 EtOAc/hexane, v/v,) afforded diol **13** (3.59 g, 60%) as a colorless oil. An impure fraction was repurified by radial chromatography to afford more diol (0.58 g, 10%) and allylic alcohol **11** (0.49 g, 9%). Diol **13** (70% combined yield) slowly crystallized into a white solid: ^1H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 4.74 (d, J = 7 Hz, 1 H), 4.67 (d, J = 7 Hz, 1 H), 4.60 (d, J = 12 Hz, 1 H), 4.52 (d, J =12 Hz, 1 H), 3.65–4.00 (m, 4 H), 3.65 (s, 3 H), 2.15–2.40 (m, 2 H), 1.75–2.10 (m, 3 H), 0.84 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 137.5, 128.5, 127.9, 127.8, 93.3, 75.9, 75.5, 71.3, 69.6, 65.6, 51.6, 37.2, 36.2, 34.2, 25.4, 17.9, −3.5, −3.6; IR (film, NaCl) 3418 (br), 1736 (m); MS m/z (rel inten) EI 91 (100); CI 455 (M + H^+, 5), 347 (100); HRMS (CI) calcd for $C_{23}H_{38}O_7Si$ (M + H^+) 455.2465, found 455.2461. Anal. Calcd for $C_{23}H_{38}O_7Si$: C, 60.76; H, 8.42. Found: C, 60.62; H, 8.37.

Methyl [1(*S*)-(1α,3β,4α,5α)]-3-[[(Benzyloxy)methyl]oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[[[bis(phenyloxy)phosphinyl]oxy]methyl]-4-hydroxycyclohexane-1-carboxylate (14). To a solution of the diol **13** (1.26 g, 2.77 mmol) in anhydrous pyridine (30 mL) was added diphenyl (phosphonooxy)chloridate (0.86 mL, 4.16 mmol). The mixture was stirred at rt under N_2 for 15 h. The solvent was then removed under vacuum. The residue was azeotroped with toluene (3×) and then dissolved in EtOAc, washed with brine (3×), dried, and concentrated to a colorless oil. Purification by flash chromatography (1:2 EtOAc/hexane, v/v) afforded **14** as a colorless oil (1.58 g, 85%): ^1H NMR ($CDCl_3$) δ 7.10–7.40 (m, 15 H), 4.66 (d, J = 7 Hz, 1 H), 4.32–4.48 (m, 3 H), 4.17 (ddd, J = 10, 10, 5 Hz, 1 H), 3.90–4.00 (m, 1 H), 3.70–3.75 (m, 1 H), 3.67 (s, 3 H), 3.30 (br, 1 H), 2.40–2.55 (m, 2 H), 1.85–2.00 (m, 2 H), 1.51 (dd, J = 12, 12 Hz, 1 H), 0.82 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 151.1, 150.9 (2), 138.0, 130.4 (2), 129.0, 128.4, 128.3, 126.1, 120.7, 120.6 (2), 120.5, 92.8, 75.4, 74.4, 69.8 (J = 7 Hz), 65.6, 52.0, 36.3 (J = 5 Hz), 35.6, 32.1, 25.8, 18.3, −2.8, −3.2; MS m/z (rel inten) EI 91 (100), CI 365 (100), 687 (27, M + H^+); HRMS (CI) calcd for $C_{35}H_{47}O_{10}PSi$ (M + H^+) 687.2754 , found 687.2756; Anal. Calcd for $C_{35}H_{47}O_{10}PSi$: C, 61.21; H, 6.90. Found: C, 61.05; H, 6.96.

1(*S*)-4-*exo*-1,4-Dihydroxy-3-*exo*-[[[bis(phenyloxy)phosphinyl]oxy]methyl]-6-oxabicyclo[3.2.1]octan-7-one (15). To a solution of compound **14** (0.67 g, 1.0 mmol) in CH_3CN (25 mL) was added 49% aqueous HF (5 mL). After 24 h at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (3×). The combined organic layers were dried and concentrated to an oil. Purification by radial chromatography (2 mm plate, 1:1 EtOAc/hexane, v/v, EtOAc) gave phosphate **15** as a colorless oil (0.313 g, 75%): ^1H NMR ($CDCl_3$) δ 7.10–7.45 (m, 10 H), 4.73 (dd, J = 6, 6 Hz, 1 H), 4.48 (dd, J = 10, 10 Hz, 1 H), 4.25–4.30 (m, 1 H), 3.80–4.05 (m, 2 H), 2.72 (s, 1 H), 2.52 (d, J = 11.5 Hz, 1 H), 2.08–2.33 (m, 2 H), 1.58–1.63 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 178.1, 150.1, 150.0, 149.9, 149.8, 129.8, 125.7, 125.6, 120.0, 119.9, 119.8, 119.7, 76.6, 73.3, 68.0 (J = 6 Hz), 62.1, 36.9 (J = 6 Hz), 36.5, 32.3; MS m/z (rel inten) EI 250 (37), 251 (100); CI 421 (M + H^+,100), 422 (16); HRMS (CI) calcd for $C_{20}H_{21}O_8P$ (M + H^+) 421.1052, found 421.1051. Anal. Calcd for $C_{20}H_{21}O_8P$: C, 57.15; H, 5.04. Found: C, 56.88; H, 5.08.

[1(*S*)-(1α,3β,4α,5α)-5-[(Phosphonooxy)methyl)]-1,3,4-trihydroxycyclohexane-1-carboxylic acid (1). PtO_2 (0.10 g) was added to deionized water (10 mL) and reduced to Pt with H_2 (50 psi, 20 min) in a Parr hydrogenation apparatus.

A solution of the diphenyl phosphate **15** (0.64 g, 1.52 mmol) in THF (10 mL) was hydrogenated at 50 psi of H_2 over the Pt catalyst. After 24 h, the Pt catalyst was filtered through Celite and the filtrate concentrated to a foam. The residue was dissolved in water and adjusted to pH 11.5 with dilute NaOH (0.5 N). After 2 h at rt, the solution was neutralized with dilute HCl (0.5 N) to pH 7.5. The crude product was loaded onto an AG1-X8 anion-exchange column (20 mL) and eluted with water (50 mL) followed by a linear gradient (250 mL + 250 mL, 200–500 mM) of triethylammonium bicarbonate (Et_3NH^+ HCO_3^- pH = 7.2). Fractions containing phosphorus were concentrated and azeotroped with *i*-PrOH (6×). The resulting residue was dissolved in water, passed through a Dowex 50 (H^+ form) column, and then neutralized to pH 7.5 with a freshly prepared LiOH solution. Removal of water under vacuum afforded a white crystalline solid (0.72 g, 61%): ^{1}H NMR (D_2O) δ 3.70–4.00 (m, 4 H), 2.10–2.35 (m, 1 H), 2.04 (dd, J = 15, 4 Hz, 1 H), 1.94 (dd, J = 15, 4 Hz, 1 H), 1.78 (dd, J = 13, 4 Hz, 1 H), 1.64 (dd, J = 13, 11 Hz, 1 H); ^{13}C NMR (D_2O) δ 185.1, 77.8, 72.5, 71.5, 67.5 (J = 5 Hz), 39.1, 38.6 (J = 7 Hz), 35.9; MS m/z (rel inten) EI 81 (100); CI 751 (M + H^+, 25), 189 (100); HRMS (FAB) calcd for $C_8H_{15}O_9P$ (M + H^+): 287.0531, found 287.0530.

Methyl [1(*S*)-(1α,3β,4α,5α)]-4-(Acetyloxy)-3-[[(benzyloxy)methyl]oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-(iodomethyl)cyclohexane-1-carboxylate (16). Diol **13** (2.19 g, 4.82 mmol) was dissolved in anhydrous pyridine (20 mL) under Ar, and *p*-TsCl (1.01 g, 5.30 mmol) was added in one portion. The reaction mixture was stirred at rt for 16 h, and acetic anhydride (Ac_2O, 3.0 mL) was added via syringe. Stirring was continued for an additional 18 h. The reaction mixture was then concentrated under high vacuum, and the residue azeotroped with toluene (2×). Water and EtOAc were added, and the organic layer was washed successively with aqueous $CuSO_4$ (1×), brine (1×), saturated aqueous $NaHCO_3$ (1×), and brine (1×). The resulting organic layer was dried and concentrated to an orange residue which was recrystallized from EtOAc and hexane. The crystalline solid obtained was dried under high vacuum to afford the desired intermediate (1.88 g, 60%): ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 4 Hz, 2 H), 7.25–7.40 (m, 7 H), 4.93 (dd, J = 3,3 Hz, 1 H), 4.69 (d, J = 7 Hz, 1 H), 4.61 (d, J = 7 Hz, 1 H), 4.60 (d, J = 11 Hz, 1 H), 4.49 (d, J = 11 Hz, 1 H), 3.95–4.10 (m, 3 H), 3.68 (s, 3 H), 2.55–2.70 (m, 1 H), 2.43 (s, 3 H), 2.05–2.20 (m, 1 H), 1.97 (s, 3 H), 1.20–1.75 (m, 3 H), 0.84 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.7, 169.7, 144.7, 137.4, 132.7, 129.8, 128.4, 128.0, 127.9, 127.8, 127.7, 92.4, 74.5, 70.3, 69.8, 69.6, 68.3, 51.8, 36.1, 33.3, 25.5, 21.6, 20.8, 18.0, −3.1, −3.5; MS m/z (rel inten) EI 91 (100); CI 359 (100). Anal. Calcd for $C_{32}H_{46}O_{10}SSi$: C, 59.05; H, 7.12. Found: C, 59.00; H, 7.17.

The intermediate tosylate (1.75 g, 2.69 mmol) and NaI (4.12 g, 27.5 mmol) were dissolved in dry acetone (50 mL). During subsequent heating of the yellow solution at reflux for 18 h, a precipitate formed. Heating was then stopped and 10% aqueous $Na_2S_2O_3$ was added. The aqueous phase was repeatedly extracted with EtOAc (5x). The combined organic layers were dried and concentrated to a heterogeneous oil. The oil was taken up in EtOAc/hexane (1:5, v/v), and the resulting suspension was filtered through a short pad of silica gel under reduced pressure. The colorless filtrate was concentrated to afford iodide **16** (1.64 g, 100%) as a slightly yellow oil: ^{1}H NMR (CDCl3) δ 7.25–7.40 (m, 5 H), 5.05–5.10 (m, 1 H), 4.71 (d, J = 7 Hz, 1 H), 4.65 (d, J = 7 Hz, 1 H), 4.64 (d, J = 11 Hz, 1 H), 4.50 (d, J = 11 Hz, 1 H), 4.05 (dd, J = 7, 3 Hz, 1 H), 3.70 (s, 3 H), 3.12 (d, J = 7 Hz, 2 H), 2.35–2.65 (m, 3 H), 2.10 (s, 3 H), 1.70 (dd, J = 14, 3 Hz, 1 H), 1.49 (dd, J = 12, 12 Hz, 1 H), 0.86 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (CDCl3) δ 172.8, 169.7, 137.4, 128.4, 128.1, 127.7, 92.4, 74.8, 70.9, 70.7, 69.6, 51.8, 37.2, 36.3, 36.0, 25.5, 20.9, 18.0, 6.7, −2.9, −3.5; IR (neat, NaCl) 1744 (s); MS m/z (rel inten) EI 91 (100); CI 471 (100); FAB 607 (M + H^+). Anal. Calcd for $C_{25}H_{39}IO_7Si$: C, 49.50; H, 6.48. Found: C, 49.57; H, 6.43.

Methyl [1(*S*)-(1α,3β,4α,5α)]-4-(Acetyloxy)-3-[[(benzyloxy)methyl]oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[(dimethoxyphosphinyl)methyl]cyclohexane-1-carboxylate (17). Iodide **16** (0.87 g, 1.44 mmol) was dissolved in $P(OMe)_3$ (20 mL). The colorless solution was refluxed under N_2 for 24 h. The solvent was removed by vacuum distillation, and the yellow residue was purified by radial chromatography (2 mm plate, 1:1 EtOAc/hexane, v/v, EtOAc). Phosphonate **17** (0.419 g, 49%) was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 4.91 (dd, J = 3, 3 Hz, 1 H), 4.72 (d, J = 7 Hz, 1 H), 4.64 (d, J = 12 Hz, 1 H), 4.63 (d, J = 7 Hz, 1 H), 4.51 (d, J = 12 Hz, 1 H), 4.00–4.10 (m, 1 H), 3.65–3.85 (m, 6 H), 2.35–2.80 (m, 3 H), 2.09 (s, 3 H), 1.35–1.90 (m, 4 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 169.9, 137.4, 128.3, 128.0, 127.6, 92.3, 74.7, 71.3 (J = 11 Hz), 70.6, 69.4, 54.2 (J = 6 Hz), 52.3 (J = 6 Hz), 51.7, 37.5 (J = 9 Hz), 28.6 (J = 3 Hz), 27.0 (J = 142 Hz), 25.5, 20.9, 18.0, −3.0, −3.6; MS m/z (rel inten) EI 91 (100); CI 590 (24), 589 (M + H^+, 100); HRMS (CI) calcd for $C_{27}H_{45}O_{10}PSi$: 589.2598, found 589.2588. Anal. Calcd for $C_{27}H_{45}O_{10}PSi$: C, 55.08; H, 7.71. Found: C, 54.91; H, 7.76.

[1(*S*)-(1α,3β,4α,5α)]-1,3,4-Trihydroxy-5-(phosphonomethyl)cyclohexane-1-carboxylic Acid (2). Phosphonate **17** (0.512 g, 0.87 mmol) was dissolved in THF (30 mL), and $Bu_4N^+F^-$ in THF (1.0 M, 5.0 mL, 5 mmol) was added at 0 °C. After 15 min, the reaction mixture was quenched with dilute aqueous HCl (0.06 M). Water and EtOAc were added, and the resulting aqueous layer was extracted with more EtOAc (3×). The combined organic layers were dried and concentrated to a yellow oil. This oil was dissolved in CH_3OH (7 mL), and the solution was hydrogenated at 50 psi H_2 pressure, over 10% Pd on C (0.102 g) for 1 h. The suspension was filtered through Celite, and the filtrate was concentrated to a colorless film. This was dissolved in a solution of Et_3N (0.5 mL) in CH_2Cl_2 (10 mL), and bromotrimethylsilane (TMSBr, 1.0 mL, 7.58 mmol) was added via syringe under Ar. After 12 h at rt, the brown solution was concentrated under reduced pressure, and water (10 mL) was added. The solution was then concentrated under high vacuum, and aqueous NaOH (1 N, 10 mL) added at rt. After 2 h, the solution was neutralized by addition of Dowex 50 H^+. The resulting suspension was loaded onto a short column of Dowex 50 H^+ and washed with water. Column filtrate was concentrated under high vacuum and the residue brought to pH 11.5 upon addition of 1 N aqueous NaOH. After a few minutes, the solution was neutralized to pH 7.5 with 1 N aqueous HCl. The solution was then loaded onto a column of AG-1 X8 (20 mL) which had been equilibrated with 200 mM Et_3NH^+ HCO_3^- (pH 7.2). The column was washed with water (40 mL) and eluted with a linear gradient (150 mL + 150 mL, 200–500 mM) of Et_3NH^+ HCO_3^- (pH 7.2). Fractions containing phosphonic acid were concentrated to dryness. The resulting white residue was azeotroped six times with *i*-PrOH, dissolved in water, and passed down a short column of Dowex 50 (H^+). Concentration under high vacuum was followed by neutralization to pH 11.5 with 1 N aqueous NaOH. After a few minutes, the solution was neutralized to pH 7.5 with 1 N aqueous HCl and concentrated to afford 5-(phosphonomethyl)-5-deoxyquinate **2** (0.12 g, 48%) as a white foam: ^{1}H NMR (D_2O, pH 7.5) δ 3.90 (dd, J = 11, 5 Hz, 1 H); 3.73 (dd, J = 5, 3 Hz, 1 H), 2.20–2.50 (m, 1 H); 1.55–2.05 (m, 6 H); ^{13}C NMR (D_2O, pH 7.5) δ 185.5, 78.7, 76.4 (J = 9 Hz), 71.3, 40.0, 39.6 (J = 7 Hz), 34.5, 32.1 (J = 131 Hz); HRMS (FAB) calcd for $C_8H_{15}O_8P$ (M + H^+) 271.0583, found 271.0582.

Methyl [1(*R*)-(1α,4α,5β)]-5-[[(Benzyloxy)methyl]oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-(1-ethoxy-2-bromoethoxy)-2-cyclohexene-1-carboxylate (18). Ethyl vinyl ether (1.70 g, 23.6 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL) under Ar, and the solution was cooled to −78 °C. Neat Br_2 (1.15 mL, 22.3 mmol) was added dropwise via syringe. After 15 min, the reaction mixture was allowed to stir at rt. A solution of allylic alcohol **11** (6.24 g, 14.8 mmol) and Et_3N (4.15 mL, 29.8 mmol) in CH_2Cl_2 (40 mL) was slowly added via cannula to the 1,2-dibromoethyl ether solution at −78 °C. After 30 min at −78 °C, the cold bath was removed, and the reaction mixture was stirred at rt for 12 h. The reaction mixture was then diluted with ether and washed successively with water (2×), aqueous $CuSO_4$ (1×), and brine (2×). Drying, filtration, and concentration under reduced pressure afforded a brown oil. Purification by flash chromatography (1:5 EtOAc/hexane, v/v) afforded bromoacetal **18** (7.15 g, 84%) as a slightly yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 5.86 (s, 2 H), 4.80–4.95 (m, 3 H), 4.55–4.75 (m, 2 H), 4.05–4.25 (m, 2 H), 3.73 (s,

3 H), 3.55–3.80 (m, 2 H), 3.35–3.45 (m, 2 H), 2.25–2.40 (m, 1 H), 1.95–2.10 (m, 1 H), 1.15–1.35 (m, 3 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.6 (2), 137.7 (2), 131.0, 129.8, 129.5, 129.3, 128.4, 128.2, 127.7, 127.6, 127.5, 102.9, 100.6, 94.3, 94.0, 77.4, 75.3, 75.1, 75.0, 73.8, 69.4, 69.2, 62.2, 62.0, 52.2, 39.1, 39.0, 32.1, 31.8, 31.7, 25.6, 18.2, 15.1 (2), −3.0, −3.4; MS *m/z* (rel inten) EI 107 (100); CI 244 (12), 243 (100); FAB 573 (M + H$^+$).

Methyl [3a(*S*)-(3aα,5α,7β,7aα)]-7-[[(Benzyloxy)methyl]-oxy]-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-ethoxy-octahydrobenzofuran-5-carboxylate (19). Ar was bubbled through a solution of bromoacetal **18** (7.15 g, 12.5 mmol) in anhydrous benzene (500 mL) for 15 min followed by heating to reflux under Ar. Bu_3SnH (3.80 mL, 13.7 mmol) and AIBN (0.203 g, 1.25 mmol) dissolved in anhydrous benzene (45 mL) were then slowly added via syringe pump. Addition was complete after 16 h. After heating at reflux for an additional 2 h, the colorless solution was concentrated under reduced pressure to a yellow oil. The oil was dissolved in ether, and I_2 was added until the brown color persisted. DBU (2.7 mL) was then added, and the resulting cloudy suspension was filtered through a short pad of silica gel under reduced pressure. The filtrate was washed with 10% $Na_2S_2O_3$, dried, and concentrated to a yellow oil. Purification by flash chromatography (hexane, 1:5 EtOAc/hexane, v/v) afforded the cyclic acetal **19** (4.83 g, 78% combined yield) as a faster eluting diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 5.19 (dd, J = 4, 4 Hz, 1 H), 4.80 (d, J = 7 Hz, 1 H), 4.75 (d, J = 7 Hz, 1 H), 4.63 (d, J = 12 Hz, 1 H), 4.57 (d, J = 12 Hz, 1 H), 4.05–4.20 (m, 1 H), 3.98 (dd, J = 5, 5 Hz, 1 H), 3.65–3.85 (m, 1 H), 3.69 (s, 3 H), 3.30–3.65 (m, 1 H), 2.60–2.75 (m, 1 H), 1.85–2.30 (m, 5 H), 1.30–1.50 (m, 1 H), 1.12 (t, J = 7 Hz, 3 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) 173.7, 137.7, 128.2, 127.7, 127.5, 103.1, 92.5, 78.2, 75.4, 72.1, 69.2, 63.2, 51.6, 39.6, 37.8, 36.7, 34.5, 25.6, 18.1, 15.1, −3.2, −3.5; and a slower eluting diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 5.11 (dd, J = 6, 2 Hz, 1 H), 4.86 (s, 2 H), 4.63 (s, 2 H), 4.19 (dd, J = 13, 6 Hz, 1 H), 3.94 (dd, J = 6, 6 Hz, 1 H), 3.70–3.85 (m, 1 H), 3.70 (s, 3 H), 3.30–3.50 (m, 1 H), 2.45–2.65 (m, 1 H), 1.90–2.25 (m, 6 H), 1.14 (t, J = 7 Hz, 3 H), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) 174.5, 137.8, 128.2, 127.6, 127.4, 104.3, 93.2, 82.4, 76.4, 73.9, 69.1, 63.1, 51.7, 38.4, 37.9, 36.9, 34.8, 25.7, 25.5, 18.2, 15.1, −3.3, −3.4; IR (neat, NaCl) 1742 (s); MS *m/z* (rel inten) EI 91 (100); CI 450 (29), 449 (100); FAB 494 (M + H$^+$).

Methyl [1(*S*)-(1α,3β,4α,5α)]-4-(Acetyloxy)-3-[[(benzyloxy)-methyl]oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]cyclo-hexane-1-carboxylate (20). Acetal **19** (4.74 g, 9.58 mmol) was dissolved in a mixture of THF (90 mL) and dilute aqueous HCl (1.5%, 35 mL) at rt. The reaction mixture was stirred until disappearance of the starting material (ca. 24 h) and was then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether (3×) and the combined organic layers were dried and concentrated to an oil. Purification by radial chromatography (4 mm plate, hexane, 1:5 EtOAc/hexane, 1:1 EtOAc/hexane, v/v, EtOAc) afforded a colorless oil (3.32 g, 74%).

The lactol intermediate (2.34 g, 5.02 mmol) was dissolved in CH_3OH (30 mL) and added at 0 °C to a suspension of $NaBH_4$ (0.386 g, 10.0 mmol) in CH_3OH (20 mL). Acetone (1 mL) was added after 5 min, followed by a few drops of glacial acetic acid. The clear solution was concentrated under reduced pressure and the solid residue was partitioned between EtOAc and water. The aqueous layer was saturated with NaCl and extracted with EtOAc (3×). The combined organic layers were dried and concentrated to a slightly yellow oil (2.46, 100%): ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 4.75 (d, J = 7 Hz, 1 H), 4.65 (d, J = 7 Hz, 1 H), 4.60 (d, J = 12 Hz, 1 H), 4.53 (d, J = 12 Hz, 1 H), 3.91 (dd, J = 8, 4 Hz, 1 H), 3.55–3.80 (m, 3 H), 3.68 (s, 3 H), 3.20–3.40 (br, 2 H), 2.39 (dd, J = 14, 5 Hz, 1 H), 2.10–2.30 (m, 1 H), 1.97 (dd, J = 14, 3 Hz, 2 H), 1.60–1.80 (m, 3 H), 0.85 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) 173.7, 137.5, 128.4, 127.8, 92.9, 75.8, 75.2, 69.9, 69.6, 60.4, 51.6, 36.2, 35.9, 34.2, 33.3, 25.6, 18.0, −3.1, −3.3; IR (neat, NaCl) 3420 (br), 1740 (s); MS *m/z* (rel inten) EI 91 (100); CI 469 (M + H$^+$, 7), 361 (100); HRMS (CI) calcd for $C_{24}H_{40}O_7Si$ (M$^+$ + H$^+$): 469.2622, found 469.2628.

The above diol (0.816 g, 1.74 mmol) was dissolved in CH_2Cl_2 (10 mL) and anhydrous Et_3N (0.73 mL, 5.22 mmol) added via syringe. *tert*-Butyldimethylsilyl chloride (0.297 g, 1.91 mmol) was then rapidly added as a solid at rt. After 12 h, water and ether were added. The organic layer was washed with aqueous $CuSO_4$ (2×) and brine (2×). Drying, filtration, and concentration under reduced pressure afforded a yellow oil (0.86 g, 84%): ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 4.76 (d, J = 7 Hz, 1 H), 4.62 (d, J = 7 Hz, 1 H), 4.61 (d, J = 12 Hz, 1 H), 4.50 (d, J = 12 Hz, 1 H), 4.01 (dd, J = 7, 4 Hz, 1 H), 3.55–3.80 (m, 3 H), 3.67 (s, 3 H), 2.40–2.50 (m, 1 H), 2.10–2.30 (m, 1 H), 1.92 (dd, J = 14, 3 Hz, 1 H), 1.55–1.80 (m, 4 H), 0.90 (s, 9 H), 0.84 (s, 9 H), 0.08 (s, 6 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$) 173.5, 137.8, 128.3, 127.8, 127.6, 92.5, 75.6, 74.4, 69.4, 69.2, 61.1, 51.5, 35.9, 35.3, 34.6, 33.6, 25.8, 25.6, 18.2, 18.0, −2.9, −3.3, −5.6.

This intermediate (0.86 g, 1.47 mmol) and a catalytic amount of DMAP (0.032 g) were dissolved in anhydrous pyridine (10 mL). Ac_2O (3 mL) was added via syringe and the resulting solution was stirred at rt for 22 h. Water and EtOAc were added and the organic layer obtained was washed successively with aqueous $CuSO_4$ (2×) and brine (2×). The organic layer was dried and concentrated to a yellow oil. Purification by radial chromatography (4 mm plate, hexane, 1:5 EtOAc/hexane, v/v) gave **20** (0.798 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 4.90–5.00 (m, 1 H), 4.70 (d, J = 7 Hz, 1 H), 4.63 (d, J = 11 Hz, 1 H), 4.62 (d, J = 7 Hz, 1 H), 4.49 (d, J = 11 Hz, 1 H), 3.95–4.05 (m, 1 H), 3.60–3.75 (m, 2 H), 3.67 (s, 3 H), 2.50–2.65 (m, 1 H), 2.30–2.50 (m, 1 H), 2.15–2.30 (m, 1 H), 2.06 (s, 3 H), 1.73 (dd, J = 14, 3 Hz, 1 H), 1.45–1.65 (m, 3 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 6 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) 172.8, 169.7, 137.4, 128.2, 128.0, 127.9, 127.6, 127.5, 92.1, 74.8, 70.7 (2), 69.3, 60.6, 51.4, 37.0, 35.7, 34.4, 29.9, 25.8, 25.4, 20.7, 18.0, 17.9, −3.1, −3.6, −5.5, −5.6. MS *m/z* (rel inten) CI 625 (M$^+$ + H$^+$, 6), 517 (100); Anal. Calcd for $C_{32}H_{56}O_8Si_2$: C, 61.50; H, 9.03. Found: C, 61.56; H, 9.05.

Methyl [1(*S*)-(1α,3β,4α,5α)]-4-(Acetyloxy)-3-[[(benzyloxy)-methyl)oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-(2-bromoethyl)cyclohexane-1-carboxylate (21). Silyl ether **20** (0.570 g, 0.91 mmol) and a catalytic amount of *p*-TsOH monohydrate (0.049 g) were dissolved in anhydrous CH_3OH. The solution was stirred 1.5 h at rt,) and pyridine (1 mL) was added. The solution was concentrated under reduced pressure, and the residue obtained was dissolved in EtOAc. The organic layer was successively washed with water (1×), aqueous $CuSO_4$ (1×), and brine (1×), dried, and concentrated to a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.85–4.95 (m, 1 H), 4.68 (d, J = 7 Hz, 1 H), 4.60 (d, J = 7 Hz, 1 H), 4.59 (d, J = 11 Hz, 1 H), 4.47 (d, J = 11 Hz, 1 H), 3.90–4.00 (m, 1 H), 3.55–3.70 (m, 2 H), 3.65 (s, 3 H), 2.67 (br, 1 H), 2.45–2.60 (m, 1 H), 2.10–2.45 (m, 2 H), 2.03 (s, 3 H), 1.72 (dd, J = 14, 3 Hz, 1 H), 1.40–1.60 (m, 3 H), 0.84 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$) 172.9, 169.9, 137.3, 128.1, 127.7, 127.4, 92.1, 74.7, 70.9, 70.8, 69.3, 59.7, 51.4, 36.4, 35.7, 34.0, 29.7, 25.3, 20.6, 17.7, −3.1, −3.7.

This intermediate was dissolved in THF (10 mL) and a mixture of CBr_4 (0.746 g, 2.28 mmol) and PPh_3 (0.461 g, 1.82 mmol) was added. The resulting yellow solution became cloudy after a few min. After 2.5 h at rt, CH_3OH (1 mL) was added and the resulting clear solution was concentrated under reduced pressure. Purification by radial chromatography (4 mm plate, hexane, 1:5 EtOAc/hexane, v/v) afforded bromide **21** (0.409 g, 78% from silyl ether), as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H), 4.91 (dd, J = 3, 3 Hz, 1 H), 4.72 (d, J = 7 Hz, 1 H), 4.64 (d, J = 7 Hz, 1 H), 4.63 (d, J = 11 Hz, 1 H), 4.51 (d, J = 11 Hz, 1 H), 3.99 (dd, J = 7, 3 Hz, 1 H), 3.70 (s, 3 H), 3.41 (t, J = 7 Hz, 2 H), 2.35–2.60 (m, 2 H), 2.10–2.25 (m, 1 H), 2.08 (s, 3 H), 1.65–1.95 (m, 3 H), 1.49 (dd, J = 13, 13 Hz, 1 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) 172.8, 169.9, 137.4, 128.3, 127.9, 127.6, 92.4, 74.8, 71.0, 70.4, 69.5, 51.6, 36.2, 36.0, 34.5, 32.2, 30.6, 25.4, 20.8, 17.9, −3.0, −3.5. MS *m/z* (rel inten) CI 575 (M$^+$ + H$^+$, 2), 467 (100); Anal. Calcd for $C_{26}H_{41}O_7SiBr$: C, 54.44; H, 7.20. Found: C, 54.38; H, 7.22.

Methyl [1(*S*)-(1α,3β,4α,5α)]-4-(Acetyloxy)-3-[[(benzyloxy)methyl]oxy]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[2-(dimethoxyphosphinyl)ethyl]cyclohexane-1-carboxylate (22). Bromide **21** (0.41 g, 0.71 mmol) was dissolved in $P(OMe)_3$ (10 mL) and the resulting solution was refluxed under Ar for 24 h. Removal of the solvent by distillation followed by purification of the residue by radial chromatography (4 mm plate, 1:1 EtOAc/hexane, v/v, EtOAc, 9:1 EtOAc/CH_3OH, v/v) afforded protected phosphate **22** as a colorless oil (0.320 g, 75%): ^1H NMR ($CDCl_3$) δ 7.10−7.35 (m, 5 H), 4.80−4.90 (m, 1 H), 4.35−4.70 (m, 4 H), 3.85−3.95 (m, 1 H), 3.68 (s, 3 H), 3.62 (s, 6 H), 2.40−2.60 (m, 1 H), 2.00−2.25 (m, 2 H), 2.02 (s, 3 H), 1.30−1.80 (m, 6 H), 0.80 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 169.8, 137.2, 128.2, 127.7, 127.5, 92.2, 74.5, 71.0, 69.6, 69.4, 52.0 (J = 6 Hz), 51.4, 36.4, 35.7, 33.8 (J = 18 Hz), 29.0, 25.3, 23.9 (J = 4 Hz), 21.8 (J = 141 Hz), 20.7, 17.8, −3.1, −3.7; MS m/z (rel inten) EI 91 (100); CI 604 (20), 603 ($M + H^+$, 100); HRMS (CI) calcd for $C_{28}H_{47}O_{10}PSi$ ($M^+ + H^+$): 603.2754, found 603.2743. Anal. Calcd for $C_{28}H_{47}O_{10}PSi$: C, 55.79; H, 7.86. Found: C, 55.57; H, 7.92.

[1(*S*)-(1α,3β,4α,5α)]-1,3,4-Trihydroxy-5-(2-phosphonoethyl)cyclohexane-1-carboxylic Acid (3). Phosphonate **22** (0.29 g, 0.48 mmol) was dissolved in THF (10 mL), and $Bu_4N^+F^-$ in THF (1.0 M, 2.4 mL, 2.4 mmol) was added at 0 °C. After 15 min, the reaction mixture was quenched with dilute aqueous HCl (0.06 M). Water and EtOAc were added, and the resulting aqueous layer was extracted with more EtOAc (3×). The combined organic layers were dried and concentrated to a yellow oil. This oil was dissolved in CH_3OH (7 mL), and the solution was hydrogenated at 50 psi H_2 pressure, over 10% Pd on C (0.047 g), for 3 h. The suspension was filtered through Celite, and the filtrate was concentrated to a colorless oil. This was dissolved in a solution of Et_3N (0.35 mL) in CH_2Cl_2 (10 mL), and TMSBr (0.70 mL) was added via syringe under Ar. After 18 h at rt, the orange solution was concentrated under reduced pressure. The yellow residue was dissolved in THF (10 mL) and aqueous NaOH (1 N, 15 mL). After 4 h, the biphasic mixture was concentrated under reduced pressure, and the resulting yellow aqueous solution was carefully neutralized with Dowex 50 H^+. The resulting suspension was loaded onto a short column of Dowex 50 H^+ which was washed with water. The filtrate obtained was washed with CH_2Cl_2 (2×), concentrated under high vacuum, and then basified to pH 11.5 with 1 N aqueous NaOH. After a few minutes, the solution was neutralized to pH 7.5 with 1 N aqueous HCl. The solution was subsequently loaded onto AG-1 X8 anion exchange resin (20 mL) which had been equilibrated with 200 mM Et_3NH^+ HCO_3^- (pH 7.2). The column was washed with water (40 mL) and eluted with a linear gradient (150 mL + 150 mL, 200−500 mM) of Et_3NH^+ HCO_3^- (pH 7.2). Fractions containing phosphonic acid were concentrated to dryness. The resulting white residue was azeotroped six times with *i*-PrOH, dissolved in water, and passed down a short column of Dowex 50 (H^+). The solution obtained was concentrated under high vacuum and basified to pH 11.5 with 1 N aqueous NaOH. After a few minutes, the solution was neutralized to pH 7.5 with 1 N aqueous HCl. Concentration afforded 5-(phosphonoethyl)-5-deoxyquinate **3** (60%): ^1H NMR (D_2O, pH 7.5) δ 3.85−4.00 (m, 1 H), 3.65−3.80 (m, 1 H), 1.30−2.10 (m, 8 H); ^{13}C NMR (D_2O, pH 7.5) δ 185.3, 78.0, 73.8, 71.8, 38.6, 38.4 (J = 4 Hz), 38.0 (J = 17 Hz), 28.6 (J = 132 Hz), 27.6; HRMS (FAB) calcd for $C_9H_{17}O_8P$ ($M + H^+$): 285.0739, found 285.0732.

Benzyl [1(*S*)-(1α,3β,4α,5α)-3,4-Bis[[(benzyloxy)methyl]oxy]-1,5-dihydroxycyclohexane-1-carboxylate (24). To a solution of methyl ester **23**[1c] (1.22 g, 2.73 mmol) in THF (30 mL) was added NaOH (0.2 N, 30 mL). After 40 min at rt, a solution of $NaHSO_4$ (0.5 N, 100 mL) was added and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were dried over Na_2SO_4 and concentrated to a white solid (1.06 g, 90%): ^1H NMR ($CDCl_3$) δ 7.25−7.40 (m, 10 H), 5.30 (br, 1 H), 4.98 (d, J = 7 Hz, 1 H), 4.93 (d, J = 7 Hz, 1 H), 4.88 (d, 7 Hz, 1 H), 4.83 (d,J = 7 Hz, 1 H), 4.66 (s, 2 H), 4.63 (s, 2 H), 4.34 (dd, J = 6, 3 Hz, 1 H), 4.10−4.25 (m, 1 H), 3.72 (dd, J = 9, 3 Hz, 1 H), 3.05 (br, 1 H), 2.33 (ddd, J = 13, 5, 3 Hz, 1 H), 1.95−2.25 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.2, 137.4, 137.2, 128.5, 128.4, 127.9, 127.8, 127.7, 94.5, 94.1, 80.2, 75.5, 71.9, 70.0, 69.3, 39.6, 36.1; MS m/z (rel inten) EI 91 (100); CI 91 (100); HRMS (FAB) calcd for $C_{23}H_{28}O_8$ ($M + Na^+$): 455.1682, found 455.1684.

To a solution of the above carboxylic acid (1.03 g, 2.38 mmol) in DMF (30 mL) was added Cs_2CO_3 (0.58 g, 1.79 mmol) followed by benzyl bromide (0.57 mL, 4.76 mmol). The reaction mixture was stirred at rt for 5 h, then diluted with EtOAc (100 mL), washed with brine (3×), dried, and concentrated to a light yellow oil. Purification by radial chromatography (4 mm plate, 1:5 EtOAc/hexane, 1:1 EtOAc/hexane, v/v) afforded **24** as a colorless oil (0.86 g, 69%): ^1H NMR δ 7.25−7.40 (m, 15 H), 5.21 (s, 2 H), 4.98 (d, J = 7 Hz, 1 H), 4.93 (d, J = 7 Hz, 1 H), 4.89 (d, J = 7 Hz, 1 H), 4.83 (d, J = 7 Hz, 1 H), 4.55−4.75 (m, 2 H), 4.61 (s, 2 H), 4.20−4.35 (m, 2 H), 4.03 (s, 1 H), 3.67 (dd, J = 10, 6 Hz, 1 H), 3.35 (d, J = 6 Hz, 1 H), 2.32 (ddd, J = 13, 5, 3 Hz, 1 H), 2.16 (ddd, J = 15, 3, 3 Hz, 1 H), 2.04 (dd, J = 15, 3 Hz, 1 H), 1.90 (dd, J =13, 11 Hz, 1 H); ^{13}C NMR δ 173.8, 137.7, 137.4, 135.0, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 94.5, 94.4, 80.4, 75.4, 72.0, 69.7, 69.5, 69.3, 67.6, 40.2, 36.8; MS m/z (rel inten) EI 91 (100); CI 91 (100); HRMS (FAB) calcd for $C_{30}H_{34}O_8$ ($M + Na^+$) 545.2151, found 545.2154. Anal. Calcd for $C_{30}H_{34}O_8$: C 68.95, H 6.59. Found: C 69.06, H 6.63.

Benzyl [1(*R*)-(1α,3α,4α,5β)-4,5-Bis[[(benzyloxy)methyl]oxy]-3-[[bis(benzyloxy)phosphinyl]oxy]-1-hydroxycyclohexane-1-carboxylate (25). To a solution of the alcohol **24** (0.72 g, 1.38 mmol) in THF (10 mL) cooled at −78 °C was added a solution of *n*-butyl lithium in hexane (1.6 M, 0.95 mL, 1.52 mmol) followed after 15 min by addition via cannula of a solution of tetrabenzyl pyrophosphate (0.817 g, 1.52 mmol) in THF (10 mL). The reaction mixture was stirred at −78 °C for 1 h then at 0 °C for 2 h. After being quenched with saturated aqueous NH_4Cl (100 mL), the reaction mixture was extracted with EtOAc (3×), and the combined organic layers were dried followed by concentration to an oil. Purification by radial chromatography (4 mm plate, CH_2Cl_2, 10:1 CH_2Cl_2/acetone, v/v) gave protected phosphate **25** as a colorless oil (0.57 g, 53%): ^1H NMR ($CDCl_3$) δ 7.25−7.40 (m, 25 H), 5.17 (s, 2 H), 5.09 (s, 2 H), 5.05 (s, 2 H), 4.95−5.10 (m, 1 H), 4.83 (s, 2 H), 4.72 (s, 2 H), 4.61(s, 2 H), 4.54 (s, 2 H), 4.29 (ddd, J = 9, 9, 4 Hz, 1 H), 3.79 (ddd, J = 9, 3, 3 Hz, 1 H), 3.11 (s, 1 H), 2.15−2.30 (m, 3 H), 1.99 (dd, J = 14, 9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.1, 137.6 137.5, 135.9, 135.8, 135.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 93.9, 76.8 (d, J = 4 Hz), 74.8(d, J = 6 Hz), 74.0, 71.5, 69.5, 69.3, 69.2 (d), 39.3, 36.4; HRMS (FAB) calcd for $C_{44}H_{47}O_{11}P$ ($M + Na^+$) 805.2754, found 805.2790. Anal. Calcd for $C_{44}H_{47}O_{11}P$: C ,67.51; H, 6.05. Found: C, 67.36; H, 6.11.

[1(*R*)-(1α,3α,4α,5β)]-3-(Phosphonooxy)-1,4,5-trihydroxycyclohexane-1-carboxylic Acid (4). Water (7 mL) was added to a solution of the fully benzylated quinate phosphate **25** (0.41 g, 0.54 mmol) in THF (20 mL). The solution was then hydrogenated at 50 psi H_2 pressure over 10% Pd on C for 12 h. The catalyst was filtered through Celite. After removal of solvent under vacuum, phosphate **4** was obtained as a foam: ^1H NMR δ 4.72 (4.6−4.8, 1 H), 4.08 (ddd, J = 10, 10, 4 Hz, 1 H), 3.67 (ddd, J = 10, 3, 3 Hz, 1 H), 2.20−2.30 (m, 2 H), 2.16 (dd, J = 14, 4 Hz, 1 H), 1.97 (dd, J = 14, 10 Hz, 1 H); ^{13}C NMR δ 180.3, 77.9 (d, J = 6 Hz), 77.3, 76.0 (d, J = 6 Hz), 68.9, 42.3, 38.7; MS m/z (rel inten) EI 94 (100); CI 237 (100).

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