as reported.[19,23] 4-Oxa-1,6-heptadien-2-ol tosylate (**25**) (1.12 g, 42%, based on alkene **23** starting material) was also isolated: ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3 H), 3.85 (m, 4 H), 5.20 (m, 4 H), 5.80 (m, 1 H), 7.35 (d, 2 H, J = 10.6 Hz), 7.80 (d, 2 H, J = 10.8 Hz).

Determination of Macrorcycle Sites and Separation of Mercury(II) from Zinc(II) and Cadmium(II). The silica gel bound crown compound **1a** (Scheme III) was prepared as reported from **1**.[11] Columns containing macrocycle-bonded silica gel and plain silica gel were prepared by using 2.3 g of the particular silica material supported in 19-mm-diameter glass columns by tampon (cellulose) material. For the macrocycle site determination, solutions at pH 8 with 0.167 M $Mg(NO_3)_2$ and various concentrations of Ag^+ both greater and less than 10 ppm were used to load the column until the pH and concentration of Ag^+ coming out of the column equaled that for the original solution. The Ag^+ on the columns was eluted by using a solution of 0.1 M sodium acetate and 1 M acetic acid. The amount of Ag^+ bound to the column was constant when Ag^+ loading concentrations of 10 ppm or greater were used indicating the column was being loaded to capacity. For the Hg^{2+} separation, the column was preconditioned to pH 2 by using 500 mL of 0.01 M nitric acid. A 100-mL solution (in 25-mL aliquots) of 1×10^{-4} M Hz^{2+}, Cd^{2+}, and Zn^{2+} nitrates and 0.01 M HNO_3 was passed through the column. A total of 50 mL of either 0.03 M EDTA (pH 10.5) or 0.1 M $Na_2S_2O_3$ in 10-mL aliquots was then passed through the column. The pH values were adjusted by using sodium hydroxide. The amounts of Ag^+ or Hg^{2+}, Cd^{2+}, and Zn^{2+} in each solution were determined by atomic absorption spectroscopy. The concentrated Mg^{2+} or acid was present in the solutions subjected to the columns to minimize (in the case of Hg^{2+}, Zn^{2+}, and Cd^{2+}) or negate (Ag^+) the interaction of plain silica gel with the heavy metal ions. Commercially available reagent-grade chemicals and distilled, deionized water were used in all experiments. These experiments were performed in triplicate with standard deviation of less than 10%.

Acknowledgment. We thank the Utah State Center of Excellence Program and Serpentix Conveyor Corporation, Westminster, CO, for funding this research. We thank M. L. Bruening, D. Griffin, and J. Butler for the analytical chemistry part of this work.

Registry No. **1**, 114719-03-8; **1a**, 114719-04-9; **2**, 114719-05-0; **2a**, 114719-06-1; **3**, 114719-07-2; **3a**, 114719-08-3; **5**, 107106-37-6; **6**, 66582-26-1; **7**, 105399-99-3; **8**, 114719-09-4; **9**, 114719-10-7; **10**, 114719-11-8; **11**, 114719-12-9; **12**, 114719-13-0; **13**, 114719-14-1; **14**, 107106-38-7; **15**, 107106-39-8; **16**, 114719-15-2; **17**, 114719-16-3; **18**, 113585-52-7; **19**, 113585-54-9; **20**, 106-92-3; **21**, 114719-17-4; **22**, 114719-18-5; **23**, 114719-19-6; **24**, 94195-16-1; **25**, 114719-20-9; Hg^{2+}, 14302-87-5; $H(CH_3)Si(OC_2H_5)_2$, 2031-62-1; triethoxysilane, 998-30-1; 5-[[3-(triethoxysilyl)propoxy]methyl]-1,10-dibenzyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane, 114719-21-0; 5-[[3-(triethoxysilyl)propoxy]methyl]-1,10-dihexyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane, 114719-22-1; 5-[[3-(triethoxysilyl)propoxy]methyl]-1,10-diethyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane, 114719-23-2; allyl bromide, 106-95-6.

Chorismate Mutase Inhibitors: Synthesis and Evaluation of Some Potential Transition-State Analogues

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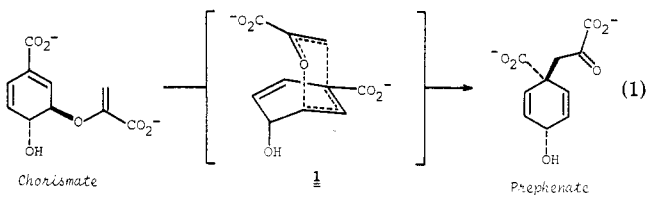
A number of bicyclic diacids have been synthesized as potential transition state analogue inhibitors of chorismate mutase, including the oxa- and carbabicyclic diacids **5**, **8**, **9**, and **13**. An unsuccessful attempt was made to generate the oxabicyclic nitronate **10**, which proved to be very labile toward hydrolysis; instead, the oximinolactone **11** and carbabicyclic nitronate **12** were prepared as potentially more accurate mimics of the postulated transition state **1**. The oxabicyclic diacids were prepared from the Diels–Alder adduct of butadiene and dimethyl itaconate, via selenocyclization of cyanohydrin **17**, elimination of the selenoxide and epoxidation of the olefin **18**, isomerization of epoxide **19** to the allylic alcohol **20**, hydrolysis of the nitrile, and stereochemical manipulation of the bridge carboxyl group. The carbabicyclic compounds were similarly accessible by electrophilic cyclization of β-keto ester **37**, affording ketone **43** via the cyclopropane **40** and selenide **41**. Methylenation of **43** and formation and selective rearrangement of the diepoxide **49** were key steps in further elaboration to the diester **36**. A shorter route to diene **48** was also developed, involving the one-pot bismethylenation of lactone **45** with an excess of $Cp_2Ti(Cl)CH_2AlMe_2$. The oximinolactone **11** and nitronate **12** were prepared by nitrosation or nitration of the protected diesters **30** and **53**, respectively, followed by hydrolysis and decarboxylation. The endo isomer of oxabicyclic diacid **5** proved to be the most potent inhibitor known for a chorismate mutase, with a K_i value of 0.12 μM against the chorismate mutase–prephenate dehydrogenase from *Escherichia coli*. The related isomeric and carbabicyclic analogues **8**, **9**, and **13** are less tightly bound (13 μM < I_{50} < 100 μM), and the oximinolactone **11** and nitronate **12** are poor inhibitors (I_{50} > 4 mM).

Introduction

Organic synthesis in a bioorganic setting often has the added challenge of design of the target molecule in addition to its actual construction. This point is underscored in the development of inhibitors of the chorismate mutases, enzymes that catalyze the rearrangement of chorismic acid to prephenic acid (eq 1). In this paper, we describe the three phases of such a project, namely, the design, synthesis, and evaluation of several bicyclic molecules designed to mimic the presumed transition state **1**.



(1)

Transition-State Analogues

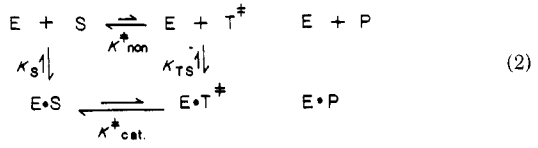
A number of fundamental strategies have been developed for the design of enzyme inhibitors based on considerations of the catalytic reaction mechanism.[1,2] A particularly effective approach is to devise a molecule that

(1) "Suicide inhibition": Walsh, C. *Tetrahedron* **1982**, *38*, 871–909. Abeles, R. H. *Pure Appl. Chem.* **1980**, *53*, 149–160.

(2) Transition-state analogues: Wolfenden, R. *Annu. Rev. Biophys. Bioeng.* **1976**, *5*, 271–306. Stark, G. R.; Bartlett, P. A. *Pharmacol. Ther.* **1984**, *23*, 45–78.

0022-3263/88/1953-3195$01.50/0

mimics in some manner the presumed structure of the transition state or a high-energy intermediate in the transformation.[2] This strategy relies on the principle that enhanced binding, and hence partial stabilization, of the transition state relative to the ground state is an important component in enzymatic rate acceleration.[3] Indeed, theoretical considerations indicate that the affinity of an enzyme for its transition state should be higher than that of the ground state by the same factor by which the enzymatic transformation is accelerated over that of the solution, noncatalyzed reaction (eq 2–4).[2] Quantitative



(2)

$$K_S K^{\ddagger}_{cat.} = K^{\ddagger}_{non} K_{TS};\ k_{non} \propto 1/K^{\ddagger}_{non},\ k_{cat.} \propto 1/K^{\ddagger}_{cat.} \quad (3)$$

$$K_{TS} = K_S \frac{k_{non}}{k_{cat.}} \quad (4)$$

assessment of this prediction can be frustrated experimentally for a number of reasons, including (1) the inherent difficulty in comparing a unimolecular enzymatic transformation with its multimolecular solution counterpart,[4] (2) the unavailability of the appropriate rate constant for reaction via the same mechanism in solution,[5] (3) uncertainty as to whether the rate of the enzymatic transformation is limited by a discrete, chemical step with a predictable transition-state structure,[6] and (4) the impossibility of devising an exact mimic of this metastable species. Some of these limitations can be factored out when the enzyme accepts a related series of substrates and comparison can be made among a series of transition-state analogs.[7] Nevertheless, for most enzymes the absolute magnitude of "transition-state binding" remains generally inaccessible.

Chorismate Mutase

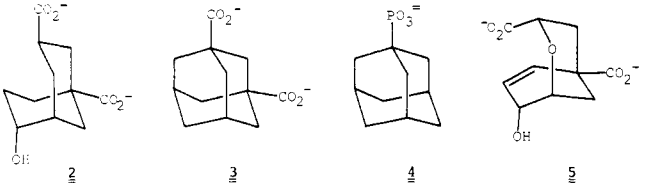
In the context of transition-state analogues, the chorismate mutases are of special interest, since the reaction they catalyze is formally a Claisen rearrangement (eq 1),[8] a transformation that not only is intramolecular but that has an observable, noncatalyzed solution counterpart.[9,10] Complications 1 and 2 referred to above are therefore removed, and, within the uncertainty imposed by 3, the possibility exists that an inhibitor that is a good mimic of the transition state may be able to extract the 1 000 000-fold rate acceleration of the enzymatic process[11,12] in the form of increased affinity in comparison to the substrate. This possibility has not gone unnoticed; indeed it has been the goal of a number of programs directed toward the development of inhibitors of the chorismate mutases.[13-16]

Initial quantitative evaluations of the rate acceleration produced by chorismate mutase were based on the assumption that the rearrangement itself is the rate-limiting step for the enzymatic process. Theoretical calculations[11] which suggested that the pseudodiaxial conformer of chorismate is significantly less stable than the pseudodiequatorial form, coupled with the observation that the entropy of activation for the catalyzed rearrangement is very low (in contrast to that for the solution reaction), were consistent with the view that the enzyme accelerates the rearrangement simply by binding the substrate firmly in the diaxial conformation. The demonstration that the solution and enzymatic rearrangements follow the same stereochemical pathway was also consistent with this view.[13,17] Later studies on the mechanism of the noncatalyzed Claisen rearrangement indicated that a highly polarized transition state is involved,[18-20] and a variety of opportunities on the part of the enzyme for electronic stabilization of this transition state were suggested.

The recent work of Knowles and his co-workers has ruled out a number of these interpretations. Direct observation of the conformational equilibrium of chorismate in solution indicates that the pseudodiequatorial form is only 0.9–1.4 kcal/mol lower in energy than the reactive, diaxial one.[20] Moreover, careful studies using isotopically labeled material revealed that the rate-limiting step for the enzymatic transformation is unlike that of the solution reaction;[21,22] these results have been interpreted in favor of an intermediate covalently linked to the enzyme.[22]

Inhibitor Design

All prior approaches to the design of inhibitors of the chorismate mutases have been based on the assumptions that the enzymatic reaction proceeds through a transition state or high-energy intermediate resembling the bicyclic species **1** and that this is the structure that should be mimicked. The bicyclic diacid **2**[11] and the adamantane derivatives **3**[13] and **4**[14] exemplify this strategy, as does the bicyclic ether **5**, which we described in an earlier paper.[16]



2 3 4 5

In our application of this strategy to the design of an inhibitor (Scheme I), we attempted to incorporate the specific functional groups and reproduce the characteristic geometry of **1** as faithfully as possible. From the 2-oxa-

(3) Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *43*, 219–410. Pauling, L. *Nature (London)* **1948**, *161*, 707.
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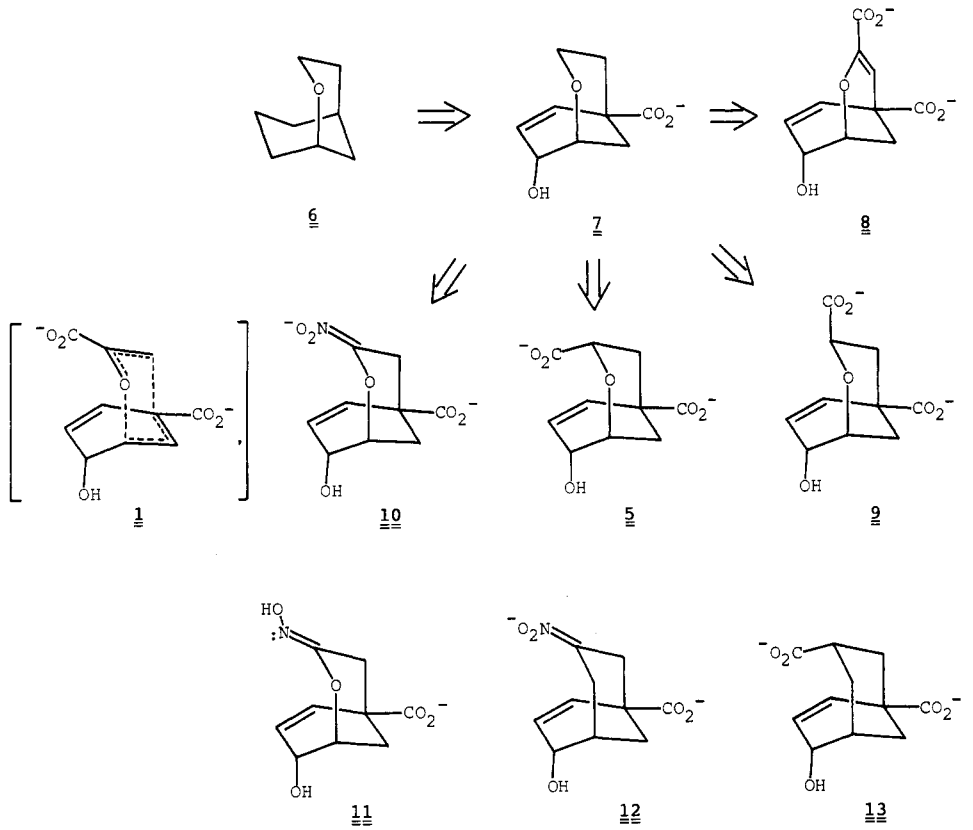
Scheme I



bicyclo[3.3.1]nonane skeleton, **6**, incorporation of the bridgehead carboxylate and the allylic alcohol functionality, as in **7**, are conceptually straightforward. More challenging was devising the counterpart of the other carboxylate and its mode of attachment to the bridging chain. Attachment of a carboxyl group to an sp^2-hybridized carbon, to give **8**, necessitates incorporation of a double bond and considerable distortion of the bridge. On the other hand, a carboxyl group attached to a saturated carbon is forced to adopt either the exo (**9**) or endo (**5**) configuration, deviations from the planar orientation in **1** which we wanted to avoid. Andrews et al. had previously shown that the endo carboxylate isomer of **2** does not detectably inhibit the chorismate mutase-T from *E. coli*.[13]

In another context, namely, the inhibition of enzymatic reactions that involve carboxylate enolates, anionic nitro compounds have been effective analogues of carboxylate groups attached to sp^2-hybridized carbons.[23] We therefore thought to resolve our design dilemma by substituting the unmanageable carboxylate with a nitro group, in the form of its *aci*-anion (**10**). Although the nitronate moiety is not free to rotate relative to its point of attachment, as the carboxylate is, we considered it probable for both steric and electronic reasons that the carboxylate in **1** would be coplanar with the enol moiety. Although the pK_a of alicyclic nitro derivatives is typically in the range of 8–9, reprotonation on carbon is slow and, under appropriate conditions, nitronate anions remain ionized down to the pK_a of the *aci*-nitronic acid form, which is about 6.[24] The most thoroughly documented examples of α-nitro ethers are the anomeric nitro-sugar derivatives described by Baumberger and Vasella, who noted their sensitivity toward hydrolysis.[25] As described below, this lability proved to be an insurmountable problem in our attempted synthesis of **10**. We were therefore forced to compromise in our inhibitor design, retaining the ether with the dicarboxylates **5**, **8**, and **9** and in the oximinolactone **11**, or incorporating the nitronate in the carbacycle **12**. The carbacyclic diacid **13** was also prepared to allow direct comparison of the effect of the various substitutions.

Synthesis

Oxabicyclic Structures. The penultimate step in our envisaged synthesis of the nitronate ether **10** was nitration[26,27] of the enolate derived from an appropriately protected form of the diacid, **9**. The synthesis of this key intermediate, as well of the endo isomer **5**, is outlined in Scheme II. The less hindered ester of Diels–Alder adduct **14** is hydrolyzed selectively in alkali and converted via the acid chloride **15** and aldehyde[28] **16** to cyanohydrin **17**. Not surprisingly, this hydroxy ester lactonizes readily and we were only able to obtain it by using the exceptionally mild method developed by Evans and Truesdale for cyanohydrin formation via the silyl ether.[29] Of a variety of cyclization methods investigated (including I_2, NBS, and PhSeCl), the use of *N*-(phenylseleno)phthalimide,[30] followed by oxidative elimination, proved to be the most efficient for conversion of **17** to bicyclic olefin **18**. This material is produced as a 1:1 mixture of epimers, which was carried on without separation. The double bond in **18** is inert to singlet oxygenation; however, it undergoes

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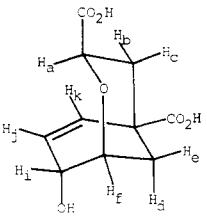
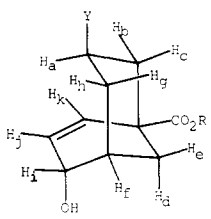
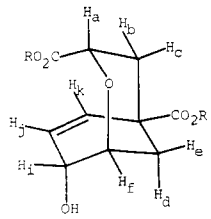
Table I. Selected ^{1}H NMR Assignments for Bicyclic Compounds[a]



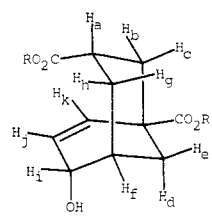
9



36: Y = CO_2Me, R = Me
57: Y = NO_2, R = H



5: R = H
5a: R = Me

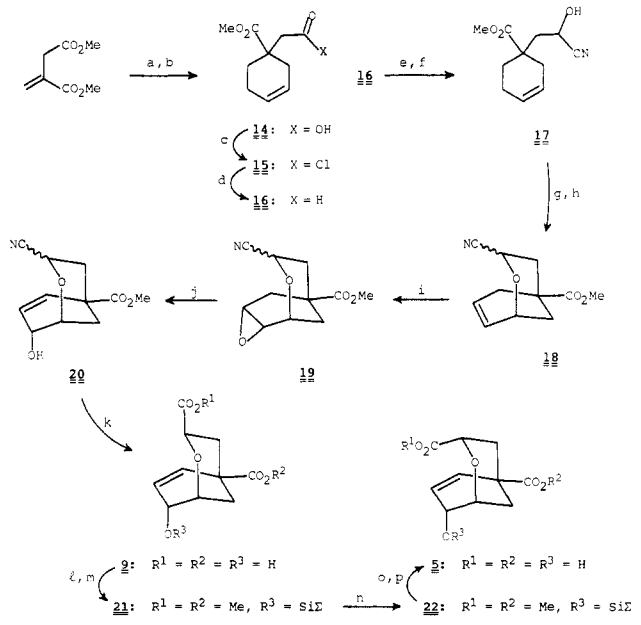


13: R = H
13a: R = Me

	9[b]	36[c]	57[d]	5[e]	5a[c]	13[f]	13a[c]
ab	2.8	4.6	4.7	3.9	1.9	–	1.9
ac	12.2	12.7	12.1	7.1	7.5	6.7	6.7
ag	na	12.7	12.1	na	na	7.0	7.1
ah	na	4.6	4.7	na	na	–	1.9
bc	13.0	13.7	12.3	13.7	13.7	13.7	13.3
bd	1.2	1.8	–	≈1	2.0	–	1.9
bh	na	1.8	–	na	na	–	1.9

[a] Dash indicates that coupling constant could not be discerned; na = not applicable. [b] Triethylammonium salt in MeOH/acetone solution. [c] $CDCl_3$ solution. [d] Triethylammonium salt in D_2O. [e] Bis(dicyclohexylammonium salt) in D_2O. [f] Disodium salt in D_2O.

Scheme II[a]

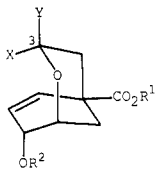


[a] SiΣ = Si-*t*-BuMe$_2$. (a) Dimethyl itaconate, butadiene, $AlCl_3$, PhH, 50 °C (92%); (b) NaOH, aqueous MeOH (85%); (c) ClCOCOCl, PhH; (d) $(Ph_3P)_2CuBH_4$, MeCOMe (71% for two steps); (e) Me_3SiCN, ZnI_2; (f) HCl, aqueous THF; (g) *N*-(phenylseleno)phthalimide, *p*-TsOH, CH_2Cl_2, −78 °C; (h) H_2O_2, THF (39% for four steps); (i) *m*-CPBA, CH_2Cl_2, Δ, 24 h (85%); (j) Me_3SiBr, Ph_3P, MeCN; DBU, MeCN, Δ; then aqueous HCl (71%); (k) KOH, H_2O, Δ (95%); (l) CH_2N_2, ether/MeOH (95%); (m) ΣSiCl, DBU, CH_2Cl_2 (85%); (n) LiTMP, THF, −78 °C, → NH_4Cl/NH_3, −78 °C (77%); (o) Bu_4NF, THF (96%); (p) NaOH, aqueous MeOH (89%).

epoxidation with *m*-chloroperbenzoic acid specifically from the exo face to give **19**. Isomerization of this material to the allylic alcohol **20** is carried out by opening the epoxide with bromotrimethylsilane, with catalysis by triphenylphosphine, and subsequent elimination of the silyl bromohydrin with diazabicycloundecene (DBU) in the same flask.[31] Saponification of the mixture of epimeric nitrile esters, **20**, occurs with concurrent isomerization to a 5–6:1 mixture of exo/endo diacids (**9** and **5**, respectively).

The exo diacid **9** is isolated in pure form by recrystallization of the bis(diethylammonium salt). Isomerization of the exo isomer to the endo stereochemistry can be accomplished by kinetically controlled protonation of the lithium enolate derived from the protected diester **21**. The enolate of **21** is generated with lithium tetramethylpiperidide in THF at −78 °C and then transferred quickly into a solution of ammonium chloride in liquid ammonia at the same temperature.[32] Alkaline saponification of the resulting endo diester **22** takes place without epimerization to afford diacid **5**, which is purified by crystallization of the bis(dicyclohexylammonium salt). The endo and exo configurations of **5** and **9**, respectively, were revealed by the ^{1}H NMR coupling constants depicted in Table I.

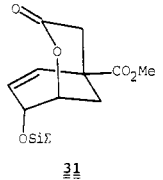
As alluded to above, our projected route to nitronate **10** called for nitration of a protected derivative of **9**, via the enolate, followed by decarboalkoxylation.[26] Our initial experiments indicated that the intermediate α-nitro ester and, especially, the desired product are very labile toward hydrolysis. For example, attempted saponification of the diester **23** by treatment with sodium hydroxide in aqueous



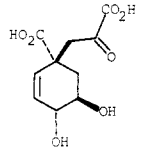
	X	Y	R^1	R^2
23*	CO_2Me	NO_2	Me	SiΣ
24	H	CO_2Et	TMSE	H
25	H	CO_2Et	TMSE	CMe_2OMe
26*	CO_2Et	NO_2	TMSE	CMe_2OMe
27*	CO_2Et	NO_2	H	CMe_2OMe
28*	CO_2Et	NO_2	H	H
29*	CO_2Et	NO_2	Et	SiΣ
30	H	CO_2TMSE	TMSE	SiΣ

TMSE = 2-(Trimethylsilyl)ethyl
SiΣ = t-Butyldimethylsilyl

* *Stereochemistry at C-3 presumed to be as indicated (nitro exo) based on kinetic protonation studies; see text*



31



32

methanol, followed by extraction into an organic solvent after only a few minutes at room temperature, leads to the

(31) Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* 1984, *106*, 7854–7860.

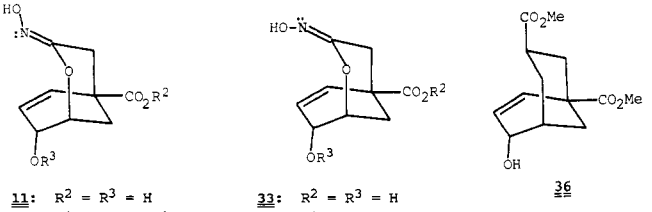
(32) Procedure suggested by Dr. S. D. Rychnovsky (personal communication).

Nef product **31** in 50% yield. We therefore chose protecting groups for the bridgehead carboxyl and allylic alcohol moieties which could be removed under mild conditions, prior to alkaline cleavage of the ester adjacent to the nitro group. We anticipated that the presence of this ester would retard solvolysis of the α-nitro ether. While a number of strategies were investigated, the one that we ultimately pursued involved protecting the bridgehead carboxyl group as the 2-(trimethylsilyl)ethyl ester,[33] the allylic hydroxyl as the α-methoxyisopropyl ketal,[34] and the carboxyl group at C-3 as the ethyl ester.

Sequential treatment of the diacid **9** with excess oxalyl chloride, 2-(trimethylsilyl)ethanol, and sodium ethoxide in ethanol affords the mixed ester **24** via cleavage of the allylic oxalate and exchange of the less encumbered ester. After introduction of the α-methoxyisopropyl ketal and formation of the enolate, reaction with the nitrate ester of acetone cyanohydrin[35] provides the nitro ether **26** in 51% yield. The silylethyl ester can be cleaved with tetrabutylammonium fluoride, and the product, as the ether-soluble tetrabutylammonium salt, can be separated from excess reagent by partitioning between ether and water. A number of methods were explored to liberate the acid from the tetrabutylammonium counterion; however, we found that those that involve polar solvents or partitioning between an organic solvent and aqueous acid simply lead to loss of the nitro group. Neutralization can be accomplished by elution of a chloroform solution of the tetrabutylammonium salt through a column of silica coated with 0.05 N sulfuric acid. In this manner, the monoester **27** is obtained in ca. 50% yield from the diester **26**. The α-methoxyisopropyl ketal is removed quickly with pyridinium *p*-toluenesulfonate in isopropyl alcohol, to give **28**, which we anticipated would be the immediate precursor to the desired target. To our dismay, alkaline hydrolysis of **28** affords, after only 5 min, exclusively the ring-opened keto diol **32**, arising from solvolysis of the nitro moiety prior to ester cleavage. Confronted with this result, and with the earlier evidence that the α-alkoxy nitronate moiety, which was presumably present in an intermediate en route to lactone **31**, is itself very sensitive toward hydrolysis, we abandoned our attempts to synthesize the nitronate **12**.

In addition to the endo and exo diacids **5** and **9**, the efforts described above yielded an additional analogue in the form of enol ether **8**. A protected form of this material is obtained from the nitro diester **29** on treatment with triethylamine in hot chloroform; it is also observed as a byproduct during formation or deprotection of related nitro diesters.

The last compounds investigated in the oxabicyclic series were the *E* and *Z* oximinolactones **11** and **33**, which we thought could serve as more stable, albeit uncharged, analogues of the nitronate **12**. The route that we employed to obtain these materials is conceptually the same as that envisaged for the elusive nitronate, namely, nitrosation of the enolate of **30** with isoamyl nitrite. The products of this transformation include the *E* oximinolactone **34** and a less polar material which we presume to be the nitrite ester of the *Z* isomer **35**, since it is reduced to the latter with ferrous ion.[36] The more stable *E* isomer **34** was saponified, and the resulting diacid **11** was purified and isolated as the disodium salt; however, the *Z* isomer **33** undergoes partial isomerization under comparable conditions and was not isolated in pure form.[37-40]



11: $R^2 = R^3 = H$ **33**: $R^2 = R^3 = H$

34: R^2 = TMSE, $R^3 = Si\Sigma$ **35**: R^2 = TMSE, $R^3 = Si\Sigma$

36

Carbabicyclic Structures. The synthesis of the carbabicyclic structures begins with the Diels–Alder adduct **14** and proceeds via the exo diester **36**, which is a precursor to both the nitronate **12** and endo isomer **13**; the route is in many respects similar to that of the oxabicyclic analogues. The key intermediate is the unsaturated ketone **43**, for which two methods of preparation were developed (Schemes III and IV).

Cyclization of the β-keto ester **37** with *N*-(phenylseleno)phthalimide (NPSP) was carried out in the presence of an equivalent of stannic chloride to isomerize the kinetically produced enol ether **38** to carbacyclic material, according to the method of Ley.[41] However, under these conditions, chloride **39** is formed instead of the expected selenide **41**. The ready conversion of the chloride to cyclopropane **40** on chromatography over Florisil or exposure to basic conditions suggests not only that **40** is an intermediate in formation of **39** but also a means of obtaining the desired selenide. Indeed, treatment of **40** with lithium phenyl selenide[42] gives bicyclic selenide **41** in 86% yield. The overall transformation of keto ester **37** to the selenide can be streamlined by not isolating either the chloride **39** or cyclopropane **40**. Decarboethoxylation of the seleno diester **41** with water in hot DMSO[43] followed by oxidative elimination of the selenide leads to the unsaturated ketone **43**.

The alternative route developed for synthesis of ketone **43** begins with iodolactonization of the monoester **14** and subsequent elimination to give allylic lactone **45**. Treatment of this material with the Tebbe reagent[44] at −40 °C gives, transiently, enol ether **46**. This *exo*-methylene derivative can be isolated if the reaction is quenched at low temperature; however, it isomerizes readily to the endocyclic enol ether **47** on standing or during attempted chromatographic purification. However, if the reaction

(33) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711–2716. Gerlach, H. *Helv. Chim. Acta* **1977**, *60*, 3039–3044.

(34) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827–7832.

(35) Freeman, J. P.; Shepard, I. G. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 839–842.

(36) Such selective reactivity of oxime isomers is precedented. See, e.g.: Buehler, E. *J. Org. Chem.* **1967**, *32*, 261–265.

(37) The configurations of the two oxime isomers were assigned on the basis of several precedents: the *E* isomer is both (1) more polar[38] and (2) more stable thermodynamically,[39] and (3) the tosylate of **34** is stable toward Beckmann rearrangement.[40]

(38) Sidgwick, N. V. *Organic Chemistry of Nitrogen*, 3rd ed.; Millar, I. T., Springall, H. D., Eds.; Clarendon: Oxford, 1966; pp 333–338.

(39) Kjaer, A.; Larsen, I. K.; Sivertsen, P. *Acta Chem. Scand., Ser. B* **1977**, *B31*, 415–423.

(40) Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284–294.

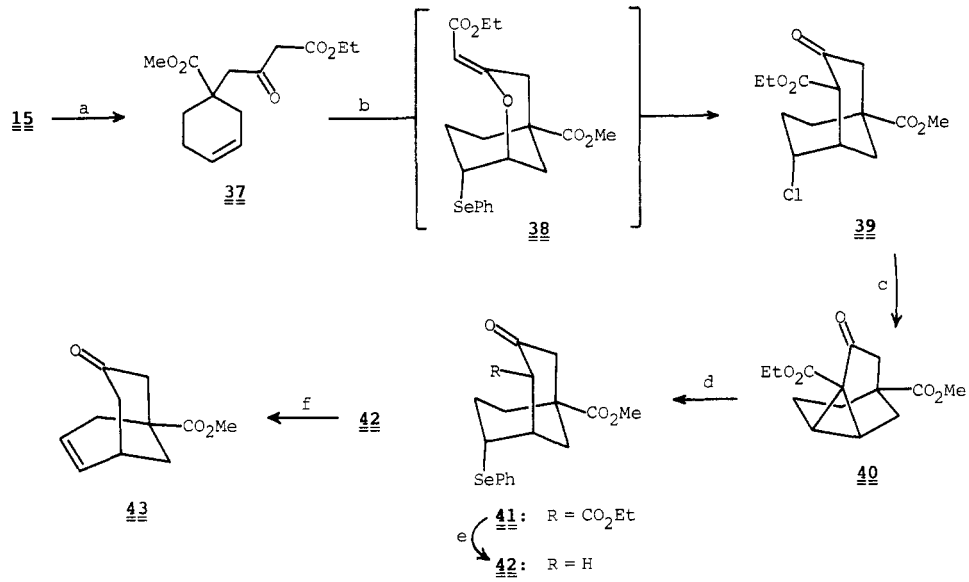
(41) Jackson, L. P.; Ley, S. V.; Morton, J. A. *J. Chem. Soc., Chem. Commun.* **1980**, 1028–1029. Jackson, W. P.; Ley, S. V.; Whittle, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1173–1174. Ley, S. V.; Murray, P. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1252–1253. Ley, S. V.; Lygo, B.; Molines, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2403–2405.

(42) Gladysz, J. A.; Wong, W. K.; Jick, B. S. *J. Chem. Soc., Chem. Commun.* **1978**, 838–839.

(43) Krapcho, A. P.; Jahngen, E. G. E., Jr.; Lovey, A. J. *Tetrahedron Lett.* **1974**, 1091–1094.

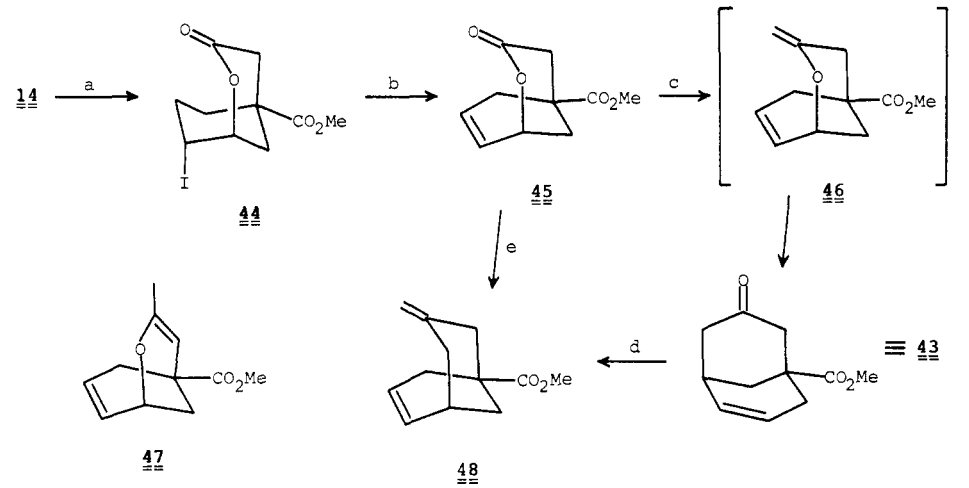
(44) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270–3272. (c) Pine, S. H.; Petit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212–1216. (d) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386–2387.

Scheme III[a]



[a] (a) $MeO_2CHLiCO_2Li$, THF, −78 °C (79%); (b) NPSP, $SnCl_4$, CH_2Cl_2; (c) DBU, CH_2Cl_2 (85%); (d) PhSeLi, THF, 0 °C (86%); (e) DMSO, H_2O, Δ (95%); (f) H_2O_2, THF (90%).

Scheme IV[a]



[a] (a) I_2, KI, aqueous $NaHCO_3$ (72%); (b) DBU, CH_3CN, Δ (87%); (c) $Cp_2Ti(Cl)CH_2AlMe_2$, CH_2Cl_2, −40 °C → 21 °C (40%); (d) CH_2Br_2, Zn, $TiCl_4$, CH_2Cl_2 (87%); (e) excess $Cp_2Ti(Cl)CH_2AlMe_2$, CH_2Cl_2, 21 °C (52%).

mixture is allowed to warm to room temperature before workup, Claisen rearrangement occurs and ketone **43** is obtained directly in 52% yield from the lactone.

The next step in the synthesis of diester **36** called for formation of a carbon–carbon bond at the keto position. A number of approaches were investigated; however, the combination of steric hindrance and ready enolization of **43** foiled those that involve carbanionic or ylide reagents.[45] In contrast, electrophilic organometallic reagents are effective. For example, the complex derived from zinc, CH_2Br_2, and $TiCl_4$ described by Nozaki and Lombardo[50] provides the diene **48** in 87% yield. The synthesis of this diene from lactone **45** can be simplified by carrying out the two methylenations and Claisen rearrangement in one operation: treatment of the lactone with 2 equiv of the Tebbe reagent and allowing the reaction mixture to come to room temperature overnight provides diene **48** in ca. 50% yield.

The subsequent functional-group manipulations leading from diene **48** to diester **36**, and thence to nitronate **12** and endo diacid **13**, are depicted in Scheme V. The double epoxidation of diene **48** is effected in high yield with *m*-chloroperbenzoic acid (*m*CPBA); functionalization of the endocyclic double bond is stereospecific; however, a ca. 10:1 ratio of epoxymethylene epimers is formed. Brief exposure of diepoxide **49** to $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −50 °C leads to rearrangement of the exocyclic epoxide and formation of an unstable aldehyde, **50**, in 54% purified yield. Buffered

(45) For example, Ph_3PCH_2,[46] Me_2SCH_2,[47] and the anions of $ClCH_2SiMe_3$[48] and $THPOCH_2PO_3Et_2$[49] lead to deprotonation and not addition.

(46) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128–1129.

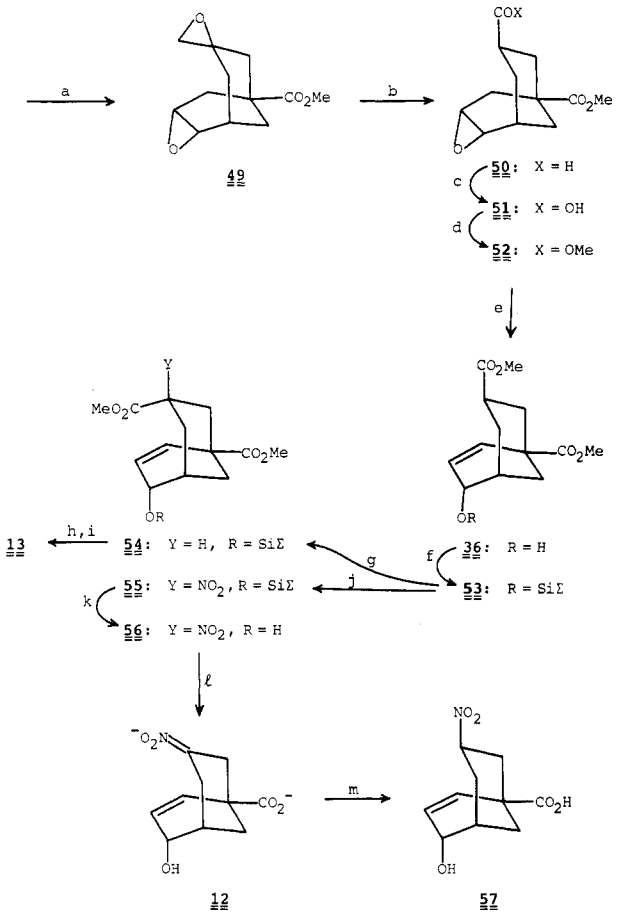
(47) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.

(48) Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1983**, *39*, 867–876.

(49) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847–4852.

(50) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417–2420. (b) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293–4296.

Scheme V[a]



[a] (a) *m*-CPBA, CH_2Cl_2 (98%); (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −50 °C, 1 min (54%); (c) $KMnO_4$, NaH_2PO_4, aqueous *t*-BuOH; (d) CH_2N_2 (93%); (e) Me_3SiBr, Ph_3P, MeCN; DBU, MeCN, Δ; then aqueous HCl; (f) ΣSiCl, DBU, CH_2Cl_2 (93%); (g) LiTMP, THF, −78 °C, → NH_4Cl/NH_3 (52%); (h) HF, CH_3CN, 0 °C; (i) NaOH, aqueous MeOH (53%); (j) LDA, $Me_2C(CN)ONO_2$, THF, −78 °C (50%); (k) HF, CH_3CN, 0 °C (74%); (l) NaOH, aqueous MeOH; (m) Dowex 50W-X8 (H^+ form) (67%).

potassium permanganate[51] proved to be the most efficient oxidant for the epoxy aldehyde, affording diester **52** in >90% yield after treatment with diazomethane. Stepwise rearrangement of the remaining epoxide moiety to the allylic alcohol of exo diester **36** can be accomplished as described above for the related oxabicyclic compound. Kinetic protonation[33] and nitration[26] of the enolate derived from the protected diester **53** are also analogous to corresponding transformations in the oxabicyclic series. Alkaline hydrolysis of the endo diester **54** affords the diacid **13** without epimerization, and the disodium salt is obtained in stereochemically homogeneous form after purification by reverse-phase HPLC and ion exchange.

In contrast to the behavior observed in the oxabicyclic series, the nitro group in diesters **55** and **56** is relatively stable. Alkaline hydrolysis of **56** affords the nitronate dianion **12** almost quantitatively. The stability of this material was followed by UV spectroscopy, monitoring the absorbance of the nitronate anion at 230 nm (ε 12 200). The nitronate is stable for at least 1 h in pH 7.0 phosphate buffer; however, the UV absorbance is lost with a half-life of ca. 15 min in pH 4.0 acetate buffer as the compound undergoes C-protonation or decomposes. The nitronate

(51) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537–4540.

Table II. Inhibitors of Chorismate Mutase[a,b]

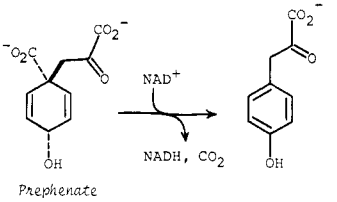
entry	inhibitor	I_{50}, μM	I_{50}/K_m[c]
1	*E* oximinolactone **11**	>10 000	>500
2	nitronate **12**	4200 ± 300	120
3	exo oxa diacid **9**	100 ± 10	5.5
4	endo carba diacid **13**	67 ± 4	2
5	ene diacid **8**	13 ± 2	0.7
6	adamantane-1-phosphonate, **4**	4.2 ± 0.9	0.23
7	endo oxa diacid **5**	0.14 ± 0.08	0.008
8	endo oxa diacid **5**	0.26 ± 0.06	0.008
9	endo oxa diacid **5**	K_i = 0.121 ± 0.014 μM	–

[a] Assayed at pH 7.5. [b] The I_{50} values reported previously[16] were computed incorrectly, hence they differ somewhat from those reported here. [c] K_m for chorismate = 18 μM, except for entries 2, 4, 8, and 9, when it was 34 μM.

can be purified by either ion-exchange chromatography on DEAE-Sephadex or reverse-phase HPLC, eluting with triethylammonium bicarbonate buffer, pH 7.4. Lyophilization of the eluant results in C-protonation of the nitronate, as evidenced by complete loss of the chromophore and its restoration on treatment with dilute alkali. Finally, the neutral nitro acid **57** can be isolated by exchange of the triethylammonium salt with Dowex 50X8-400 (H^+ form), extraction into ether, and chromatography on silica gel (0.5% HOAc/EtOAc).

Enzymatic Evaluation of Inhibitors

The ability of the bicyclic derivatives described above to inhibit chorismate mutase was evaluated with the chorismate mutase–prephenate dehydrogenase from *Escherichia coli*. This enzyme contains the mutase activity as well as the ability to catalyze the oxidative decarboxylation of prephenate to (*p*-hydroxyphenyl)pyruvic acid (eq 5). There has been considerable interest in determining whether these quite different transformations are catalyzed in the same, in overlapping, or in separate active sites.[15,52] Investigations with a variety of inhibitors have suggested that the sites are overlapping but not identical.[15]

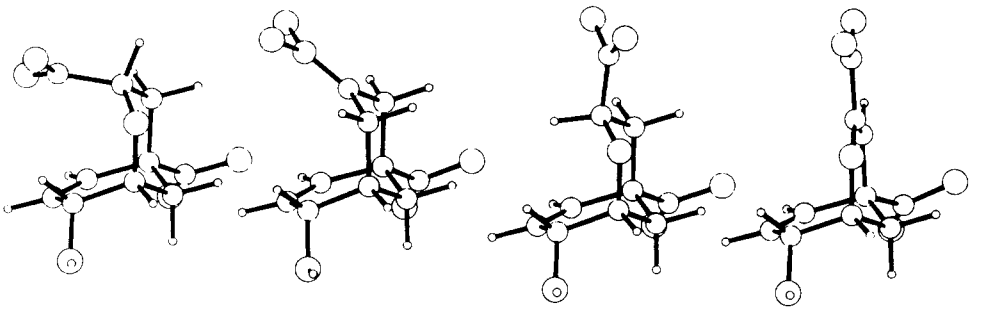


Prephenate (5)

Chorismate mutase activity was assayed under the conditions described by Morrison and SampathKumar[53] by monitoring the loss of absorbance at λ 274 nm as chorismic acid is converted to prephenate in the absence of NAD. An alternative assay was also employed for the more potent inhibitors, namely, by including NAD in the mixture and following the increase in absorbance at λ 340 nm as NADH is formed by the action of the dehydrogenase. For the most part, the inhibition results were determined as I_{50} values, the concentration of inhibitor that leads to a 50% reduction in the rate of reaction when the substrate is present at a concentration equal to its K_m value; for competitive inhibitors, the I_{50} value is equal to twice the inhibition constant, K_i. To provide a comparison with previous work, we also synthesized adamantane-1-phosphonate, **4**,[14] and evaluated it under the same conditions as our inhibitors. The results are presented in

(52) Christopherson, R. I.; Morrison, J. F. *Biochemistry* **1985**, *24*, 1116–1121.

(53) SampathKumar, P.; Morrison, J. F. *Biochim. Biophys. Acta* **1982**, *702*, 212–219.



5 12 9 8

Figure 1. Comparison of inhibitor structures predicted by molecular mechanics minimization.[55] For compounds **5**, **8**, and **9**, minimizations were performed on the neutral diacids; as a model for nitronate **12**, minimization was performed on the corresponding neutral enediol (carbon in place of the nitrogen).

Table II. Note that, except for adamantane-1-phosphonate, all of the inhibitors are chiral, but were prepared and tested in racemic form.

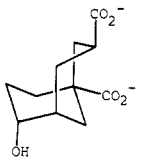
The inhibitors were evaluated at two different times and with different preparations of enzyme and buffers, with the result that the K_m values observed for the substrate chorismate differed by a factor of 2. The endo oxa diacid **5** served as a common denominator for the two sets of experiments, and the I_{50} values obtained for this compound differed by the same factor of 2.[54]

Of primary interest is the finding that the nitronate **12** is a poor inhibitor of the mutase, with an I_{50} value some 120-fold above the K_m value for chorismate (Table II, entry 2). Incubation of the nitronate with the enzyme prior to addition of substrate does not lead to increased inhibition, ruling out the possibility that the weak inhibition simply reflects slow binding behavior. We are confident that under the conditions of the assay at pH 7.5 the nitronate is present as the anion and not as the neutral *aci*-nitronic acid or the C-protonated nitro compound. As discussed above, a strong and persistent UV absorbance at λ 230 nm is observed for the inhibitor, consistent only with the nitronate anion or the *aci*-nitronic acid tautomer. Moreover, the pK_a expected for the *aci*-nitronic acid, ca. 6.3,[24] is well below the pH of the assay mixture. We are therefore forced to conclude that the bridging oxygen atom is an important element in the transition-state structure and that its replacement with a methylene group engenders significant unfavorable interactions, or that we were incorrect in our conception of the conformation of chorismate as it undergoes rearrangement in the enzyme active site.

Direct comparison of the two endo diacids, the carbabicyclic derivative **13** (entry 4) and the oxabicyclic analogue **5** (entries 8 and 9), indicates that the CH_2-for-O substitution reduces the binding affinity by a factor of 250. Nevertheless, the carbabicyclic diacid **13** is still bound 60-fold more tightly than the nitronate **12**, indicating that the methylene substitution is not the entire explanation for the poor affinity of the latter compound.

It is of interest to compare the three oxabicyclic diacids: the exo isomer **9** (entry 3), the dehydro derivative **8** (entry 5), and the endo epimer **5** (entry 7). Figure 1 displays the structures of these compounds as predicted by molecular mechanics calculations[55] and emphasizes the different orientations of the bridge carboxylate moiety. Although the bridging carbon atoms in **9** and **8** differ in their hybridization and geometry, if the carbacyclic rings of these molecules are superimposed, the bridge carboxylate carbons are only 0.25 Å apart. It is not surprising, therefore, that these compounds differ in their affinity for the enzyme by less than an order of magnitude. The fact that the endo isomer **5** is more than 100-fold more potent than the other two indicates that the specific orientation of the bridge carboxylate is significant.[13] In this light, the I_{50} value observed for nitronate **12** is not inconsistent: the 60-fold reduction in affinity in comparison with that of the endo carbabicyclic diacid **13** is less than the almost 700-fold difference between the endo and exo isomers **5** and **9** in the oxabicyclic series. Nevertheless, these results are contrary to our expectation that the most favored orientation of the group intended to represent the enol pyruvyl carboxylate would be the intermediate position adopted by nitronate **12** (and also displayed in Figure 1).

The increased affinity of the endo over the exo isomer in the oxabicyclic series stands in contrast to the ordering of the corresponding isomers of the saturated carbabicyclic diacids **2** and **58**. As Andrews et al.[13] described in the first



58

report of potential transition state analogue inhibitors for a chorismate mutase, the exo isomer **2** is at least threefold more tightly bound than the endo analogue **58**, for which no inhibition was observed. The explanation for this difference lies in the preferred conformations of the two endo derivatives. The chair–chair form of the saturated carbabicycle **58** experiences severe steric interactions, and thus the stable conformer is that with the carboxyl-containing ring in the boat conformation. In contrast, the corresponding interaction is sufficiently reduced in the unsaturated systems that the carboxyl-containing rings remain in the chair form in both **5** and **13**. This interpretation is supported by molecular mechanics calculations and verified by the ^{1}H NMR coupling constants observed for these compounds and various intermediates in their synthesis (see Table I).

A full kinetic analysis was performed for the most potent inhibitor, endo diacid **5**.[56] This compound was shown to bind competitively with the substrate and to have an inhibition constant, K_i, of 0.12 μM, under conditions in which chorismate shows a K_m value of 34 μM. It is thus the most potent inhibitor known for a chorismate mutase. If K_m is indicative of the affinity of the enzyme for the substrate, it is clear that **5** captures only part of the additional

(54) As we noted previously,[16] the ratio I_{50}/K_m facilitates comparison of results with various chorismate mutases and assay conditions.

(55) Calculated by using the program MACROMODEL, Version 1.5, by W. C. Still et al. (1987).

(56) Cleland, W. W. *Methods Enzymol.* **1979**, *63*, 103–138.

binding affinity expected for a good transition-state analogue; moreover, the nitronate **12**, envisaged as a more "accurate" mimic of the putative transition state, is only poorly bound. A straightforward interpretation of these results is that the inhibitors we have devised are simply poor mimics of the transition state; however, the possibility exists that the rate-limiting step for the enzymatic process is not the actual rearrangement per se. Indeed, Knowles et al. have recently provided evidence that the bond-breaking step is not rate-limiting in the enzymatic transformation.[21,22]

Evidence that the mutase and dehydrogenase active sites in the bifunctional enzyme with *E. coli* are overlapping comes from the observation that adamantane-based inhibitors show similar K_i values against the two activities.[15] In preliminary experiments, we evaluated the endo oxabicyclic diacid **5** as an inhibitor of the prephenate dehydrogenase reaction. Under conditions in which adamantane-1-carboxylate shows significant inhibition of this reaction, compound **5** shows none, in spite of the fact that **5** is considerably more potent as an inhibitor of the mutase activity. These results, which have been confirmed and extended by Morrison,[57] suggest that there may be a greater distinction between the active sites than initially envisaged.

Experimental Section[58]

Preparation of 3-*endo*,8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, Bis(dicyclohexylammonium salt) (Salt of 5). 3-*endo*,8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, Dimethyl Ester. To a stirring solution of silyl ether **22** (see below) (120 mg, 0.32 mmol) in THF (2 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (0.64 mL of a 1 M solution in THF, 0.64 mmol). After 1.5 h, the solution was diluted with brine (5 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 4 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated to afford 80 mg (96% yield) of the hydroxy diester as a white solid after chromatography (5:1 ether/hexanes): mp 114–115 °C; IR (film) 3380, 2950, 1730, 1600 cm^{-1}; ^1H NMR δ 6.02 (dd, 1, J = 10.0, 0.9), 5.90 (ddd, 1, J = 10.0, 4.1, 1.1), 4.42 (dd, 1, J = 7.5, 1.9), 4.40 (m, 1), 4.23 (m, 1), 3.75 (s, 3), 3.68 (s, 3), 2.49 (ddd, 1, J = 13.7, 1.9, 1.9), 2.23 (dd, 1, J = 13.7, 7.4), 2.12 (d, 1, J = 13.1, 2.0), 2.03 (dd, 1, J = 13.1, 4.3), 1.88 (br s, 1); ^{13}C NMR δ 174.7, 173.3, 131.8, 129.4, 72.6, 69.2, 64.8, 52.4, 51.8, 40.1, 31.6, 27.9. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.22; H, 6.30. Found: C, 56.22; H, 6.19.

3-*endo*,8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, Bis(dicyclohexylammonium salt) (Salt of 5). A solution of the endo diester above (366 mg, 1.42 mmol) and 17 mL of 0.5 N NaOH (8.6 mmol) in 70 mL of 50% aqueous methanol was kept at 21 °C for 3 h. A solution of 1 N triethylammonium bicarbonate (TBK) (70 mL, pH 8) was added, and the mixture was lyophilized. The crude product was purified by ion-exchange chromatography on DEAE-Sephadex (20 mL, ammonium form), eluting with 0.5–1 M TBK. Fractions were analyzed by spotting on a TLC plate (no elution), evaporating, and visualizing with sulfuric acid/MeOH solution. The fractions containing product were lyophilized to give 545 mg (89% yield) of the hygroscopic bis(triethylammonium salt). To a small portion of this salt (79 mg) in MeOH (1 mL) was added dicyclohexylamine (0.367 mmol), and the solution was evaporated. The clear, glassy residue was dissolved in MeOH (0.5 mL), and the solution was diluted with acetone/hexanes, 1:1 (0.25 mL), and placed in the freezer for 3 days. The needle-like crystals obtained were washed with cold hexanes to afford 117 mg of the bis(dicyclohexylamine salt) of **5**: mp 232–233 °C; ^1H NMR (D_2O) δ 5.87 (d, 1, J = 10.0), 5.56 (ddd, 1, J = 10.0, 4.0, 0.9), 4.12 (m, 1), 4.0 (dd, 1, J = 7.0, 4.1), 3.95 (m, 1), 3.04 (m, 4), 2.02 (dd, 1, J = 3.7, 13.7), 1.90 (dd, 1, J = 7.2, 13.7), 1.84 (m, 8), 1.73 (br s, 2), 1.61 (m, 8), 1.47 (d, 4, J = 12.2), 1.10 (m, 20). Anal. Calcd for $C_{34}H_{58}O_6N_2$: C, 69.11; H, 9.89; N, 4.74. Found: C, 68.93; H, 9.92; N, 4.73.

Preparation of 8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]nona-3,6-diene-3,5-dicarboxylic Acid, Bis(dicyclohexylammonium salt) (Salt of 8). 8-*exo*-8-[(*tert*-Butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.1]nona-3,6-diene-3,5-dicarboxylic Acid, Diethyl Ester. A solution of 0.092 g (0.207 mmol) of nitro diethyl ester **29** (prepared by a sequence similar to that described below for **26**) and 0.20 mL (1.4 mmol) of triethylamine in 6 mL of chloroform was heated to reflux for 18 h. The mixture was partitioned between ether and 1 M potassium phosphate buffer at pH 5.7, dried ($MgSO_4$), and evaporated, and the residue was chromatographed (9:1 hexane/ether) to give 0.049 g (60% yield) of the enol ether as a colorless oil: IR (film) 1734, 1633, 1250, 1072; ^1H NMR δ 6.26 (d, 1, J = 1.8), 6.13 (d, 1, J = 9.6), 5.74 (ddd, 1, J = 9.7, 3.8, 0.9), 4.70 (br s, 1), 4.25–4.19 (m, 4), 4.12 (br s, 1), 2.29 (ddd, 1, J = 12.7, 1.6, 1.6), 1.88 (dd, 1, J = 12.7, 4.5), 1.28 (t, 3, J = 7.1), 1.28 (t, 3, J = 7.1), 0.85 (s, 9), 0.078 (d, 6, J = 4.1). Anal. Calcd for $C_{20}H_{32}O_6Si$: C, 60.57; H, 8.13. Found: C, 60.32; H, 8.24.

8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]nona-3,6-diene-3,5-dicarboxylic Acid, Bis(dicyclohexylammonium salt) (Salt of 8). A solution of 0.045 g (0.11 mmol) of the above diester enol ether in 2 mL of 1:1 D_2O and methanol-d_4 was treated with 0.65 mmol of sodium deuterioxide. After 72 h at 21 °C, the mixture was chromatographed on DEAE-Sephadex, eluting with a gradient of 0.1–1.0 M TBK (pH 9). The fractions near 0.3 M TBK were lyophilized, dissolved in methanol, treated with 0.040 g (0.22 mmol) of dicyclohexylamine, and evaporated. The residue was dissolved in methanol and crystallized by the addition of acetone. The resulting white solid was recrystallized from methanol and acetone to give 0.029 g (43%) of the salt of **8** as a white solid: IR (Nujol) 3200, 1630–1550 (br), 1259, 1045, 780 cm^{-1}; ^1H NMR (CD_3OD) δ (d, 1, J = 9.7), 6.05 (d, 1, J = 1.3), 5.65 (dd, 1, J = 9.8, 3.5), 4.59 (br s, 1), 3.96 (br s, 1), 3.23–3.06 (m, 4), 2.08–1.96 (m, 9), 1.90–1.66 (m, 9), 1.41–1.11 (m, 24).

Preparation of 3-*exo*,8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, Bis(diethylammonium salt) (Salt of 9). 3-*endo*/*exo*,8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, Dimethyl Ester. A solution of KOH (206 mg, 85%, 3.12 mmol) in 3 mL of H_2O was added to cyano ester **20** (see below) (280 mg, 1.25 mmol), and a few drops of MeOH were added to effect solution of the ester. The mixture was then heated at reflux for 2 h, allowed to cool to 21 °C, acidified to pH 2 with 2 N HCl, and evaporated. Trituration of the residue with acetone, filtration, and evaporation of the filtrate afforded the crude diacid (mixture of **9** and **5**) as a white solid (320 mg). To this mixture in 9 mL of Et_2O and 1 mL of MeOH at 0 °C was added ethereal diazomethane until a yellow color persisted; the solution was then brought to 21 °C and treated with AcOH until the color was discharged. Evaporation of this solution afforded 303 mg (95% yield) of the diester as a 5:1 endo/exo mixture of epimers at C-3. This material was used directly in the following step: IR ($CDCl_3$) 3625, 1740, 1446, 1260 cm^{-1}; major (exo) isomer, ^1H NMR δ 6.09 (br s, 2), 3.92–4.40 (m, 4), 3.67 (s, 6), 1.75–2.12 (m, 4). Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.29; H, 6.20.

3-*exo*,8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, Bis(diethylammonium salt) (Salt of 9). A solution of a mixture of the diacids **9** and **5** prepared as described above (0.80 g, 3.37 mmol) in 5 mL of methanol was made basic with diethylamine, warmed, and diluted with acetone until cloudy. Over a period of hours as crystallization proceeded, additional acetone was added (final volume 100 mL). The resulting crystals were recrystallized twice in a similar fashion from

(57) Morrison, J. F., personal communication.

(58) General (unless otherwise indicated): "Evaporation" refers to removal of volatile solvent with a rotary evaporator under water aspirator pressure and then with a vacuum pump; distillation (bulb-to-bulb) was performed with an Aldrich Kugelrohr apparatus at the indicated temperature and pressure; chromatography was performed according to Still[59] by utilizing silica gel 60 (E. Merck, Darmstadt) and the indicated eluting solvent; IR spectra were obtained in $CHCl_3$ solution, and NMR spectra were obtained in $CDCl_3$ solution. NMR spectra were obtained on a variety of Fourier-transform, superconducting instruments operating at frequencies (for protons) of ≥200 MHz. ^1H NMR data are reported as follows: chemical shift, multiplicity, number of hydrogens, coupling constant(s) in hertz. ^{13}C chemical shifts are reported relative to $CDCl_3$ or MeOH solvent.

methanol/acetone to give 0.130 g (10%) of the salt of the exo isomer **9** as a white, slightly hygroscopic solid: mp, bubbles and whitens at 180 °C, melts at 214–218.5 °C; IR (Nujol) 3300, 1618, 1420 cm^{-1}; ^1H NMR (D_2O) δ 6.03–5.90 (m, 2), 3.96 (br s, 1), 3.9–3.8 (m, 2), 2.91 (q, 8, J = 7.3), 1.75–1.46 (m, 4), 1.11 (t, 12, J = 7.3). Anal. Calcd for $C_{18}H_{34}N_2O_6$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.57; H, 9.09; N, 7.33.

(3*E*)-8-*exo*-3-Hydroximino-8-hydroxy-2-oxabicyclo-[3.3.1]non-6-ene-5-carboxylic Acid, Sodium Salt (11). A solution of 0.062 g (0.14 mmol) of hydroximinolactone **34** (see below) in 2 mL of THF was treated with 0.70 mL (0.7 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF. After 15 min at 21 °C, the mixture was evaporated, and the residue was dissolved in water and chromatographed on 5 mL of DEAE-Sephadex eluting with a gradient of TBK (pH 9). The fractions eluting between 0.1 M and 0.2 M buffer were combined and lyophilized, and the residue was dissolved in methanol and evaporated. The resulting triethylamine salt, free from buffer, was ion exchanged on Dowex 50W-X8 in the Na^+ form to give 0.042 g (93% yield) of **11**: IR (Nujol) 3190, 1669, 1556, 1238, 1030, 934 cm^{-1}; ^1H NMR (D_2O) δ 6.17 (d, 1, J = 10.4), 5.92 (dd, 1, J = 10.4, 4.0), 4.76 (br s, 1), 4.13 (br s, 1), 2.69 (d, 1, J = 15.5), 2.50 (dd, 1, J = 15.6, 2.4), 2.30 (ddd, 1, J = 14.0, 2.0, 2.0), 2.19 (dd, 1, J = 14.0, 4.2); ^{13}C NMR (D_2O) δ 167.8, 166.7, 134.6, 124.9, 77.2, 64.6, 34.0, 27.5, 23.2.

Preparation of 3-*endo*,6-*exo*-6-Hydroxy-7-bicyclo[3.3.1]-nonene-1,3-dicarboxylic Acid, Disodium Salt (13). Dimethyl 3-*endo*,6-*exo*-6-Hydroxy-7-bicyclo[3.3.1]nonene-1,3-dicarboxylate. A solution of the endo diester **54** (see below) (0.12 g, 0.33 mmol) in 5 mL of CH_3CN was cooled to 0 °C, and one drop of 48% HF was added. The reaction was monitored by TLC for the disappearance of starting material, and after 1.5 h, it was quenched by the addition of saturated $NaHCO_3$. The solvent was evaporated, the residue was partitioned between brine and EtOAc, and the aqueous layer was extracted again with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated to give a quantitative yield (83 mg) of the allylic alcohol, which was used directly in the saponification procedure described below. An analytical sample was prepared by chromatography (55% EtOAc/hexanes): IR 3600, 3020, 2960, 1720, 1460, 1435, 1300, 1240, 1060, 1020 cm^{-1}; ^1H NMR δ 5.84 (dd, 1, J = 10.0, 1.3), 5.65 (ddd, 1, J = 10.0, 4.4, 1.3), 4.07 (d, 1, J = 4.1), 3.71 (s, 3), 3.60 (s, 3), 2.60 (dd, 1, J = 6.9, 6.9), 2.50 (dddd, 1, J = 12.5, 1.9, 1.9, 1.9), 2.47 (ddddd, 1, J = 14.5, 1.9, 1.9, 1.9, 1.9), 2.18–2.20 (m, 1), 2.09 (dddd, 1, J = 12.7, 2.4, 2.4, 2.4), 1.91 (dd, 1, J = 13.8, 6.5), 1.72 (ddd, 1, J = 14.6, 7.3, 5.5), 1.68 (br d, 1, J = 12.7); ^{13}C NMR δ 176.0, 175.0, 132.3, 129.9, 67.4, 52.2, 51.4, 43.0, 35.7, 35.2, 31.5, 29.5, 27.3. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.39; H, 7.15. Found: C, 61.14; H, 7.13.

3-*endo*,6-*exo*-6-Hydroxy-7-bicyclo[3.3.1]nonene-1,3-dicarboxylic Acid, Disodium Salt (13). The diester above (36 mg, 0.14 mmol) and 0.56 mL of 1 N NaOH were dissolved in 0.8 mL of a 1:1 MeOH/water mixture at room temperature. The hydrolysis reaction was monitored by ^1H NMR, and complete conversion to the diacid was achieved in 4 h. The mixture was lyophilized to yield a white powder, which was purified by reverse-phase HPLC (Whatman ODS-3, C18, 20 × 50 cm), eluting with 100 mM TBK (pH 7.4) and monitoring at 210 nm. Fractions containing product were lyophilized to afford the bis(triethylammonium salt), which was converted to the disodium salt by passage through a Dowex cation-exchange column (Na^+ form). After lyophilization, 21 mg (53%) of **13** was isolated as a hygroscopic solid: ^1H NMR (D_2O) δ 5.76 (d, 1, J = 10.0), 5.50 (ddd, 1, J = 10.0, 4.4, 1.1), 3.91 (d, 1, J = 4.1), 2.32 (br dd, 1, J = 6.8, 6.8), 2.04–2.08 (m, 2), 1.86–1.90 (m, 1), 1.70 (br d, 1, J = 12.5), 1.65 (dd, 1, J = 13.7, 6.6), 1.55 (ddd, 1, J = 14.4, 7.2, 5.7), 1.41 (br d, 1, J = 12.2); ^{13}C NMR (D_2O) δ 184.9, 182.3, 135.6, 128.1, 67.7, 44.6, 37.0, 35.1, 30.0, 27.7. Anal. Calcd for $C_{11}H_{12}O_5Na_2 \cdot H_2O$: C, 45.83; H, 4.89. Found: C, 45.63; H, 5.18.

Preparation of 1-(Methoxycarbonyl)-3-cyclohexene-1-acetic Acid (14). Methyl 1-(Methoxycarbonyl)-3-cyclohexene-1-acetate. To a suspension of $AlCl_3$ (50.6 g, 379 mmol) in 1.9 L of benzene was added a solution of dimethyl itaconate (60 g, 379 mmol) in 100 mL of benzene, dropwise, with vigorous stirring. The resulting solution was heated to 50 °C and was treated with butadiene gas delivered through a sintered-glass tube over a 4-h period, at which time no starting ester remained (TLC analysis). After cooling to 21 °C, the mixture was partitioned between dilute HCl and ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated, and the crude product was distilled through a 10-in. Vigreux column to give 73.2 g (92% yield) of the Diels–Alder adduct: bp 94–96 °C (0.5 mmHg); IR (film) 1745, 1440 cm^{-1}; ^1H NMR δ 5.65 (br s, 2), 3.70 (s, 3), 3.65 (s, 3), 2.65 (m, 2), 2.10–1.7 (m, 6). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.41; H, 7.68.

1-(Methoxycarbonyl)-3-cyclohexene-1-acetic Acid (14). A solution of diester prepared as described above (111.8 g, 527 mmol) and NaOH (22.15 g, 557 mmol) in 3.5 L of 80% aqueous MeOH was stirred at 21 °C for 6 days. The MeOH was evaporated, an additional 500 mL of water was added, and the aqueous phase was washed with CH_2Cl_2. After acidification with concentrated HCl to a pH of 2, extraction of the aqueous layer with CH_2Cl_2 (3 × 300 mL), drying over Na_2SO_4, and evaporation afforded the crude monoacid. Recrystallization from hexanes yielded in two crops 88.5 g (85% yield) of **14** as white needles: mp 63–64 °C; IR 3500, 1710 cm^{-1}; ^1H NMR δ 9.30 (br s, 1), 5.60 (br s, 2), 3.66 (s, 3), 2.70 (br s, 2), 1.62–2.57 (m, 6). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.55; H, 7.05.

1-(Methoxycarbonyl)-3-cyclohexene-1-acetyl Chloride (15). To a solution of monoacid **14** (10.0 g, 50.5 mmol) in 250 mL of benzene was added two drops of dimethylformamide followed by oxalyl chloride (19.2 g, 152 mmol), dropwise, with stirring. After gas evolution had ceased (ca. 15 min.), the solution was heated to 45 °C for 2 h. The mixture was evaporated by using a water aspirator equipped with a $CaCl_2$ drying tube. The crude yellow oil (10.9 g, 100% crude) was used directly in the subsequent step. It could also be distilled [bulb-to-bulb, 120 °C (0.8 mmHg)] to afford a colorless product: IR (film) 1800, 1730, 1440 cm^{-1}; ^1H NMR δ 5.60–5.73 (m, 2), 3.72 (s, 3), 3.28 (d, 2, J = 3.2), 2.56–2.64 (br d, 1), 1.8–2.2 (m, 5).

1-(Methoxycarbonyl)-3-cyclohexene-1-acetaldehyde (16). A solution of the acid chloride **15** described above (10.9 g, 50.3 mmol) in 30 mL of acetone was added dropwise at 0 °C to a rapidly stirring solution of triphenylphosphine (28 g, 106.6 mmol) and bis(triphenylphosphine)copper(I) borohydride (36.4 g, 60.4 mmol) in 200 mL of acetone (freshly distilled from anhydrous K_2CO_3). The ice bath was removed, and the mixture was stirred for 4 h at 21 °C. The mixture was filtered, the supernatant was evaporated, and the residue was diluted with 50 mL of ether and again filtered and evaporated. Kugelrohr distillation [oven temperature 60–79 °C (0.5 mmHg)] afforded 6.46 g (71% yield from monoacid **14**) of aldehyde **16** as a clear oil: IR (film) 2750, 1720, 1440, 1210 cm^{-1}; ^1H NMR δ 9.83 (t, 1, J = 2.0), 5.43–5.81 (m, 2), 3.63 (s, 3), 2.64 (d, 2, J = 2.0), 2.33–2.55 (m, 1), 1.50–2.33 (m, 5). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.68; H, 7.61.

Preparation of 1-(Methoxycarbonyl)-α-hydroxy-3-cyclohexene-1-propanenitrile (17). 1-(Methoxycarbonyl)-α-[(trimethylsilyl)oxy]-3-cyclohexene-1-propanenitrile. A mixture of the aldehyde ester (2.89 g, 15.8 mmol) and anhydrous ZnI_2 (2.6 g, 8.0 mmol) was stirred with ice-bath cooling, and TMSCN (2.38 g, 24 mmol) was added dropwise. After being stirred overnight at 21 °C, the reaction mixture was diluted with CH_2Cl_2 and filtered. Evaporation of the filtrate provided 5.9 g of crude cyanohydrin silyl ether, which was used immediately in the subsequent step. A pure sample could be obtained by Kugelrohr distillation [oven temperature 110–125 °C (0.7 mmHg)]: IR (film) 2270, 1735, 1445 cm^{-1}; ^1H NMR δ 5.58 (m, 2), 4.38–4.57 (m, 1), 3.63 (s, 3), 1.40–2.77 (m, 8), 0.29 (s, 9). Anal. Calcd for $C_{14}H_{23}NO_3Si$: C, 59.75; H, 8.24; N, 4.98. Found: C, 59.46; H, 8.23; N, 4.88.

1-(Methoxycarbonyl)-α-hydroxy-3-cyclohexene-1-propanenitrile (17). To the crude trimethylsilyl cyanohydrin described above (5.9 g, ≤15.8 mmol) in 30 mL of THF and 15 mL of H_2O was added HCl (3.2 mL of a 0.25 M aqueous solution, 0.8 mmol) with rapid stirring at 21 °C. After exactly 10 min, the mixture was diluted with ice-cold brine (50 mL) and extracted with ether, and the combined organic layers were washed with brine and dried with Na_2SO_4. Evaporation afforded 3.66 g of the cyanohydrin **17** as an orange-red solid; this material was utilized immediately in the following step. The product could be recrystallized from 9:1 hexanes/EtOAc: mp 109–112 °C; IR (film) 3425, 2250, 1710, 1450, 1220 cm^{-1}; ^1H NMR δ 5.58–5.74 (m, 2), 4.50–4.67 (m, 1), 3.69, 3.70 (s, 3), 3.05 (br d, 1, J = 18.0), 2.55 (t,

1, J = 18.0), 1.78 (m, 7). Anal. Calcd for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.70. Found: C, 63.03; H, 7.20; N, 6.67.

Methyl 3-Cyano-2-oxabicyclo[3.3.1]non-7-ene-5-carboxylate (18). A solution of the crude cyanohydrin **17** described above (3.66 g, ≤15.8 mmol; dried by evaporation from 1:1 CH_3CN/benzene) in CH_2Cl_2 (50 mL) was cooled to −78 °C and treated with *N*-(phenylseleno)phthalimide (6 g, 19.8 mmol) and *p*-toluenesulfonic acid (190 mg of hydrate, 1 mmol, dried by evaporation from 1:1 CH_3CN/benzene) with stirring. The cooling bath was removed, and the reaction mixture was stirred at 21 °C overnight. The solution was diluted with CH_2Cl_2 and washed with 2 N NaOH and brine, and the organic layer was dried ($MgSO_4$) and evaporated. The resulting selenide was diluted with THF (100 mL) and treated with 6 mL of 30% H_2O_2 with stirring. After 1.5 h, triethylamine (4.4 mL) was added and the reaction mixture was stirred for an additional 2 h. The mixture was evaporated, diluted with CH_2Cl_2 (50 mL), washed with 2 N HCl and saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated again to afford 2 g of a brown oil. Chromatography of this material (2:1 hexanes/Et_2O) afforded 1.27 g (39% yield based on aldehyde **16**) of the bicyclic ether **18**, as a 1:1 mixture of cyano epimers: IR (film) 2260, 1733, 1438, 1249 cm^{-1}; ^1H NMR δ 5.53–6.31 (m, 2), 4.49–4.53 (m, 1), 4.27–4.50 (m, 1), 3.65 (s, 3), 1.60–2.73 (m, 6). Anal. Calcd for $C_{11}H_{13}O_3N$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.54; H, 6.36; N, 6.66.

Methyl (1*R,2*S**,4*R**,6*S**,8*R***S**)-8-Cyano-3,9-dioxatricyclo[4.3.1.0^{2,4}]decane-6-carboxylate (19).** A solution of cyano olefin **18** (1.25 g, 6.0 mmol) and *m*-chloroperbenzoic acid (2.6 g, 12 mmol) in 30 mL of CH_2Cl_2 was heated at reflux for 24 h. A solution of K_2SO_3 (1.0 g) in 12 mL of H_2O was added, and the mixture was stirred overnight. The resulting suspension was washed with saturated $NaHCO_3$, 2 N NaOH, H_2O, and finally brine, and the organic layer was dried over $MgSO_4$ and evaporated to give 1.2 g of crude epoxide as a white solid. Chromatographic purification of this material (2:1 hexanes/Et_2O) afforded 1.10 g (85% yield) of **19** as a 1:1 mixture of cyano epimers: IR 2360, 1725, 1435, 1240 cm^{-1}; ^1H NMR δ 4.73–4.98 (m, 1), 4.35–4.52 (m, 1), 3.64 (s, 3), 3.30 (m, 1), 3.10 (m, 1), 1.60–2.64 (m, 6). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 58.90; H, 5.81; N, 5.99.

Methyl 8-*exo*-3-Cyano-8-hydroxy-2-oxabicyclo[3.3.1]non-6-ene-5-carboxylate (20). A stirring solution of the epoxide **19** (400 mg, 1.78 mmol) and triphenylphosphine (94 mg, 0.36 mmol) in 2.5 mL of acetonitrile was treated with TMSBr (560 mg, 3.66 mmol) at 0 °C. After 0.5 h, the mixture was warmed to 21 °C and stirred for an additional 1.5 h. 1,5-Diazabicyclo[5.4.0]undec-5-ene (DBU) (580 mg, 3.8 mmol) was then added dropwise and the mixture heated at reflux for 17 h. After evaporation of the mixture, the residue was triturated with Et_2O, leaving a brown precipitate of DBU·HBr. The supernatant was filtered through Celite and evaporated, and the residue was dissolved in 4.5 mL of THF. Concentrated HCl was added dropwise until a pH of 1 was attained. The mixture was evaporated, the residue was dissolved in CH_2Cl_2, and the solution was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Chromatography of the resulting yellow oil (4:1 ether/hexanes) gave 254 mg (71% yield) of allylic alcohol **20** as a 1:1 mixture of cyano epimers: IR 3615, 3470, 2270, 1735 cm^{-1}; ^1H NMR δ 6.20 (m, 2), 4.90 (d, 1, J = 7.3), 4.54 (dd, 0.5, J = 3.4, 12.2), 4.42 (br s, 1), 4.23 (m, 1), 4.10 (br s, 0.5), 3.78 (s, 3), 2.32 (dd, 1, J = 7.5, 13.9), 2.10–2.25 (m, 1), 1.85–2.05 (m, 2). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 58.98; H, 5.78; N, 6.15.

Dimethyl 3-*endo*/*exo*,8-*exo*-8-[(*tert*-Butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylate (21 and 22). A solution of the diester **20** (295 mg, 1.15 mmol), *tert*-butyldimethylsilyl chloride (295 mg, 1.96 mmol), and DBU (245 mg, 1.61 mmol) in 11 mL of CH_2Cl_2 was stirred at 21 °C overnight. Methanol (5 mL) was added, and the mixture was stirred for 10 min before it was washed with saturated aqueous NH_4OH. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give 469 mg of the crude product as a viscous oil. Chromatography of this material (5:1 hexanes/Et_2O) afforded 361 mg (85% yield) of the silyl ether epimers **21** and **22** as a light yellow oil: IR (CCl_4) 2960, 2860, 1770, 1740, 1250, 1080 cm^{-1}; ^1H NMR δ 6.05 (s, 2), 4.29 (dd, 1, J = 10.1, 5.2), 4.14 (br s, 1), 4.01 (br s, 1), 3.75 (s, 6), 1.81–2.02 (m, 4), 0.87 (s, 9), 0.09 (s, 6); ^{13}C NMR δ 174.7, 172.0, 132.1, 129.2, 73.6, 68.6, 66.4, 66.3, 52.2, 52.1, 41.4, 33.7, 28.5, 25.6, 25.5, 17.9, −4.7, −4.9. Anal. Calcd for $C_{18}H_{30}O_6Si$: C, 58.35; H, 8.16; Si, 7.58. Found: C, 58.08; H, 8.13; Si, 7.40.

Dimethyl 3-*endo*,8-*exo*-8-[(*tert*-Butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylate (22). A 1.9-g sample (5.1 mmol) of the epimeric mixture of silyl diesters described above was dried by evaporation twice from 3 mL of CH_3CN/benzene, dissolved in 20 mL of THF, and added dropwise to a stirring solution of lithium tetramethylpiperidide (15.4 mmol, prepared at 0 °C from 6.5 mL of a 2.37 M solution of *n*-BuLi in hexanes and freshly distilled 2,2,6,6-tetramethylpiperidine, 2.18 g, 15.4 mmol) in 40 mL of THF at −78 °C. After 1.2 h, the reaction mixture was transferred quickly via cannula to a rapidly stirring solution of NH_4Cl (8 g) in liquid anhydrous ammonia at −78 °C. This mixture was stirred at −78 °C for 20 min, and the ammonia was allowed to evaporate. Dilution of the residue with saturated aqueous $NaHCO_3$ and extraction of the aqueous layer with CH_2Cl_2 (3 × 20 mL) followed by drying (Na_2SO_4) and evaporation afforded 1.97 g of crude product. Purification of this material (6:1 hexanes/Et_2O) yielded 1.47 g (77% yield) of the endo diester **22** as a clear oil (no exo isomer **21** was observed by NMR): IR (CCl_4) 2965, 2935, 2865, 1750, 1740, 1240 cm^{-1}; ^1H NMR δ 5.94 (dd, 1, J = 10.2, 1.4), 5.73 (ddd, 1, J = 9.9, 4.1, 1.1), 4.41 (dd, 1, J = 7.3, 1.9), 4.32 (m, 1), 4.11 (m, 1), 3.74 (s, 3), 3.68 (s, 3), 2.46 (dt, 1, J = 13.6, 2.1), 2.22 (d, 1, J = 7.5), 2.18 (m, 1), 1.95 (br dd, 1, J = 13.1, 4.4), 0.88 (s, 9), 0.10 (s, 3), 0.09 (s, 3); ^{13}C NMR δ 174.9, 173.2, 130.3, 130.2, 73.2, 69.3, 65.5, 52.3, 51.7, 40.0, 32.0, 27.7, 25.7, 18.0, −4.6, −4.9. Anal. Calcd for $C_{18}H_{30}O_6Si$: C, 58.35; H, 8.16. Found: C, 58.19; H, 7.95.

Preparation of 3-*exo*,8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, 3-Ethyl 5-[2-(Trimethylsilyl)ethyl] Diester (24). 3-*exo*,8-*exo*-8-[1,2-Dioxo-2-[2-(trimethylsilyl)ethoxy]ethoxy]-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, Bis[2-(trimethylsilyl)ethyl ester]. A suspension of 0.250 g (0.821 mmol) of the dried dipotassium salt of **9** in 5 mL of CH_2Cl_2 and 0.030 mL of pyridine was cooled in an ice bath and treated with 0.30 mL (3.69 mmol) of oxalyl chloride. After being stirred at 21 °C for 4.5 h, the mixture was filtered through Celite, evaporated, dissolved in CH_2Cl_2, and reevaporated. A solution of this acid chloride in 10 mL of CH_2Cl_2 was treated with 0.30 mL of pyridine followed by 0.43 g (3.6 mmol) of 2-(trimethylsilyl)ethanol and stirred for 16 h. The mixture was partitioned between ether and 2 N HCl, and the ether was washed with brine, dried ($MgSO_4$), and evaporated to a dark oil. Chromatography (4:1 hexane/EtOAc) of the residue gave 0.243 g (49%) of a white solid: mp 91–94 °C; IR (film) 1768, 1743, 1730, 1249, 1163, 836 cm^{-1}; ^1H NMR δ 6.31 (d, 1, J = 10.3), 6.16 (ddd, 1, J = 10.1, 3.8, 1.1), 5.22 (d, 1, J = 3.0), 4.39–4.29 (m, 3), 4.27–4.16 (m, 5), 2.13–1.88 (m, 4), 1.17–0.095 (m, 6), 0.02 (s, 27). Anal. Calcd for $C_{27}H_{48}O_9Si_3$: C, 53.96; H, 8.05. Found: C, 53.80; H, 7.89.

3-*exo*,8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, Bis[2-(trimethylsilyl)ethyl ester]. A solution of 2.60 g (4.33 mmol) of the above oxalate in 30 mL of ethanol was treated with 0.11 g (0.8 mmol) of powdered K_2CO_3 and stirred at 21 °C for 20 min. Acetic acid (0.10 mL, 1.6 mmol) was added, and the mixture was evaporated and chromatographed (2:1 hexane/EtOAc) to give 1.82 g (98%) of the diester as a white solid; this material proved to be a 6:1 mixture of epimers at C-7. The major 7-exo isomer was isolated in pure form from the chromatography: mp 104–106 °C; IR ($CDCl_3$) 3630, 2970, 1730 cm^{-1}; ^1H NMR δ 6.17 (s, 2), 4.46–4.20 (m, 8), 2.01–1.89 (m, 4), 1.05–0.98 (m, 4), 0.05 (s, 9), 0.04 (s, 9). Anal. Calcd for $C_{20}H_{36}O_6Si_2$: C, 56.04; H, 8.47. Found: C, 55.94; H, 8.37.

3-*exo*,8-*exo*-8-Hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, 3-Ethyl 5-[2-(Trimethylsilyl)ethyl] Diester (24). A solution of 1.02 g (2.38 mmol) of the above bis-[2-(trimethylsilyl)ethyl ester] in 30 mL of dry ethanol was treated with 0.168 g (1.22 mmol) of anhydrous powdered K_2CO_3 and stirred for 3 h and 20 min at 21 °C. Acetic acid (0.5 mL) was added, and the mixture was evaporated and chromatographed (2:1 hexane/EtOAc) to give 0.565 g (66%) of the mixed diester **24** as a colorless solid: mp 97–100 °C; IR (film) 3488, 1741, 1725, 1227 cm^{-1}; ^1H NMR δ 6.12 (br s, 2), 4.22–4.16 (m, 5), 4.06 (br s,

1), 1.96–1.85 (m, 6), 1.23 (t, 3, J = 7.1), 1.01–0.94 (m, 2), 0.02 (s, 9). Anal. Calcd for $C_{17}H_{28}O_6Si$: C, 57.28; H, 7.92. Found: C, 57.21; H, 7.76.

3-*exo*,8-*exo*-8-(1-Methoxy-1-methylethoxy)-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, 3-Ethyl 5-[2-(Trimethylsilyl)ethyl] Diester (25). A solution of 0.520 g (1.46 mmol) of the mixed diester **24** in 25 mL of THF was treated with 2.79 mL (29.2 mmol) of 2-methoxypropene followed by 5 mg of pyridinium p-toluenesulfonate and 0.9 g of 3-Å molecular sieves. The mixture was stirred at 23 °C for 24 h, stored at 0 °C for 17 h, stirred with 25 mg of powdered K_2CO_3 for 45 min, and evaporated. Chromatography of the residue (4:1 hexane/EtOAc) gave 0.468 g (75%) of ketal **25** as a colorless oil. The remainder of the product proved to be starting material, recovered in a later chromatographic fraction. **25**: IR (film) 1763, 1733, 1375, 1245 cm^{-1}; ^1H NMR δ 6.27–6.03 (m, 2), 4.29–4.15 (m, 6), 4.08 (br s, 1), 3.24 (s, 3), 2.03–1.82 (m, 4), 1.37 (s, 3), 1.35 (s, 3), 1.26 (t, 3, J = 7.0), 1.05–0.95 (m, 2), 0.02 (s, 9). Anal. Calcd for $C_{21}H_{36}O_7Si$: C, 58.85; H, 8.47. Found: C, 58.66; H, 8.39.

8-*exo*-3-Nitro-8-(1-methoxy-1-methylethoxy)-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, 3-Ethyl 5-[2-(Trimethylsilyl)ethyl] Diester (26). A solution of lithium diisopropylamide (0.51 mmol) in 5 mL of THF at −78 °C was treated dropwise over 25 min with a solution of 0.200 g (0.467 mmol) of ketal diester **25** in 2.5 mL of THF. The resulting mixture was stirred at −78 °C for 1.25 h and treated dropwise over 18 min with a solution of 0.189 g (1.46 mmol) of acetone cyanohydrin nitrate in 1.5 mL of THF. The mixture was warmed over 30 min to −40 °C and held at −40 °C for 40 min, and the reaction was quenched by the addition of 8 mL of 1 M (pH 5.7) potassium phosphate buffer. The mixture was extracted with ether, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated. After 20 h under high vacuum, the resulting yellow oil was chromatographed (4:1 hexane/EtOAc) to give 0.113 g (51% yield) of the nitro compound **26** as a colorless oil: IR (film) 1764, 1736, 1570, 1375, 1249 cm^{-1}; ^1H NMR δ 6.04 (dd, 1, J = 10.0, 1.5), 5.76 (ddd, 1, J = 10.0, 4.6, 1.4), 4.77 (ddd, 1, J = 4.0, 2.5, 1.5), 4.32–4.18 (m, 5), 3.23 (s, 3), 3.17 (dd, 1, J = 4, 2.5), 2.66 (d, 1, J = 15.4), 2.32 (dd, 1, J = 13.7, 2.0), 1.94 (dd, 1, J = 13.7, 4.7), 1.40 (s, 3), 1.36 (s, 3), 1.29 (t, 3, J = 7.1), 1.07–0.96 (m, 2), 0.05 (s, 9). Anal. Calcd for $C_{21}H_{35}NO_9Si$: C, 53.26; H, 7.45; N, 2.96. Found: C, 53.24; H, 7.47; N, 2.98.

8-*exo*-3-Nitro-8-(1-methoxy-1-methylethoxy)-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, 3-Ethyl Ester (27). A solution of 0.019 g (0.040 mmol) of the nitro derivative **26** in 1 mL of THF was treated with 0.20 mL (0.20 mmol) of 1 M tetrabutylammonium fluoride in THF. After 10 min, the mixture was partitioned between 2 mL of water and ether, and the combined ether layers were washed with brine, dried ($MgSO_4$), and evaporated to give 0.020 g (81%) of the tetrabutylammonium salt of **27** as a colorless oil: IR (film) 1755, 1590, 1574, 1380, 1215 cm^{-1}; ^1H NMR 6.08 (ddd, 1, J = 10.0, 1.2, 1.2), 5.78–5.69 (m, 1), 4.79–4.72 (m, 1), 4.31–4.14 (m, 3), 3.23 (s, 3), 3.16 (dd, 1, J = 15.4, 2.4), 3.02–2.92 (m, 8), 2.69 (d, 1, J = 15.4), 2.32 (br d, 1, J = 13.6), 1.93 (dddd, 1, J = 13.6, 5.2, 2.5, 1.0), 1.75–1.62 (m, 8), 1.45–1.16 (m, 17), 0.96 (t, 12, J = 8.0).

A solution of 0.024 g (0.04 mmol) of this salt in 1 mL of chloroform was chromatographed on a partition column of 12 mL of silica coated with 0.05 N H_2SO_4, eluting with chloroform. The elutant was dried ($MgSO_4$), passed through a short column of $MgSO_4$, and evaporated to give 9 mg (60%) of the acid **27** as a colorless oil: IR (film) 3500, 1759, 1733, 1567, 1210, 1032 cm^{-1}; ^1H NMR δ 6.05 (dd, 1, J = 9.9, 1.6), 5.81 (ddd, 1, J = 9.9, 4.7, 1.3), 5.77–5.50 (br s, 1), 4.79 (br s, 1), 4.36–4.18 (m, 3), 3.24 (br s, 3.5), 3.16 (d, 0.5, J = 2.0), 2.72 (d, 1, J = 15.6), 2.36 (br d, 1, J = 13.6), 1.96 (dd, 1, J = 13.6, 5.2), 1.41 (s, 3), 1.37 (s, 3), 1.29 (t, 3, J = 7.1).

8-*exo*-3-Nitro-8-hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, 3-Ethyl Ester (28). A solution of 9 mg (0.024 mmol) of protected nitro ester **27** in 1.0 mL of 2-propanol was treated with 0.05 mL of a 0.74 mM solution of anhydrous pyridine hydrochloride in 2-propanol. The mixture was stirred at 21 °C for 20 min and evaporated to give a quantitative yield of the deprotected nitro ester **28** and pyridine hydrochloride. **28**: IR (film) 3400, 1750, 1732, 1575 cm^{-1}; ^1H NMR δ 6.05 (dd, 1, J = 10.0, 1.7), 5.84 (ddd, 1, J = 10.0, 4.5, 1.4), 4.78 (br s, 1), 4.35–4.06 (m, 3), 3.12 (d, 1, J = 15.7), 2.72 (d, 1, J = 15.7), 2.28 (br d, 1, J = 13.8), 1.87 (dd, 1, J = 13.8, 5.0), 1.28 (t, 3, J = 7.2).

3-*exo*,8-*exo*-8-[(*tert*-Butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic Acid, Bis[2-(trimethylsilyl)ethyl ester] (30). A solution of 1.00 g (2.33 mmol) of the corresponding hydroxy diester described above in the preparation of **24**, 0.703 g (4.67 mmol) of *tert*-butyldimethylsilyl chloride, 0.65 mL (4.66 mmol) of triethylamine, and 0.085 g (0.7 mmol) of 4-(dimethylamino)pyridine in 12 mL of CH_2Cl_2 was stirred for 12 h. After partitioning between additional CH_2Cl_2 and water, the organic layer was washed with brine, dried ($MgSO_4$), evaporated, and chromatographed (8:1 hexane/ether) to afford 1.17 g (92% yield) of **30** as a white solid: mp 61.5–67 °C; IR (film) 2970, 1732 cm^{-1}; ^1H NMR δ 6.03 (br s, 2), 4.27–4.19 (m, 5), 4.12 (m, 1), 4.00 (t, 1, J = 2.0), 2.02–1.85 (m, 4), 1.04–0.97 (m, 4), 0.87 (s, 9), 0.09 (s), 0.08 (s), 0.05 (s), 0.035 (s) (24 total); ^{13}C NMR δ 174.4 (s), 171.7 (s), 131.9 (d), 129.4 (d), 73.6 (d), 68.7 (d), 66.5 (d), 63.4 (m), 41.4 (s), 33.8 (t), 28.5 (t), 25.6 (q), 17.9 (s), 17.3 (t), 17.2 (t), −1.6 (q), −4.7 (q), −4.9 (q). Anal. Calcd for $C_{26}H_{50}O_6Si_3$: C, 57.52; H, 9.28. Found: C, 57.35; H, 9.14.

(1α,4α,5β)-1-Carboxy-4,5-dihydroxy-α-oxo-2-cyclohexenepropanoic Acid, Dipotassium Salt (32). A mixture of 0.024 mmol of the nitro ester **28** and pyridine hydrochloride from the above procedure was treated with a solution of 40 mg of K_2CO_3 in 1 mL of D_2O. After 5 min at 21 °C, the NMR spectrum showed complete conversion to the keto acid **32**. The solution was lyophilized to give a yellow solid: IR (Nujol) 3458, 1621, 1564 cm^{-1}; ^1H NMR (D_2O) δ 5.79 (ddd, 1, J = 10.1, 1.9, 1.8), 5.61 (dd, 1, J = 10.1, 1.8), 4.06 (ddd, 1, J = 8.0, 1.9, 1.9), 3.78 (ddd, 1, J = 12.0, 8.3, 3.7), 3.21 (d, 1, J = 17.6), 3.03 (d, 1, J = 17.6), 2.28 (ddd, 1, J = 12.6, 3.4, 1.6), 1.60 (dd, 1, J = 12.8, 12.6); ^{13}C NMR (D_2O) δ 214.4, 192.2, 180.4, 142.7, 140.1, 83.2, 81.2, 59.5, 49.2.

(3*E*)-8-*exo*-3-Hydroximino-8-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.1]non-6-ene-5-carboxylic Acid, 2-(Trimethylsilyl)ethyl Ester (34). A solution of lithium diisopropylamide (0.336 mmol) in 2 mL of THF at −78 °C was treated dropwise over 12 min with a solution of 0.44 g (0.306 mmol) of diester **30** in 1 mL of THF. This mixture was stirred at −78 °C for 80 min and treated dropwise over 12 min with 0.123 mL (0.918 mmol) of isoamyl nitrite in 1 mL of THF. The reaction mixture was allowed to warm to −38 °C over 30 min and held at this temperature for 1.5 h. The mixture was partitioned between saturated aqueous NH_4Cl and ether, and the ether layer was washed with brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue (2:1 hexane/EtOAc) gave 0.037 g (28%) of the *E* hydroximinolactone **34** as a colorless oil: IR (film) 3346, 1734, 1622, 1252, 1076, 838 cm^{-1}; ^1H NMR δ 6.01 (dd, 1, J = 10.1, 1.5), 5.78 (ddd, 1, J = 10.1, 4.3, 1.4), 4.54 (br s, 1), 4.26–4.19 (m, 2), 4.04 (br s, 1), 2.58 (s, 2), 2.37 (dd, 1, J = 12.9, 0.9), 2.09 (dddd, 1, J = 12.9, 3.6, 0.7, 0.7), 1.60 (br s, 1), 1.03–0.96 (m, 2), 0.85 (s, 9), 0.08 (s, 3), 0.07 (s, 3), 0.03 (s, 9); ^{13}C NMR δ 178.1 (s), 135.1 (d), 132.6 (d), 81.7 (s), 70.5 (d), 68.8 (t), 45.7 (s), 39.1 (t), 32.0 (t), 30.5 (q), 22.7 (s), 22.0 (t), 3.3 (q), 0.3 (q). Anal. Calcd for $C_{20}H_{37}NO_5Si_2$: C, 56.16; H, 8.72; N, 3.28. Found: C, 56.47; H, 8.85; N, 3.23.

A second, similar compound (0.029 g, 22% yield), presumed to be the *O*-nitrite of the *Z* isomer **35**, was isolated from the above chromatography as a yellow oil: IR (film) 3270, 1730, 1667, 1250, 1072, 834 cm^{-1}; ^1H NMR δ 6.04 (dd, 1, J = 9.9, 1.3), 5.76 (ddd, 1, J = 9.9, 4.2, 1.0), 4.40 (br s, 1), 4.27–4.20 (m, 2), 4.07 (br s, 1), 3.24 (br d, 1, J = 16.7), 2.43 (br d, 1, J = 16.0), 2.30 (br d, 1, J = 13.2), 2.10 (dd, 1, J = 13.2, 4.2), 1.04–0.93 (m, 2), 0.85 (s, 9), 0.08 (s, 3), 0.07 (s, 3), 0.03 (s, 9).

(3*Z*)-8-*exo*-3-Hydroximino-8-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.1]non-6-ene-5-carboxylic Acid, 2-(Trimethylsilyl)ethyl Ester (35). An ether solution of 70 mg of the presumed nitrite described above was shaken with a solution of saturated aqueous $FeSO_4$. The ether solution was washed with water and brine, dried ($MgSO_4$), and evaporated to give 17 mg of an oil, which was chromatographed (4:1 hexane/EtOAc). The slower eluting compound (4 mg) proved to be the *E* hydroximinolactone **34**; the faster eluting material was 6 mg of the *Z* hydroximinolactone **35**: IR (film) 3442, 1734, 1646, 1468, 1255, 1075, 840 cm^{-1}; ^1H NMR δ (dd, 1, J = 10.1, 1.6), 5.77 (ddd, 1, J = 10.1, 4.4, 1.3), 4.57 (br s, 1), 4.26–4.20 (m, 2), 4.02 (dd, 1, J = 3.4, 3.4), 2.79 (dd, 1, J = 15.9, 2.7), 2.63 (d, 1, J = 15.9), 2.40 (d,

1, J = 13.7), 2.08 (dd, 1, J = 13.7, 4.2), 1.60 (br s, 1), 1.02–0.95 (m, 2), 0.86 (s, 9), 0.10 (s, 3), 0.08 (s, 3), 0.03 (s, 9); MS, m/z 426 (M − 1), 412 (M − 15), 398, 384, 368, 342.

Dimethyl 3-*exo*,6-*exo*-6-Hydroxy-7-bicyclo[3.3.1]nonene-1,3-dicarboxylate (36). Dimethyl ester **52** (see below) (0.164 g, 0.643 mmol) that had been dried by evaporation from CH_3CN was dissolved in 3.3 mL of dry CH_3CN along with triphenylphosphine (0.029 g, 0.110 mmol) and cooled to 0 °C under nitrogen. Trimethylsilyl bromide (0.17 mL, 0.197 g, 0.286 mmol) was added, and the solution was warmed to room temperature over 2 h. DBU (0.27 mL, 0.274 g, 1.80 mmol) was added, and the reaction mixture was heated to reflux for 16 h. After cooling, ether was added to precipitate the DBU·HBr salts and the solid was washed thoroughly with ether. The supernatant was evaporated, and 3 mL of THF was added. The cloudy solution was brought to pH 1 with 6 N HCl and stirred at 21 °C for 2 h. After dilution with 10 mL of CH_2Cl_2, the mixture was washed twice with saturated $NaHCO_3$. The aqueous layer was back-extracted with CH_2Cl_2 (2 × 10 mL), and the organic layers were combined, dried (Na_2SO_4), and evaporated to yield 0.209 g of the crude allylic alcohol **36** as a colorless oil. An analytically pure sample could be obtained by chromatography (55% EtOAc/hexanes) (80% yield) or by recrystallization from diisopropyl ether: mp 73–75 °C; IR 3610, 3020, 2960, 1730, 1440, 1260, 1075, 1015 cm^{-1}; ^1H NMR δ 6.07 (ddd, 1, J = 1.1, 3.5, 10.0), 6.03 (dd, 1, J = 1.3, 10.0), 3.87 (br d, 1, J = 3.0), 3.73 (s, 3), 3.66 (s, 3), 2.51 (dddd, 1, J = 4.6, 4.6, 12.7, 12.7), 2.26 (br m, 1), 1.93 (br d, 1, J = 14.0), 1.9 (br m, 2), 1.79 (d, 1, J = 12.4), 1.59–1.74 (m, 3); ^{13}C NMR δ 175.7, 175.5, 131.4, 131.0, 67.8, 52.1, 51.7, 43.5, 36.1, 35.3, 32.8, 31.1, 29.0. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.39; H, 7.15. Found: C, 61.31; H, 7.20.

Ethyl 1-(Methoxycarbonyl)-β-oxo-3-cyclohexenebutanoate (37). Monomethyl malonate (1.32 g, 10.0 mmol) was dissolved in THF (25 mL) containing a few milligrams of 2,2′-bipyridyl as indicator and cooled to −78 °C. *n*-Butyllithium (13.5 mL of a 1.54 M solution, 20.0 mmol) was added slowly while the temperature was allowed to rise to −5 °C. When a persistent red color was obtained, the heterogeneous solution was recooled to −78 °C and a solution of acid chloride **15** (1.08 g, 5.0 mmol) dissolved in 1 mL of THF was added slowly. The mixture was stirred at −78 °C for 30 min and then partitioned between ether (40 mL) and 5% HCl saturated with NaCl (20 mL). The aqueous layer was extracted twice with ether, and the combined organic phase was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed (25% EtOAc/hexane) to yield 1.056 g (79%) of the β-keto ester **37**: IR (CCl_4) 2955, 1745, 1725, 1233 cm^{-1}; ^1H NMR δ 5.64 (m, 2), 4.19 (q, 2, J = 7.1), 3.68 (s, 3), 3.41 (s, 2), 2.99 (d, 1, J = 18.4), 2.87 (d, 1, J = 18.4), 2.40–2.66 (m, 1), 1.80–2.05 (m, 5), 1.27 (t, 3, J = 7.1); ^{13}C NMR δ 200.6, 176.5, 176.4, 166.7, 125.3, 124.2, 61.0, 51.7, 49.4, 47.2, 41.8, 32.2, 29.0, 21.7, 13.8. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.76; H, 7.47.

3-Oxotricyclo[3.3.1.0^{2,8}]nonane-2,5-dicarboxylic Acid, 2-Ethyl 5-Methyl Diester (40). A solution of β-keto ester **37** (0.300 g, 1.12 mmol), *N*-(phenylseleno)phthalimide (0.372 g, 1.23 mmol), and $SnCl_4$ (0.13 mL, 0.292 g, 1.12 mmol) in CH_2Cl_2 (12 mL) was stirred at 21 °C. After 20 h, starting material was still apparent by TLC, so additional NPSP was added every 30 min until starting material was consumed. The reaction mixture was then cooled to 0 °C and diluted with petroleum ether to precipitate the phthalimide. After filtration, the solution was washed with saturated $NaHCO_3$, which was back-extracted with EtOAc. The combined organic phase was dried (Na_2SO_4), filtered, and evaporated to give a yellow solid, which was shown by ^1H NMR to be predominantly the chloride **39**, contaminated with residual diphenyl diselenide. This material was redissolved in CH_2Cl_2 (35 mL) with DBU (0.42 mL, 0.426 g, 2.8 mmol), and the solution was stirred at 21 °C for 4 h and then washed with saturated NH_4Cl. The organic layer was dried (Na_2SO_4), filtered, and evaporated, and the residue was chromatographed (30% EtOAc/hexane) to give 0.249 g (85% yield) of the cyclopropane **40**: IR (CCl_4) 2950, 1740, 1708, 1270, 1221, 1088 cm^{-1}; ^1H NMR δ 4.18 (q, 2, J = 7.0), 3.70 (s, 3), 2.57 (d, 1, J = 18.7), 2.48 (d, 1, J = 18.7), 2.24–2.40 (m, 4), 1.70–1.93 (m, 4), 1.27 (t, 3, J = 7.0); ^{13}C NMR δ 201.0, 175.3, 169.2, 61.3, 52.3, 44.8, 42.0, 41.2, 29.1, 27.6, 26.7, 17.2, 14.0; MS, m/z 266. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.99; H, 6.77.

6-*exo*-3-Oxo-6-(phenylseleno)bicyclo[3.3.1]nonane-1,4-dicarboxylic Acid, 1-Methyl 4-Ethyl Diester (41). A solution of lithium phenyl selenide in THF was generated by dissolving diphenyl diselenide (0.175 g, 0.56 mmol) in THF (3 mL) at −78 °C and adding lithium triethylborohydride (2.5 mL of a 0.5 M solution, 0.12 mmol) until the yellow solution turned clear and colorless. The anion solution was warmed to 21 °C and added slowly to a solution of cyclopropane **40** (0.23 g, 0.86 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, diluted with saturated NH_4Cl, and extracted twice with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and evaporated, and the residue was chromatographed (7% EtOAc/hexane) to give 0.310 g (86% yield) of the phenyl selenide **41** as a colorless oil: IR (CCl_4) 1738, 1650, 1618, 1290, 1220, 1078 cm^{-1}; ^1H NMR δ 7.57–7.61 (m, 2), 7.24–7.30 (m, 3), 4.16, 4.15 (2 q, 2, J = 7.1), 3.72 (s, 3), 3.69 (br s, 1), 3.09 (m, 1), 2.86 (d, 1, J = 19.6), 2.47 (dd, 1, J = 2.0, 13.0), 2.33 (dd, 1, J = 1.0, 19.6), 1.60–2.12 (m, 4), 1.0 (t, 3, J = 7.1); ^{13}C NMR δ 176.6, 173.3, 171.0, 134.1, 130.1, 128.9, 127.2, 100.5, 60.4, 52.2, 44.4, 41.4, 36.9, 33.0, 31.7, 29.3, 29.2, 23.7, 23.5, 14.2. Anal. Calcd for $C_{20}H_{24}SeO_5$: C, 56.73; H, 5.72. Found: C, 57.01; H, 5.65.

Methyl 6-*exo*-3-Oxo-6-(phenylseleno)bicyclo[3.3.1]nonane-1-carboxylate (42). A solution of β-keto ester **41** (3.3 g, 7.7 mmol) in 8 mL of DMSO and 0.30 mL (15.5 mmol) of water was heated to 150 °C under nitrogen for 3.25 h. After cooling to room temperature, water and NaCl were added and the mixture was extracted three times with Et_2O. The combined ether layers were washed with brine, dried (Na_2SO_4), and evaporated to give 2.7 g (100% yield) of **42** as a yellow oil, which was carried on to the next step without purification. An analytically pure sample could be obtained (74% yield) by chromatography (25% EtOAc/hexanes): mp 86–89 °C; IR 2496, 1740, 1715, 1480, 1460, 1440, 1410, 1350, 1330, 970 cm^{-1}; ^1H NMR δ 7.52–7.56 (m, 2), 7.26–7.31 (m, 3), 3.74 (s, 3), 3.57 (s, 1), 2.37–2.73 (m, 6), 2.19–2.28 (m, 1), 1.93 (d, 1, J = 13.3), 1.80–1.87 (m, 2), 1.73 (ddd, 1, J = 13.0, 5.7, 3.3); ^{13}C NMR δ 209.1, 175.7, 134.1, 129.2, 129.0, 127.5, 52.1, 48.4, 46.7, 46.0, 44.1, 35.0, 30.3, 29.7, 29.5, 23.7. Anal. Calcd for $C_{17}H_{20}SeO_3$: C, 58.11; H, 5.75. Found: C, 58.34; H, 5.85.

Methyl 3-Oxo-6-bicyclo[3.3.1]nonene-1-carboxylate (43), from Oxidative Elimination of Selenide 42. To a solution of selenide **42** (1.5 g, 4.3 mmol) in THF (15 mL) was added 30% H_2O_2 (1.3 mL, 12.9 mmol) slowly, with the reaction mixture kept at 21 °C with a water bath. After the reaction mixture was stirred for 1.5 h, triethylamine (0.87 g, 8.6 mmol) was added, and the solution changed in color from yellow to colorless to rose and back to yellow during the course of the elimination reaction. After 2 h, the mixture was partitioned between Et_2O and 2 N HCl, and the organic phase was washed twice with acid and with saturated $NaHCO_3$/brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed (30% EtOAc/hexanes) to yield 0.75 g (90% yield) of ketone **43** as a white crystalline solid: mp 71–72.5 °C; IR (CCl_4) 2960, 1738, 1722, 1438, 1240, 1062 cm^{-1}; ^1H NMR δ 5.74 (dd, 1, J = 10.0, 1.2), 5.65 (dd, 1, J = 10.0, 2.1), 3.73 (s, 3), 2.82 (br s, 1), 2.11–2.73 (m, 8); ^{13}C NMR δ 209.2, 176.2, 129.7, 124.6, 52.3, 50.3, 45.3, 44.2, 35.0, 32.4, 31.0. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.04; H, 7.19.

Methyl 3-Oxo-6-bicyclo[3.3.1]nonene-1-carboxylate (43), from Methylenation of 45 with the Tebbe Reagent. Generation of Tebbe reagent:[44b] Bis(cyclopentadienyl)titanium dichloride was purified by Soxhlet extraction with CH_2Cl_2. The titanocene dichloride (5.0 g, 20.0 mmol) was transferred to a flame-dried, 100-mL pear-shaped Schlenk flask in a glove box. A solution of trimethylaluminum in toluene (20 mL of a 2.0 M solution, 40.0 mmol) was syringed slowly into the flask under positive pressure of nitrogen, and the resulting deep red solution was allowed to stand at 21 °C under nitrogen for 60 h. The volatile material was removed under high vacuum, and the residual solid was recrystallized in degassed toluene (20 mL) and trimethylaluminum (3.6 mL of a 2.0 M solution). Dry hexane was carefully layered on top of this solution, and the mixture was cooled slowly to −20 °C. No evidence of crystal formation was apparent at −20 °C, hence the mixture was further cooled to −78 °C. The reagent was eventually isolated as a brown-red, powdery solid.

A solution of lactone **45** (see below) (0.098 g, 0.5 mmol) in THF (2 mL) was cooled to −40 °C. A deep maroon solution of the Tebbe

reagent (0.313 g, ca. 1.0 mmol) was prepared in 2 mL of toluene in the dry box and added slowly to the lactone, and the mixture was stirred at −40 °C for 30 min and then warmed at 21 °C for 1.5 h. After 4 h, no further change appeared to be taking place, so the mixture was diluted with 0.1 N sodium hydroxide at −10 °C. When gas evolution ceased, ether was added and the mixture was dried (Na_2SO_4), filtered through a pad of Celite, and evaporated. The residue was purified by chromatography (30% EtOAc/hexane) to yield 0.039 g (40%) of the ketone **43** and 0.029 g (30%) of recovered starting material.

Methyl 8-*exo*-8-Iodo-3-oxo-2-oxabicyclo[3.3.1]nonane-5-carboxylate (44). A solution of 0.750 g (3.41 mmol) of the sodium salt of **15** and 0.573 g (6.82 mmol) of $NaHCO_3$ in 50 mL of water was treated with a solution of 0.865 g (3.41 mmol) of iodine and 3.39 g (20.45 mmol) of KI in 25 mL of water. After being stirred for 11 h in the dark, the mixture was extracted several times with ether. The combined ether layers were washed with 30 mL of brine, dried ($MgSO_4$), and evaporated to give 0.80 g (72% yield) of the iodo lactone **44** as a white solid. A portion was recrystallized from hexane/diisopropyl ether: mp 89.8–92.5 °C; IR (film) 1740, 1200 cm^{-1}; ^1H NMR δ 4.86–4.73 (m, 1), 4.63–4.46 (m, 1), 3.61 (s, 3), 3.1–1.55 (m, 8). Anal. Calcd for $C_{10}H_{13}O_4I$: C, 37.05; H, 4.04; I, 39.15. Found: C, 37.09; H, 4.10; I, 39.12.

Methyl 3-Oxo-2-oxabicyclo[3.3.1]non-7-ene-5-carboxylate (45). A solution of 5.58 g (17.2 mmol) of iodo lactone **44** and 2.83 mL (18.9 mmol) of DBU in 80 mL of acetonitrile was heated at reflux for 5 h. The resulting mixture was partitioned between CH_2Cl_2 and 1 N HCl, the aqueous layer was extracted with additional CH_2Cl_2, and the combined organic layer was washed with brine, dried ($MgSO_4$), evaporated, and distilled [bulb-to-bulb, 160 °C (1.1 Torr)] to give 3.23 g (87% yield) of lactone **45** as a tan oil. A portion was purified from analysis by preparative GC (175 °C): IR (film) 1732, 1247, 1201, 1062 cm^{-1}; ^1H NMR δ 6.14–5.95 (m, 2), 4.89–4.86 (m, 1), 3.27 (s, 3), 3.19 (dd, 1, J = 19.0, 1.2), 2.75–2.10 (m, 5). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found: C, 61.06; H, 6.18.

Methyl 7-Methylidene-3-bicyclo[3.3.1]nonene-1-carboxylate (48), from Reaction of Ketone 43 with the Nozaki Reagent. Preparation of reagent:[50] A suspension of activated zinc (2.85 g, 44.0 mmol) in dry THF (25 mL) was stirred in a flame-dried 50-mL round-bottomed flask under nitrogen at −40 °C. Freshly distilled dibromomethane (1.00 mL, 14.4 mmol) was added via syringe, followed by addition of distilled $TiCl_4$ (1.15 mL, 10.5 mmol) over a 5-min period. The gray suspension was warmed to 5 °C and then stirred at 0 °C under nitrogen for 3 days.

To a solution of ketone **43** (0.158 g, 0.81 mmol) in dry CH_2Cl_2 (6 mL) was added the solution of the $Zn–CH_2Br_2–TiCl_4$ complex (5 mL) at 21 °C via a syringe, and the reaction was monitored by TLC for disappearance of starting material. After 10 min, another 1.5 mL of the complex was added. After an additional 10-min period, the mixture was poured into a beaker containing saturated $NaHCO_3$ solution (20 mL) and Et_2O (10 mL). Vigorous bubbling was observed, and the mixture was stirred until the organic phase became clear (ca. 5 min). The heterogeneous mixture was filtered through Celite to remove insoluble salts, and the aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give a light orange oil (0.162 g), which was chromatographed (5% EtOAc/hexanes) to give 0.136 g (87% yield) of the diene **48**: IR 3020, 2940, 2850, 1730, 1445, 1255, 1075, 905 cm^{-1}; ^1H NMR δ 5.68 (ddd, 1, J = 10.0, 3.8, 2.7), 5.58 (m, 1), 4.81 (d, 1, J = 1.6), 4.61 (d, 1, J = 1.6), 3.69 (s, 3), 1.88–2.57 (m, 9); ^{13}C NMR δ 177.6, 143.4, 129.1, 125.7, 112.0, 51.6, 44.8, 42.5, 38.2, 34.2, 32.6, 30.9. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.38. Found: C, 75.06; H, 8.41.

Methyl 7-Methylidene-3-bicyclo[3.3.1]nonene-1-carboxylate (48), from Reaction of Lactone 45 with the Tebbe Reagent. The lactone **45** (0.140 g, 0.71 mmol) was dissolved in 2 mL of dry THF in a flame-dried flask under argon, the solution was cooled to −25 °C, and 2.5 mL of the Tebbe reagent (generated in situ)[44d] was added via syringe. The mixture was stirred for 30 min at −25 °C and then allowed to warm to room temperature for 9 h. After cooling of the mixture to 0 °C and addition of diethyl ether (5 mL), excess reagent was quenched by the dropwise addition of 0.3 mL of 0.1 N NaOH. The resulting slurry was stirred open to the atmosphere for 3 h, further diluted with ether, and filtered through Celite. The filtrate was evaporated, and the residue was diluted with petroleum ether and again filtered through Celite and evaporated. The crude product was chromatographed (20% EtOAc/hexanes) to give 0.026 g (19% yield) of the intermediate ketone **43** and 0.073 g (52% yield) of the diene **48**.

Methyl (1′*R,2′*R**,4′*S**,6′*R**,8′*S**)-Spiro[oxirane-2,8′-[3]oxatricyclo[4.3.1.$0^{2,4}$]decane]-6′-carboxylate (49).** To a solution of diene **48** (0.78 g, 4.16 mmol) in 45 mL of dry CH_2Cl_2 was added *m*-chloroperbenzoic acid (3.30 g, 16.24 mmol), and the mixture, which became cloudy after 5 min, was stirred under nitrogen at 21 °C for 20 h. The mixture was washed with 1 M aqueous $NaHSO_3$ and saturated $NaHCO_3$/0.1 N NaOH, the aqueous layer was back-extracted twice with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed (40% EtOAc/hexanes) to give 0.90 g (98% yield) of diepoxide **49** as a white solid: mp 65–70 °C; IR 3020, 2970, 1735, 1490, 1450, 1440, 1410, 1255, 1075, 1020, 825 cm^{-1}; ^1H NMR δ 3.68 (s, 3), 3.15 (dd, 1, J = 4.2, 4.2), 3.08 (m, 1), 2.69 (dd, 2, J = 15.0, 1.7), 2.64 (m, 1), 2.45–2.54 (m, 1), 2.07–2.14 (m, 2), 1.96–2.03 (m, 2), 1.33–1.52 (m, 3); ^{13}C NMR δ 176.0, 55.8, 55.1, 54.9, 52.1, 49.8, 43.1, 40.4, 35.2, 31.9, 29.8, 27.4. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.94; H, 7.06.

Methyl (1*R,2*S**,4*R**,6*S**,8*R**)-8-Formyl-3-oxatricyclo-[4.3.1.$0^{2,4}$]decane-6-carboxylate (50).** The diepoxide **49** (0.100 g, 0.45 mmol) was dissolved in 8 mL of dry CH_2Cl_2, and the solution was cooled to −50 °C under a nitrogen atmosphere. Freshly distilled $BF_3{\cdot}Et_2O$ (0.41 mL, 0.474 g, 3.34 mmol) was added via a syringe, and the reaction mixture was stirred for 1 min at −50 °C and quenched quickly by the addition of 10 mL of saturated aqueous $NaHCO_3$. This procedure was repeated on another 0.100 g of epoxide, and the combined CH_2Cl_2 layers from each reaction were evaporated, taken up in EtOAc, and washed twice with saturated $NaHCO_3$/brine. The aqueous layer was reextracted with EtOAc (2 × 20 mL), and the organic portions were combined and dried over Na_2SO_4. Evaporation yielded 0.20 g of crude material, which was chromatographed (40% EtOAc/hexanes) to give 0.108 g (54% yield) of the epoxy aldehyde **50**: IR 3020, 2940, 1725, 1250 cm^{-1}; ^1H NMR δ 9.62 (d, 1, J = 1.3), 3.68 (s, 3), 3.24 (dd, 1, J = 4.4, 4.4), 3.06 (m, 1), 2.73 (ddddd, 1, J = 13.1, 13.1, 4.1, 4.1, 1.3), 2.57 (m, 1), 2.51 (d, 1, J = 16.4), 2.02–2.10 (m, 2), 1.96 (dd, 1, J = 16.4, 4.8), 1.95 (dd, 1, J = 16.4, 4.8), 1.65 (ddd, 1, J = 13.3, 13.3, 1.6), 1.64 (dd, 1, J = 13.3, 13.3), 1.40 (br d, 1, J = 13.3); ^{13}C NMR δ 203.0, 176.7, 54.6, 52.1, 50.3, 42.8, 38.2, 35.2, 31.5, 27.8, 27.7, 26.9. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.21. Found: C, 64.03; H, 7.20.

(1*R,2*S**,4*R**,6*S**,8*R**)-3-Oxatricyclo[4.3.1.$0^{2,4}$]decane-6,8-dicarboxylic Acid, 6-Methyl Ester (51).** A solution of epoxy aldehyde **50** (0.152 g, 0.676 mmol) in *tert*-butyl alcohol (4.0 mL) and 5% aqueous NaH_2PO_4 (3.0 mL, pH 4.3) was stirred vigorously at 21 °C, and a 1 M $KMnO_4$ solution (4.0 mL) was added dropwise. After 20 min, the excess permanganate was destroyed by the dropwise addition of a saturated solution of Na_2SO_3 to give a brown colloidal suspension. This mixture was cooled to 0 °C, and 2 N HCl was added dropwise until the solution turned clear and colorless (pH 1). The aqueous solution was extracted with EtOAc (3 × 10 mL), and the combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give the acid ester **51** as a clear, colorless oil, which was carried on directly to the diester (see below): IR 2500–3000 (br), 3020, 2960, 1725, 1440, 1250, 1065 cm^{-1}; ^1H NMR δ 3.68 (s, 3), 3.25 (dd, 1, J = 4.3, 4.3), 3.07 (m, 1), 2.84 (dddd, 1, J = 13.0, 13.0, 4.3, 4.3), 2.45–2.53 (m, 2), 1.91–2.16 (m, 4), 1.81 (dd, 1, J = 13.3, 13.3), 1.80 (ddd, 1, J = 13.3, 13.3, 1.3), 1.43 (br d, 1, J = 13.3); ^{13}C NMR δ 180.7, 176.7, 54.7, 52.1, 50.5, 38.4, 37.7, 35.6, 31.4, 29.5, 28.0, 27.4; HRMS, m/z 240.1001 (calcd for $C_{12}H_{16}O_5$, m/z 240.0998).

Dimethyl (1*R,2*S**,4*R**,6*S**,8*R**)-3-Oxatricyclo-[4.3.1.$0^{2,4}$]decane-6,8-dicarboxylate (52).** The above acid ester **51** was dissolved in EtOAc and treated with ethereal diazomethane at 0 °C until the yellow color persisted for longer than 10 min. The solution was warmed to room temperature and evaporated to give 0.116 g (93% yield) of the dimethyl ester **52**. This material was recrystallized from diisopropyl ether: mp 67–68 °C; IR 3020, 2960, 1730, 1440, 1260, 1070, 1015 cm^{-1}; ^1H NMR δ 3.69 (s, 3), 3.66 (s, 3), 3.24 (dd, 1, J = 4.4, 4.4), 3.05 (m, 1), 2.81 (dddd, 1, J = 13.0, 13.0, 4.2, 4.2), 2.5 (m, 1), 2.46 (d, 1, J = 13.0), 2.10–1.91

(m, 4), 1.80 (ddd, 1, J = 13.2, 13.2, 1.8), 1.79 (dd, 1, J = 13.2, 13.2), 1.42 (br d, 1, J = 13.0); ^{13}C NMR δ 176.6, 175.3, 54.7, 52.0, 51.8, 50.4, 38.5, 38.0, 35.7, 31.5, 29.7, 28.0, 27.5. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.39; H, 7.15. Found: C, 61.27; H, 7.21.

Dimethyl 3-*exo*,6-*exo*-6-[(*tert*-Butyldimethylsilyl)oxy]-7-bicyclo[3.3.1]nonene-1,3-dicarboxylate (53). A solution of allylic alochol **36** (0.155 g, 0.608 mmol), DBU (0.138 g, 0.912 mmol), and *tert*-butyldimethylsilyl chloride (0.105 g, 0.695 mmol) in 4 mL of dry CH_2Cl_2 was stirred under nitrogen at 21 °C for 19 h. An additional 10 mL of CH_2Cl_2 was added, the solution was washed twice with saturated NH_4Cl, dried (Na_2SO_4), and evaporated, and the residue was chromatographed (10% EtOAc/hexanes) to afford 0.208 g of the silyl ether **53** (93% overall yield from the epoxide **52**): IR 3020, 2960, 2940, 2860, 1735, 1255, 1140 cm^{-1}; ^{1}H NMR δ 5.87–5.98 (m, 2), 3.18 (d, 1, J = 3.2), 3.71 (s, 3), 3.65 (s, 3), 2.50 (dddd, 1, J = 12.7, 12.7, 4.4, 4.4), 2.06–2.12 (m, 2), 1.84–1.94 (m, 2), 1.75 (d, 1, J = 12.7), 1.54–1.67 (m, 2), 0.88 (s, 9), 0.07 (s, 6); ^{13}C NMR δ 175.9, 175.6, 132.0, 68.5, 52.0, 51.6, 43.4, 36.2, 36.2, 33.2, 31.2, 29.0, 25.8, 18.1, -4.7, -5.0. Anal. Calcd for $C_{19}H_{32}SiO_5$: C, 61.91; H, 8.79. Found: C, 61.59; H, 8.76.

Dimethyl 3-*endo*,6-*exo*-6-[(*tert*-Butyldimethylsilyl)oxy]-7-bicyclo[3.3.1]nonene-1,3-dicarboxylate (54). A 0.23-g sample (0.64 mmol) of diester **53** was dried by evaporation twice from 1 mL of CH_3CN, dissolved in 1 mL of dry THF, and added dropwise to a stirring solution of lithium tetramethylpiperidide [1.91 mmol, prepared at 0 °C from 0.96 mL of a 1.99 M solution of n-BuLi in hexanes and 0.27 g (1.91 mmol) of freshly distilled 2,2,6,6-tetramethylpiperidine] in 4.5 mL of THF at -78 °C. After 1.2 h, the reaction mixture was cannulated into a rapidly stirring solution of NH_4Cl (2.55 g, 47.7 mmol) in anhydrous liquid ammonia at -78 °C. The heterogeneous mixture was stirred at -78 °C for 15 min, and the ammonia was allowed to evaporate. The solid residue was dissolved in saturated $NaHCO_3$, the solution was extracted three times with ether, and the organic layer was dried (Na_2SO_4) and concentrated to afford 0.27 g of crude product. Chromatography (10% EtOAc/hexanes) of this material furnished 0.12 g (52% yield) of the endo diester **54** as a clear oil (at least 20:1 ratio of endo/exo as observed by ^{1}H NMR): ^{1}H NMR δ 5.83 (dd, 1, J = 10.0, 1.3), 5.64 (ddd, 1, J = 10.0, 4.4, 1.3), 4.06 (d, 1, J = 4.3), 3.70 (s, 3), 3.59 (s, 3), 2.56 (dd, 1, J = 6.8, 6.8), 2.46 (dddd, 1, J = 13.6, 2.0, 2.0, 2.0), 2.41 (ddd, 1, J = 14.4, 1.7, 1.7), 2.15 (dddd, 1, J = 12.7, 2.5, 2.5, 2.5), 2.04–2.08 (m, 1), 1.86 (dd, 1, J = 13.6, 6.4), 1.66 (ddd, 1, J = 14.3, 7.3, 4.5), 1.63 (br d, 1, J = 12.7), 0.87 (s, 9), 0.07 (s, 3), 0.06 (s, 3); ^{13}C NMR δ 176.2, 175.0, 130.9, 130.3, 67.8, 52.0, 51.3, 42.9, 36.0, 35.8, 29.4, 27.3, 25.9, 18.2, -4.5, -4.8.

Dimethyl 3-*exo*,6-*exo*-3-Nitro-6-[(*tert*-butyldimethylsilyl)oxy]-7-bicyclo[3.3.1]nonene-1,3-dicarboxylate (55). Dimethyl ester **53** (25 mg, 0.068 mmol) was dried by evaporation from CH_3CN and dissolved in 200 μL of dry THF in a flame-dried flask, and the solution was cooled to -78 °C. In a separate flask was placed 0.135 mL of a 1 M solution of LDA in 3:1 hexane/THF, also cooled to -78 °C. The ester solution was transferred by cannula into the LDA solution, and the enolate was allowed to form for 1.5 h at -78 °C, at which time acetone cyanohydrin nitrate (0.09 mL, 0.103 g, 0.788 mmol) was added. The cooling bath was removed, and the reaction was monitored by TLC (5% EtOAc/toluene). After 50 min, the temperature had reached -30 °C and the reaction was quenched by the addition of a saturated NH_4Cl/brine solution (5 mL). The aqueous layer was extracted with ether (3 × 5 mL), and the organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed (3% EtOAc/toluene) to give 14 mg (50% yield) of the nitrated ester **55** along with 5 mg (20%) of unreacted starting material: IR 3020, 2960, 2940, 2860, 1730, 1550, 1465, 1440, 1255, 1060, 840 cm^{-1}; ^{1}H NMR δ 5.81 (dd, 1, J = 10.0, 1.4), 5.66 (ddd, 1, J = 10.0, 4.4, 1.2), 4.05 (d, 1, J = 4.1), 3.75 (s, 6), 2.96 (dddd, 1, J = 13.4, 1.9, 1.9, 1.9), 2.93 (ddd, 1, J = 13.4, 2.1, 2.1), 2.56 (d, 1, J = 13.3), 2.29–2.33 (m, 1), 2.25 (dddd, 1, J = 12.7, 2.0, 2.0, 2.0), 2.11 (dd, 1, J = 13.9, 5.8), 1.74 (br d, 1, J = 12.5), 0.88 (s, 9), 0.08 (s, 3), 0.07 (s, 3); ^{13}C NMR δ 174.4, 166.2, 131.0, 129.5, 92.6, 66.9, 53.2, 52.5, 42.6, 36.7, 35.9, 34.2, 28.8, 25.8, 18.1, -4.6, -4.9. Anal. Calcd for $C_{19}H_{31}NSiO_7$: C, 55.17; H, 7.57; N, 3.39 Found: C, 55.4; H, 7.7; N, 3.2.

Dimethyl 3-*exo*,6-*exo*-3-Nitro-6-hydroxy-7-bicyclo[3.3.1]nonene-1,3-dicarboxylate (56). A solution of silyl ether **55** (0.030 g, 0.073 mmol) in 1 mL of CH_3CN at 0 °C with one drop of 48% HF was stirred at 0 °C, and the reaction was monitored by TLC (20% EtOAc/hexanes) for the disappearance of starting material. After 3 h, the reaction was quenched by the addition of 5 mL of saturated $NaHCO_3$, the acetonitrile was removed by rotary evaporation, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was chromatographed (50% EtOAc/hexanes) to yield 0.016 g (74% yield) of the allylic alcohol **56**: IR 3600, 3020, 2960, 1730, 1550, 1460, 1440, 1260, 1070, 1010 cm^{-1}; ^{1}H NMR δ 5.89 (d, 1, J = 10.0), 5.81 (ddd, 1, J = 10.0, 4.3, 1.0), 4.11 (d, 1, J = 4.1), 3.00 (dddd, 1, J = 13.9, 1.9, 1.9, 1.9), 2.96 (ddd, 1, J = 13.5, 2.0, 2.0), 2.60 (d, 1, J = 13.4), 2.44–2.47 (m, 1), 2.19 (dddd, 1, J = 12.7, 2.3, 2.3, 2.3), 2.16 (dd, 1, J = 14.0, 5.8), 1.80 (br d, 1, J = 12.6); ^{13}C NMR δ 174.2, 166.2, 131.4, 130.0, 92.4, 66.3, 53.3, 52.6, 42.7, 35.8, 35.7, 34.1, 28.8. Anal. Calcd for $C_{13}H_{17}NO_7$: C, 52.16; H, 5.74; N, 4.68. Found: C, 51.99; H, 5.85; N, 4.49.

4-*exo*,7-*exo*-7-Nitro-4-hydroxy-2-bicyclo[3.3.1]nonene-1-carboxylic Acid (57). A solution of nitro diester **56** (16 mg, 0.054 mmol) in 0.5 mL of MeOH and 0.27 mL of 1 N NaOH was stirred at 21 °C for 19 h and then lyophilized to yield a white powder. The crude nitronate was dissolved in 100 mM TBK (pH 7.4) and lyophilized to afford the C-protonated nitro carboxylate as the triethylammonium salt: ^{1}H NMR (D_2O) δ 5.90 (d, 1, J = 10.0), 5.80 (dd, 1, J = 3.7, 10.0), 4.42 (dddd, 1, J = 4.7, 4.7, 12.1, 12.1), 3.79 (d, 1, J = 3.6), 3.0 (q, 6, J = 7.3), 2.17–2.10 (m, 3), 2.83 (dd, 2, J = 12.3, 12.3), 1.76 (br d, 1, J = 13.0), 1.49 (br d, 1, J = 12.5), 1.1 (t, 9, J = 7.3). Passage through a Dowex cation-exchange column (H^+ form) yielded the free acid **57**, which was purified by chromatography on silica gel (0.5% HOAc/EtOAc) to give 8 mg (67% yield) of material: ^{1}H NMR (D_2O) δ 5.85 (d, 1, J = 10.0), 5.61 (dd, 1, J = 10.0, 4.0), 3.74 (d, 1, J = 4.0), 2.75 (dd, 2, J = 6.3, 6.3), 2.07–2.16 (m, 3), 1.83 (d, 1, J = 13.1), 1.57 (d, 1, J = 13.0); ^{13}C NMR (D_2O) δ 184.0, 162.6, 135.5, 126.2, 68.5, 46.1, 36.0, 35.5, 31.1, 29.1. Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.85; H, 5.78; N, 6.16. Found: C, 52.86; H, 5.87; N, 6.00.

Enzymatic Evaluation. Chorismic acid was used as obtained from Sigma. Chorismate mutase–prephenate dehydrogenase derived from *E. coli* strain JFM-30 was a gift from the research group of Prof. J. Knowles (Harvard). The enzyme had been purified by ammonium sulfate fractionation and stored at -78 °C in a stabilizing buffer containing 0.1 N *N*-ethylmorpholine, 1 mM *erythro*-1,4-dimercapto-2,3-butanediol (DTE), 21 mM trisodium citrate, 1 mM EDTA, and glycerol (10% v/v), then adjusted to pH 7.0 with concentrated HCl. Stock solutions of the enzyme were prepared by dilution with this buffer and kept at 0 °C for at least 2 h to ensure complete activation. Prior to assay, the enzyme solution was clarified by centrifugation and the buffer and chorismate solutions were passed through a 0.45-μm Millipore filter.

The assay was performed at 30 °C in a buffer consisting of 50 mM *N*-ethylmorpholine, 0.5 mM DTE, 0.5 mM EDTA, 1 mM trisodium citrate, glycerol (10% v/v), and bovine serum albumin (0.1 mg/mL), adjusted to pH 7.5 with concentrated HCl. The total volume of the assay mixture was 1.2 mL. Conversion of chorismate to prephenate was monitored by following the decrease in absorbance at λ 274 nm ($\Delta\epsilon$ = 2630). Reaction was initiated by addition of enzyme to a solution of substrate (with or without inhibitor) preincubated at 30 °C. Enzyme concentrations were adjusted to give ca. 20% conversion in 5 min at the lowest substrate concentration.

I_{50} Values for Compounds 4, 5 (First Determination), 8, 9, and 11. The I_{50} values for these compounds were determined according to Dixon[56,60] from linear regression fit to a plot of inverse reaction velocity versus inhibitor concentration, with the chorismate concentration maintained at 18 μM, the observed K_m value at the time these assays were performed. The inhibitor concentration ranges used and the I_{50} values obtained were as follows: **4**, 0–7.3 μM, I_{50} = 4.2 ± 0.9 μM; **5**, 0–0.16 μM, I_{50} = 0.14 ± 0.08 μM; **8**, 0–22 μM, I_{50} = 13 ± 2 μM; **9**, 0–95 μM, I_{50} = 100 ± 10 μM. Note: These numbers differ from those published previously[16] because the latter were not computed correctly. No inhibition was observed for the oximinolactone **11** up to a concentration of 10 mM.

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I_{50} Values for Compounds 5 (Second Determination), 12, and 13. The I_{50} values for these compounds were determined in the same manner as described above; however, at the time that these inhibitors were evaluated, the observed K_m value for chorismate was 34 μM. The inhibitor concentration ranges used and the I_{50} values obtained were as follows: **5**, 0–0.20 μM, I_{50} = 0.26 ± 0.06 μM; **12**, 0–1700 μM, I_{50} = 4.2 ± 0.3 mM; **13**, 0–120 μM, I_{50} = 67 ± 4 μM.

K_i Value for Compound 5. For determination of the inhibition constant for the endo diacid **5**, four inhibitor concentrations (0–0.20 μM) and six substrate concentrations (15–300 μM) were used. The data was fitted to the equation for linear competitive inhibition,[56] giving a K_i value of 0.121 ± 0.014 μM.

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Registry No. **5** (dimethyl ester), 114613-49-9; **5** [bis(dicyclohexylammonium) salt], 114613-48-8; **8** (diethyl ester), 114584-65-5; **8** [bis(dicyclohexylammonium) salt], 114595-89-0; **9** [bis(diethylammonium) salt], 114673-07-3; **11**, 114584-29-1; **12**, 114595-81-2; **13**, 114584-30-4; **14**, 114584-31-5; **15**, 114584-32-6; **16**, 114584-33-7; **17**, 99416-47-4; *exo*-**18**, 114584-34-8; *endo*-**18**, 114584-64-4; *exo*-**19**, 114584-35-9; *endo*-**19**, 114673-08-4; *exo*-**20**, 114613-43-3; *endo*-**20**, 114613-50-2; **21**, 114584-36-0; **22**, 114613-44-4; **23**, 114584-37-1; **24**, 114584-38-2; **25**, 114595-82-3; **26**, 114584-39-3; **27**, 114584-40-6; **28**, 114584-41-7; **29**, 114595-83-4; **30**, 114584-42-8; **31**, 114584-43-9; **32**, 114595-84-5; **33**, 114613-45-5; **34**, 114673-05-1; **35**, 114584-44-0; **35** (*O*-nitrate), 114595-92-5; **36**, 114584-45-1; **37**, 114584-46-2; **38**, 114595-85-6; **39**, 114584-47-3; **40**, 114595-86-7; **41**, 114584-48-4; **42**, 114584-49-5; **43**, 114584-50-8; **44**, 114584-51-9; **45**, 114584-52-0; **46**, 114584-53-1; **47**, 114584-54-2; **48**, 114584-55-3; **49**, 114584-56-4; **50**, 114584-57-5; **51**, 114584-58-6; **52**, 114595-87-8; **53**, 114584-59-7; **54**, 114613-46-6; **55**, 114584-60-0; **56**, 114584-61-1; **57**, 114584-62-2; **58**, 64811-86-5; 3-*exo*,8-*exo*-8-hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic acid dimethyl ester, 114584-28-0; dimethyl itaconate, 617-52-7; 1-(methoxycarbonyl)-α-[(trimethylsilyl)oxy]-3-cyclohexene-1-propanenitrile, 114595-91-4; 3-*exo*,8-*exo*-8-[1,2-dioxo-2-[2-(trimethylsilyl)ethoxy]-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic acid bis[2-(trimethylsilyl)ethyl ester], 114584-63-3; 3-*exo*,8-*exo*-8-hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic acid bis[2-(trimethylsilyl)ether ester], 114595-90-3; chorismate mutase, 9068-30-8; adamantane 1-phosphonate, 23906-88-9.

Preparation of Functionalized *trans*-Perhydroindans from Substituted Benzoic Acids: Reductive Alkylation–Halolactonization–Free Radical Cyclization

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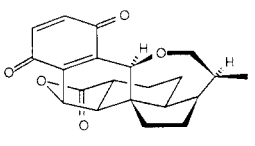
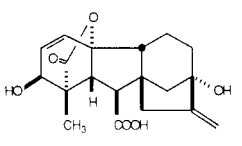
Reductive alkylation of *m*-toluic acid (**7**), *m*-anisic acid (**8**), benzoic acid (**9**), and 2,3-dimethylbenzoic acid (**31**) with selected alkyl halides followed by iodolactonization and side-chain modification gave free radical precursors **13**, **14**, **19**, **27**, and **34**. Treatment of **13**, **14**, and **19** with tri-*n*-butyltin hydride and AIBN gave mixtures of perhydroindans and perhydronaphthalenes. Similar treatment of **27** and **34** gave *trans*-perhydroindans **28** and **35**, respectively, as the major products. Iodo lactone **47** was also prepared from ethyl *m*-iodobenzoate (**38**) and converted to angularly oxygenated perhydroindans **48** and **49** by using a free radical cyclization.

The preparation of trans-fused perhydroindans has been the focal point of a number of synthetic studies. In large part this is due to the presence of this moiety as a substructure of steroids.[2,3] There are, however, a large number of nonsteroidal natural products that contain *trans*-perhydroindan substructures. The antitumor antibiotic pleurotin (**1**) and the plant growth stimulant gibberellic acid (**2**) serve as examples.[4,5] As part of a program designed to develop free radical cyclizations for use in natural product syntheses, we have examined the route to trans-

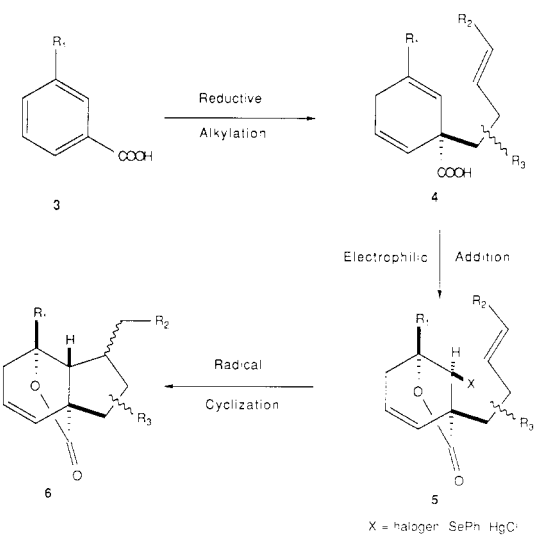


1



2

Scheme I



(1) Author to whom questions regarding crystal structures should be addressed.

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