Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 12 (2004) 4995–5010
Bioorganic & Medicinal Chemistry

Design, synthesis, and evaluation of aza inhibitors of chorismate mutase

Mark E. Hediger*

College of Chemistry, Latimer Hall, The University of California, Berkeley, CA 94720-1460, USA

Received 18 December 2003; accepted 7 June 2004
Available online 28 July 2004

Abstract—A series of aza inhibitors (**4**–**9**) of chorismate mutase (E.C. 5.4.99.5) was designed, prepared, and evaluated against the enzyme by monitoring the direct inhibition of the chorismate, **1**, to prephenate, **2**, conversion. None of these aza inhibitors displayed tighter binding to the enzyme than the native substrate chorismate or greater inhibitory action than the previously reported ether analogue, **3**. Furthermore, no time-dependent loss of enzyme activity was observed in the presence of the two potentially reactive aza inhibitors (**7** and **9**). These results in conjunction with inhibition data from a broader series of chorismate mutase inhibitors allowed a novel proposal for the mechanistic role of chorismate mutase to be developed. This proposed mechanism was computationally verified and correlated with crystallographic studies of various chorismate mutases.

1. Introduction

The shikimic acid pathway sequentially embodies several of the most chemically distinct biosynthetic transformations known. The biological conversion of erythrose-4-phosphate and two molecules of phosphoenolpyruvate to prephenic acid has fascinated the organic chemistry community for decades; recent reviews indicate interest in the chemistries of the shikimic acid pathway remain high.[1] Perhaps the most mechanistically enigmatic transformation of the shikimic acid pathway is the formal Claisen rearrangement of chorismic acid, **1**, to prephenic acid, **2** (Fig. 1). This biologically unique unimolecular reaction proceeds in solution at a significant rate;[2] it is greatly accelerated in vivo by the action of chorismate mutase (E.C. 5.4.99.5).[3] Synthetic macromolecules capable of accelerating this transformation have been prepared and described,[4] while crystallographic studies of various mutases,[5] have been reported. Recent quantum mechanical,[6] molecular dynamics,[7] synthetic analog,[8] and electrostatic binding studies[9] of the rearrangement have appeared. In order to more fully understand the role of chorismate mutase in accelerating this formal Claisen rearrangement, a series of aza bi-, tri-, and tetracycles was prepared and evaluated as inhibitors of the enzyme.

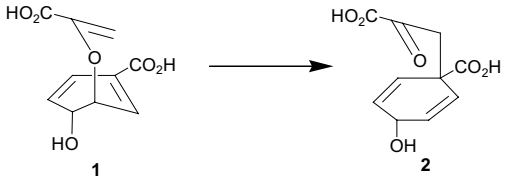


Figure 1. The formal Claisen rearrangement of chorismic acid, **1**, to prephenic acid, **2**. This reaction proceeds in solution and is greatly accelerated by the influence of chorismate mutase.

The most potent transition-state analogue inhibitor of chorismate mutase known at the outset of this work was ether bicycle **3**[10] (Fig. 2). The effectiveness of this compound coupled with the speculative protonation of the enolpyruvyl side chain oxygen of chorismate in the active site of the mutase[11] led to proposal of aza bicycles **4** and **5** as potential transition-state analogue inhibitors of the enzyme. The zwitterionic nature of these inhibitors giving mono-anions in solution at physiological pH (contrast chorismate's mutase-interacting carboxylates)[9] was judged to be of little consequence in altering the expected interaction of these inhibitors with the mutase's binding determinants at the selective and highly localized sites of carboxylate interaction in the mutase-controlled environment under consideration in this study. The greater basicity of these nitrogen analogues

* Present address: 418 Stearns Road, Marlborough, MA 01752-6099, USA. Tel./fax: +1-508-481-6293; e-mail: mhediger@comcast.net

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.06.037

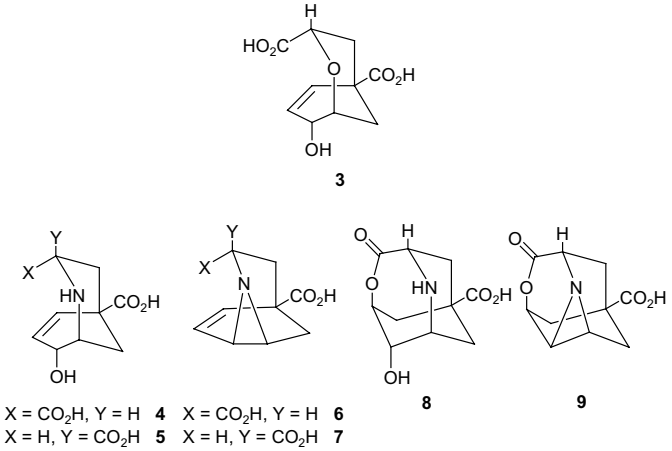


Figure 2. The bicyclic ether, **3**, and the panel of aza inhibitors, **4**–**9**, envisioned as mechanistic probes of the Claisen rearrangement as catalyzed by chorismate mutase.

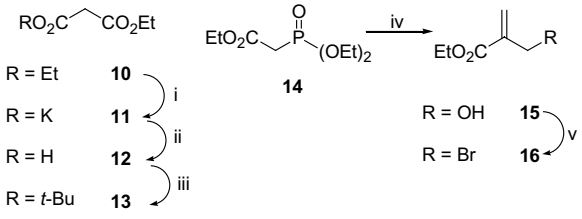
at the corresponding site of chorismate's enolpyruvyl oxygen was deemed a viable test of active site protonation of chorismate during the course of the enzyme-mediated transformation to prephenate, **2** without having a negative impact on the role of the carboxylates in serving as strong recognition elements in the inhibitors' multiple, specific, and localized interactions with the mutase as transition-state analogues. Tighter binding of the ammonium species was anticipated if enzymatic protonation was occurring in the active site of the mutase.

The secondary proposal[11] of an enzymatic X-group assisting in the cleavage of the carbon (C-5)-enolpyruvyl oxygen bond was considered addressable through preparation of aziridines **6** and **7**. Irreversible interception of an enzymatic nucleophile assisting in the cleavage of the carbon (C-5)–oxygen bond of chorismate, with or without enzymatic assistance through proton transfer to the inhibitor, was deemed possible upon specific interaction of theses molecules within the mutase's active site. Lactone **8** served as a rigid and charge-neutralized analogue probe of the conformation and ionization of the enolpyruvyl side chain carboxylate functionality of chorismate in conjunction with the basic nitrogen substitution motif described for compounds **4** and **5**. In addition to the ionic considerations previously outlined, the fixed orientation of the carboxylate surrogate in this molecule with regard to the reactive allyl vinyl ether functionality of chorismate was deemed of interest. Tetracycle **9** integrated the altered orientation and ionization of the surrogate enolpyruvyl side chain carboxylate of lactone **8** in examining the role rigid and nonionic mimicry of chorismate might play in analogue binding with the potential trapping capacity of the aziridine functionality displayed by compounds **6** and **7** into a single analogue.

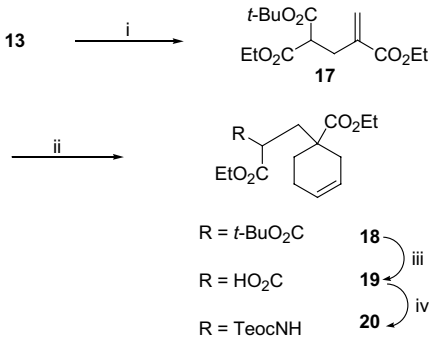
2. Results

The panel of inhibitors **4**–**9** was synthetically approached in a manifold fashion from routes significantly modified from the route to the previously described ether bicycle **3**.[10] The series of transformations necessary to establish the common 2-azabicyclo[3.3.1]nonane motif and the ensuing separation of the diastereomeric intermediates for further elaboration towards targets **4**–**9** is outlined (Schemes 1–3). With divergence of the preparative details, specific synthetic sequences for the completion of individual inhibitors are presented separately (Schemes 4–8).

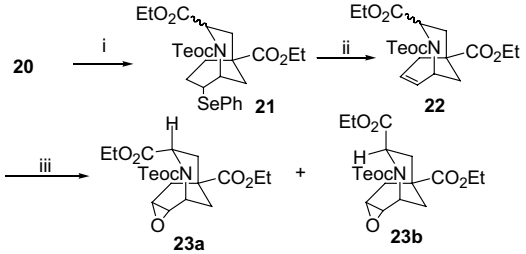
In staging for a subsequent Curtius rearrangement, preparation of an appropriate dienophile, **17**, was



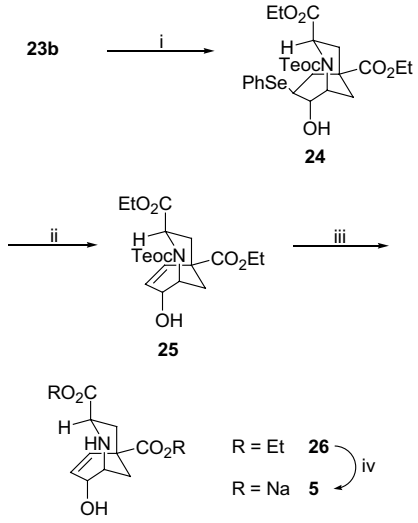
Scheme 1. Preparation of the dienophile precursors **13** and **16**. Reagents: (i) KOH, EtOH; (ii) HCl in H_2O, <5 °C; (iii) isobutylene, H_2SO_4, CH_2Cl_2; (iv) 37% formaldehyde, K_2CO_3, H_2O; (v) PBr_3, Et_2O.



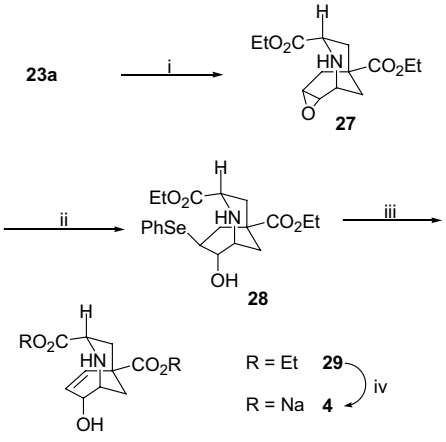
Scheme 2. Preparation of the monocyclic urethane **20**. Reagents: (i) (a) NaH, THF; (b) **16**; (c) TEA, reflux; (ii) butadiene, 110–115 °C, 8 days; (iii) TFA, 1,2-DCE; (iv) (a) DPPA, TEA, PhH, 0 °C to rt; (b) reflux; (c) 2-trimethylsilylethanol, reflux, 12 h.



Scheme 3. Preparation of the *endo* and *exo* bicyclic piperidine epoxides **23a** and **23b**. Reagents: (i) N-PSP, (±)-CSA, CH_2Cl_2, reflux; (ii) (a) *t*-BuOOH, H_2O_2, pyr, CH_2Cl_2, 0 °C; (b) CCl_4, reflux; (iii) (a) *m*CPBA, CH_2Cl_2; (b) DMS; (c) separation by MPLC.

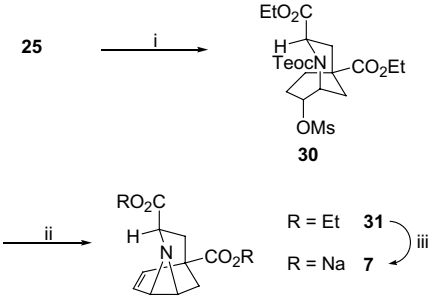


Scheme 4. Final synthetic steps and deprotections to give **5**. Reagents: (i) PhSeSePh, $NaBH_4$, EtOH; (ii) (a) *t*-BuOOH, H_2O_2, pyr, 0 °C; (b) CCl_4, reflux; (iii) TBAF, KF (anhyd.), CH_3CN; (iv) NaOH, EtOH/H_2O.

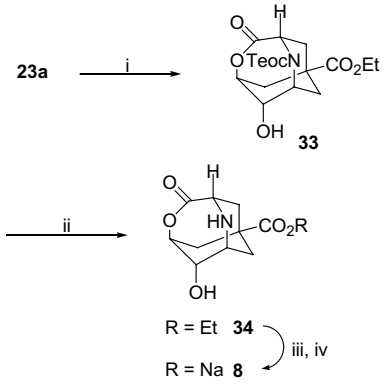


Scheme 5. Final synthetic steps and deprotection to give **4**. Reagents: (i) TBAF, KF (anhyd.), CH_3CN; (ii) (a) [PhSe-BH_3]Na, 15-crown-5, 1,2-DME; (b) TMSCl; (c) MeOH; (iii) (a) (±)-CSOA, 1,2-DME; (b) pyr, 60 °C; (iv) NaOH, EtOH/H_2O.

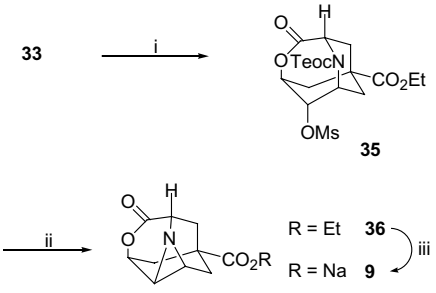
necessary. Glycinate approaches initially explored were determined to be lower yielding than the preparation



Scheme 6. Preparation of the *exo* aziridine analogue **7**. Reagents: (i) $(Ms)_2O$, TEA, DMAP (cat.) CH_2Cl_2; (ii) TBAF, KF (anhyd), CH_3CN, 60 °C; (iii) NaOH, EtOH/H_2O.



Scheme 7. Preparation of the tricyclic ε-lactone, **8**, from *endo* epoxide, **23a**. Reagents: (i) (a) TMSBr, PPh_3, CH_2Cl_2, −78 °C to rt; (b) DBU; (c) HCl/H_2O; (ii) TBAF, KF, CH_3CN 60 °C; (iii) (a) NaOH, EtOH/H_2O; (b) HCl/H_2O 50 °C.



Scheme 8. Preparation of the tetracyclic aziridine lactone, **9**, from ε-lactone intermediate, **33**.

of a suitable dienophile **17** followed by incorporation of the nitrogen functionality common to all inhibitors synthesized in this study. To this end, an improved preparation of precursor *t*-butyl ethyl malonate, **13**,[12] was completed along with the pseudo-symmetric electrophile, **16**[13] (Scheme 1).

With these precursors in hand, alkylation of *tert*-butyl ethyl malonate, **13**, with bromide **16** under atypical aprotic conditions provided this key triester, **17** (Scheme 2). As previously demonstrated in the related ether case, such a substituted acrylate, **17**, would undergo smooth [4+2] cycloaddition under thermal conditions[10b] to give

the anticipated monocyclic triester, **18**. As generalized above and detailed here, introduction of the requisite amine functionality was achieved by selective deprotection,[14] Curtius degradation,[15] and interception of the intermediate isocyanate with β-trimethylsilylethanol yielding **20** (Scheme 2).

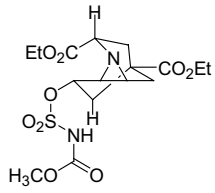
Generation of the 2-azabicylco[3.3.1]nonane core of **4**–**9** was accomplished through electrophilic cyclization mediated by freshly prepared *N*-PSP,[16] under the influence of camphorsulfonic acid catalysis[17] followed by oxidation and elimination to give the bicyclic olefins, **22**, as a 1:1 mixture of diastereomers. This mixture was oxidized with *m*CPBA[18] followed by a requisite anhydrous work-up to give the separable epoxides **23a** and **23b** (Scheme 3). In order to allow productive manipulations of the epoxide functionalities of these protected piperidines, the solution conformations of these two diastereomeric piperidine epoxides were determined through the use of a MOESY[19] multi-dimensional ^{1}H NMR experiment.

With these separated epoxides in hand, isomerization of *exo* epoxide, **23b**, to the corresponding allylic alcohol was accomplished by selenide-mediated[20] opening of the expoxide to selenohydrin, **24**, followed by oxidation and elimination to give the fully protected allylic alcohol, **25**. Fluoride-mediated deprotection of the carbamate-protected piperidine and saponification of the resultant aminodiester provided the disodio salt of target **5** (Scheme 4).

In a significant departure from the route just outlined towards inhibitor **5**, preparation of *endo* chorismate analogue **4** required a unique synthetic approach presumably due to the more hindered face of the intermediate epoxide **23a** (Scheme 5). In this case, initial removal of the carbamate protection from *endo* epoxide under nonepimerizing conditions provided the *endo* aminoepoxide, **27**.[21] The decreased steric demand of this intermediate in the region of the epoxide's *endo* face allowed development[22] of a selective, suitably nonbasic selenium reagent capable of effecting nucleophilic epoxide opening (without competing S_N2-mediated ester removal or epimerization of the α-aminoacid functionality) to provide the requisite and expected selenohydrin, **28**. Mild and selective oxidation[23] of the phenylselenyl ether of **29** with camphorsulfonyloxaziridine ((±)-CSOA) in the presence of the secondary nitrogen of the piperidine was followed by elimination to complete the formal epoxide isomerization of **27** to *endo* allylic alcohol, **29**. This diester was converted directly to the disodio salt of **4** by saponification.

Preparation of *exo* aziridine **7** was accomplished as shown in Scheme 6. Treatment of protected *exo* allylic alcohol **25** with mesyl anhydride under slightly basic conditions provided the expected mesylated allylic alcohol, **30**. Subsequent removal of the carbamate protection under basic fluoride conditions allowed deprotection followed by in situ cyclization to occur in good yield. This aziridine diester, **31**, was exhaustively saponified to give the disodio salt of *exo* aziridine **7**.

Table 1. Conditions explored towards preparation of **6** from **32**



32

Solvent	Temperature (°C)	Time (h)
PhH	50	3
PhH	80	0.33
PhMe + Hünig's base	110	12
DMSO	27	12
DMSO + Hünig's base	70	12
1,2-Dichlorobenzene + DBU	150	12

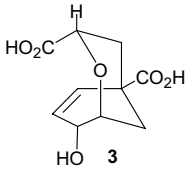
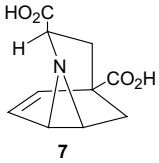
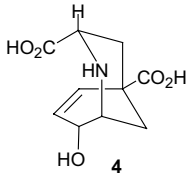
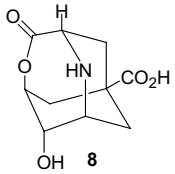
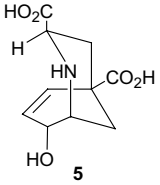
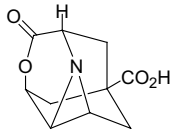
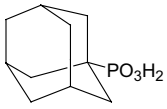
As described above in the case of the bicyclic compound **4**, synthetic approaches based upon the *exo* analogue **5** directed towards the corresponding *endo* aziridine **6** were unsuccessful. Multiple approaches to this target culminated with the preparation[24] and characterization (^{1}H, HRMS) of the sulfamoxyl adduct, **32**, which could not be coaxed into eliminating under multiple sets of conditions to yield **6** (Table 1).

The synthesis of the tricyclic lactone, **8**, was developed from a dominating side reaction observed in the initial attempts to isomerize *endo* epoxide **23a** to the corresponding allylic alcohol based upon the successful approaches to bicyclic ether **3**.[10] Attempted epoxide opening with the combination of trimethylsilylbromide in the presence of triphenylphosphine[25] gave the protected tricyclic hydroxy ε-lactone, **33** (Scheme 7). The observed cyclization of epoxide **23a** to this intermediate complemented the MOESY[19] experiments previously discussed in providing *chemically* unambiguous stereochemical information. Removal of the carbamate protection from the ε-lactone to give the piperidine, **34**, and sequential saponification and relactonization under mildly acidic conditions provided the mono-sodio salt of **8**.

Preparation of tetracyclic lactone aziridine **9** was achieved as shown in Scheme 8. Treatment of the previously prepared hydroxy ε-lactone, **33**, with mesyl anhydride gave the anticipated mesylated intermediate, **35**. One-pot deprotection and cyclization of this material in the presence of basic fluoride afforded tetracyclic lactone, **36**, as previously observed in the case of the *exo* aziridine **7**. Careful saponification gave the desired **9** as the mono-sodio salt.

This collection of racemic compounds (**3**–**5** and **7**–**9**) was evaluated against chorismate mutase as previously described.[10c] In addition to these polycyclic compounds, D-and L-glutamic acids (**37** and **38**) and 1-phosphonoadamantane (**39**)[26] were also evaluated against chorismate mutase. Higher pH assays were performed with the most potent of the aza compounds to determine the role enzymatic protonation might play in contributing to aza inhibitor binding. The results of these assays are presented in Table 2.

Table 2. Inhibition results for the panel of polycyclic compounds **3**–**5** and **7**–**9**, the corresponding glutamic acids, **37** and **38**, and 1-phosphonoadamantane, **39**, against chorismate mutase

Compound	IC_{50}/K_m (pH 7.5)	IC_{50}/K_m (pH 9.0)	Compound	IC_{50}/K_m (pH 7.5)	IC_{50}/K_m (pH 9.0)
 **3**	0.007	—	 **7**	>20	—
 **4**	1.2	0.2	 **8**	>50	—
 **5**	18	—	 **9**	42	—
D-Glutamic acid (**37**)	>150	—	 **39**	—	0.02
L-Glutamic acid (**38**)	>150	—		$K_m = 34\,\mu M$ (pH 7.5), $K_m = 2.3\,mM$ (pH 9.0)	

3. Discussion

As clearly illustrated in Table 2, none of these aza inhibitors (**4**, **5**, **7**–**9**) was bound to chorismate mutase with greater affinity than the substrate chorismate, **1**, at pH 7.5. In excellent agreement with the previously reported results with ether **3**,[10] an approximately 100-fold tighter binding affinity of this bicyclic inhibitor was observed upon normalization of the IC_{50} data to the K_m of chorismate at pH 7.5. This result was taken as a positive control surrounding the assay protocol. In addition to this thermodynamic result, no differences in the onset rates of inhibition were observed with any of the aza inhibitors as compared to the bicyclic ether standard. The zwitterionic nature of the aza inhibitors did not alter their rates of association with the mutase as measured by this assay. The inhibitor design considerations surrounding the net loss of a negative charge at physiological pH did not appear to have any observable impact on the rate of compound association with the specific active site binding determinants of the mutase.

The previously proposed[11] protonation of the enolpyruvyl side chain oxygen of chorismate during the enzyme-mediated formation of prephenate, **2**, was not supported by the modest interaction of the most potent aza inhibitor, **4**, with chorismate mutase at pH 9.0. The good agreement of the binding affinity for phosphonate **39**[26] under these conditions supports the supposition of a quality assay at this higher pH. With no observed support of general acid mechanistic involvement from chorismate mutase, no additional high pH evaluations of these inhibitors were deemed instructive.

The 10-fold less potent interaction of the *exo* aza inhibitor **5** as compared to the *endo* aza inhibitor **4** was as expected based upon the same magnitude of difference observed in the ether series.[10] It is of further interest to note the rigidification and additional functionality of both **4** and **5** presumably contributed to the greater affinity observed at the mutase's active site as compared to the unconstrained and stereochemically correlated glutamic acids **37** and **38**. The similar binding affinity observed with the *exo* aziridine, **7**, in comparison to the *exo* bicycle **5**, would point to a similar active site orientation, presumably influenced by the stereochemical orientation of the carboxylate corresponding to the enolpyruvyl carboxylate of chorismate. The influence of the additional geometric restraint imposed by the aziridine function in **7** appears minimally perturbing with regard to the binding interactions observed. The design of this compound as a potential active site mechanism-based covalent inactivator is supported by the minimally perturbed binding data if not by the lacking acidic residue at the site of the enzyme's interaction with the ether oxygen of the native substrate chorismate. With the modest level of inhibition observed for all the aza compounds, the weak interaction of **4** with the mutase at

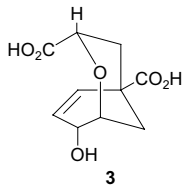
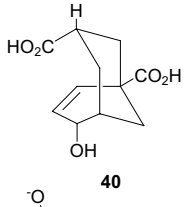
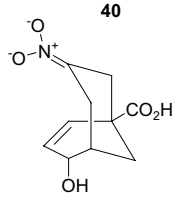
high pH and the absence of any time-dependent loss of mutase activity in the presence of **7** and **9**, none of these aza inhibitors was rigorously evaluated as a mechanism-based inactivator of chorismate mutase.

In comparison of the neutralized enolpyruvyl carboxylate analogues, **8** and **9**, another pair of very similar affinities is observed. Both are diminished in affinity as compared to the *endo*-configured, doubly anionic compound **4**. As in the pairwise comparison of compounds **5** and **7**, the very similar interactions of these more constrained *endo*-configured analogues point to a nonperturbing design with regard to active site interaction. The diminished affinity in this pair may readily be explained though the favored interaction of a doubly anionic substrate for tight interaction with the mutase's active site.[9] In the absence of such ionic binding determinant interactions, diminished affinity is observed as expected. These observations of inhibitor interaction with the mutase have stood in agreement with theoretical[27] studies of the Claisen rearrangement and were consistent with the subsequent crystallographic[5c] studies of the *E. coli* chorismate mutase.

With no support of the previously proposed mechanistic explanations for the mutase-mediated acceleration of the chorismate, **1**, to prephenate, **2**, conversion,[11] attention was directed towards integrating the body of known inhibitor interaction data into an explanation of inhibitor binding at the active site of the mutase. The modest interaction of these aza compounds with chorismate mutase in conjunction with the previously known binding data[10c] for carbo-bicycle **40**, bicyclic nitronate **41**, and bicyclic ether **3** strongly suggested the orientation of the surrogate enolpyruvyl side chain carboxylate as an important factor in conceptualizing the bound *transition-state* of chorismate at the active site of the mutase (Table 3). The fixed orientation of the nitronate's isoelectronic functionality as compared to the other analogues' freely rotating carboxylates was a key consideration in analysis of the binding data differences observed. The specific comparison of compounds **40** and **41** and their respective binding affinities drew this difference into sharpest focus.

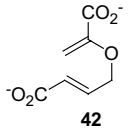
In addition to these binding interactions, prior physical chemical studies of allyl vinyl ethers substituted with electron-donating substituents at the 2 and 6 positions have shown Claisen rearrangements proceed at significantly greater rates than in the corresponding un-substituted systems.[28] It was of some interest to note the two carboxylates of chorismate occupy the corresponding 2 and 6 positions of the parent allyl vinyl ether system. Turning attention to the enzymatically mediated acceleration of the chorismate to prephenate transformation and in consideration of the demonstrated lack of an acidic mutase residue capable of protonating the enolpyruvyl oxygen of chorismate as well as the binding data from the various compounds of Table 3, one is prompted to consider the positioning of the carboxylates of chorismate in an orientation reducing or minimizing the electronic effects upon the allyl vinyl ether functionality while maximizing the potential to interact

Table 3. Comparative data for chorismate mutase inhibitor analogues

Compound	IC_{50}/K_m
 **3**	0.01
 **40**	2.1
 **41**	>100

strongly with the enzyme upon substrate binding. Both the binding and chemistry criteria appeared to be satisfied with a twisting of the carboxylates relative to the allyl vinyl ether functionality and this mechanistic consideration was offered as a fundamental consideration for the in vivo transformation.

Ab initio calculations on the minimalist system (2,6-dicarboxylate allyl vinyl ether, **42**) at the 6-31+G* level


42

(Prof. Ken N. Houk, personal communication) as well as the chorismate dianion[29] supported the supposition that the lowest energy transition-state conformation for the gas-phase Claisen rearrangement of this doubly substituted allyl vinyl ether was indeed one in which nonplanarity of both the carboxylates is observed with regard to the corresponding chair-like orientation of the atoms of the allyl vinyl ether functionality. Extension of this computational finding to the enzymatic system would suggest a chorismate binding conformation *at the transition-state* towards prephenate where both substrate carboxylates are utilized for tight electrostatic interactions (salt bridges with positively charged enzymatic residues) with the mutase allowing a favorable chair-like orientation and spacing of the reactive termini of the allyl vinyl ether system (a binding effect) while concurrently mitigating deleterious electronic effects on the allyl vinyl ether system from these same carboxylates by positioning them in a minimally interacting orientation (a favorable electronic effect for reorganiza-

tion) with respect to the sites of the formal electronic reorganizations (i.e., the formal Claisen rearrangement chemistry of the allyl vinyl ether system).

Calculations of the transition state for the rearrangement of chorismate to prephenate have indicated nonplanarity for both carboxylates (enolpyruvyl carboxylate is 22.1 degrees off-planar, why the ring carboxylate is 21.3 degrees off-planar).[29] Steric compression[30] of the transition state at the bond-forming site of the enolpyruvyl carbon with the ring carbon of chorismate would thus be well served through substrate binding while any deleterious electronic effects manifest by the substrate's carboxylates at the 2 and 6 positions might be minimized through simple single bond rotations with regard to the allyl vinyl ether system of chorismate *at the transition-state*.

4. Conclusion

The weak interaction of these aza analogues with the *E. coli* chorismate mutase in a time-independent fashion, the significant binding affinity differences observed for compounds **40** and **41** against chorismate mutase,[10] the general requirement of doubly anionic chorismate analogues for tight binding to the mutase,[9] the computationally verified diminished *transition-state* energy of the Claisen rearrangement achieved by twisting both the 2 and 6 position carboxylates from planarity with respect to the allyl vinyl ether functionality in the minimalist allyl vinyl ether system as well as the chorismate dianion,[29] the multiple and varied crystal structures of natural[5] and man-made mutases[4] and the recent dynamic conformation studies of chorismate binding[6] as well as the molecular dynamics study of the enzyme-mediated catalysis event[7] have significantly enhanced comprehensive understanding of this biologically unique unimolecular transformation. The triumvirate of computational studies, X-ray crystallography, and synthetic chemistry may yet serve to guide the design and preparation of tighter binding inhibitors for this class of enzymes. In the light of these consensus results, approaches to higher flux artificial mutases more closely mimicking Nature's chorismate mutases in catalytic function and mechanistic subtlety may indeed be within the reach of prudent chemists in collaboration with enzymatic and molecular engineers of Nature.

5. Experimental

5.1. Chemistry

Reagents were obtained from commercial suppliers and unless otherwise noted were used as received. All moisture- or air-sensitive reactions were conducted under an atmosphere of dry nitrogen in oven-dried glassware except as indicated. Dried solvents were prepared as follows: Ethereal solvents and benzene were distilled from the deep blue or purple ketyl derived from potassium and benzophenone. Toluene was distilled from sodium metal. Halogenated solvents, hexanes, acetonitrile, and amines were distilled from calcium hydride. Alcoholic solvents, DMSO, and DMF were dried based upon the protocols of Burfield and Smithers.[31] Final organic reaction solutions were dried over anhydrous $MgSO_4$ and filtered; the solvents were removed by rotary evaporation at water aspirator pressure followed by vacuum evacuation to constant mass unless noted otherwise. Flash chromatography refers to the procedure of Still, Kahn, and Mitra[32] using silica gel 60 (E. Merck, Darmstadt) with the eluant as indicated. Melting points were determined in sealed capillaries with a Büchi Schmelpunksbestimmungsapparat and are uncorrected. Infrared spectra were obtained from thin films or $CDCl_3$ solutions as indicated and were recorded with a Perkin–Elmer 1420 ratiorecording infrared spectrophotometer. Routine NMR spectra were obtained with Fourier transform instruments operating at the following frequencies: ^1H NMR: 200, 250, 400, 500 MHz; ^{13}C NMR: 100.602, 125.730 MHz. Reported NMR data are from spectra obtained at 500 MHz (^1H) and 125.730 MHz (^{13}C) unless indicated. All samples were dissolved in $CDCl_3$ and spectra obtained at ambient temperature except as noted. Chemical shifts (chemical shift (multiplicity, number of hydrogens, coupling constants (Hz))) are reported in ppm (δ units) relative to an internal standard of tetramethylsilane (0.00 ppm) for ^1H spectra and $CDCl_3$ (77.0 ppm) for ^{13}C spectra. Other NMR spectral calibrations are as noted. Electron impact mass spectra were obtained with a Kratos MS-50 mass spectrometer and fast atom bombardment (FABMS) spectra were obtained using a V.G. AZB2-EQ instrument operated by the College of Chemistry, University of California at Berkeley. First row elemental analyses were provided by the Microanalytical Laboratory, Department of Chemistry, University of California at Berkeley. Sulfur and halogen analyses were provided by Oneida Research Services, Inc. Whitesburo, New York and Desert Analytics, Tuscon, Arizona, respectively. Samples for air sensitive analyses (MS or combustion) were submitted under a He atmosphere.

5.2. Ethyl potassium malonate (11)[12]

In a dry 2-L round-bottomed flask was placed diethyl malonate (100 g, 0.625 mol) and a large magnetic stir bar. Commercial absolute ethanol (400 mL) was added and the flask was fitted with a large dropping funnel containing a solution of potassium hydroxide (35 g, 0.625 mol) dissolved in absolute ethanol (400 mL). This basic solution was added dropwise to the stirred malonate solution over 90 min. Copious precipitate formed during the course of the addition. The suspension was stirred an additional 2 h and then allowed to stand overnight. The dropping funnel was exchanged for a reflux condensor, and the suspension was vigorously refluxed for 1 h to give a nearly homogeneous solution. This hot solution was quickly filtered through a hot Büchner funnel, and the retained precipitate was washed with hot absolute ethanol (200 mL). The volume of the combined filtrate and washing was reduced to approximately 800 mL, and this solution was cooled in an ice bath.

Crystals were collected and washed with Et_2O (2×100 mL), and the mother liquor was concentrated to approximately 400 mL for a second crop. The crystals were separately dried in a vacuum oven (ambient temperature) to yield 86.6 g (first crop) and 10.5 g (second crop) of the malonate half-acid salt as a white crystalline material in 91% overall yield. IR (mull) 1739, 1595, 1380, 1310, 1230, 1155, 1045, 915 cm^{-1}. ^1H NMR (D_2O reference to residual HDO δ 4.60) δ 4.08 (q, 2H, J=7.2), 3.19 (s, 2H), 1.16 (t, 3H, J=7.2). ^{13}C NMR (D_2O referenced to a 1,4-dioxane (ca. 0.1% v/v) co-solvent δ 66.50) δ 174.18, 171.46, 60.00, 44.53, 13.20.

5.3. Ethyl malonic acid (12)[12]

Ethyl potassium malonate, **11**, (90.22 g, 530 mmol) was placed in a 500-mL round-bottomed flask equipped with a magnetic stir bar. The salt was dissolved in H_2O (56 mL) to give a colorless solution. This solution was cooled to 0 °C and HCl (12 M, 45 mL, 540 mmol) was added dropwise over 40 min, taking care to maintain the reaction solution at a temperature less than 5 °C. After stirring an additional 20 min, the suspension was filtered through a frit and the retained salt was washed with Et_2O (2×50 mL). The two-phase filtrate was separated, and the aqueous layer was extracted with Et_2O (2×70 mL). The combined organic extracts were treated with brine, dried, and evaporated to give 70.35 g (quantitative) of the half-acid as a clear viscous oil. IR (film) 3025, 2985, 1740, 1720, 1370, 1330, 1160, 1035 cm^{-1}. ^1H NMR δ 855 (bs, 1H), 4.24 (q, 2H, J=7.2), 3.44 (s, 2H), 1.30 (t, 3H, J=7.2). ^{13}C NMR δ 171.41, 166.89, 61.96, 40.85, 13.94.

5.4. *tert*-Butyl ethyl malonate (13)[12]

In an oven-dried 700-mL Parr vessel was placed ethyl malonate half-ester, **12**, (70.35 g, 532 mmol) and a small magnetic stir bar. The half-ester was dissolved in dry CH_2Cl_2 (100 mL); the resulting solution was cooled in an ice/salt bath and isobutylene (ca. 120 mL, 84 g, 1.5 mol) was added. Concentrated sulfuric acid (4.0 mL) was added and the Parr vessel was sealed with a wired stopper. The solution was stirred and allowed to warm overnight. The sealed vessel was again cooled in an ice/salt bath and then opened. The homogeneous solution was poured into a 1-L flask containing a solution of NaOH (50 g) dissolved in H_2O (200 mL) and ice (ca. 200 g). The two-phase mixture was extracted with Et_2O (3×100 mL), and the organic layers combined, treated with brine, and dried. Filtration and removal of solvents yielded a clear oil (94.88 g, 95%). This material was transferred to a base-rinsed and dried distillation apparatus and distilled from MgO to give 76.64 (77%) of the diester as a colorless oil (0.3 mmHg, bp 55–58 °C; lit.[12] 22 mmHg, 98–100 °C). IR (film) 2980, 1740, 1720, 1370, 1335, 1140, 1030, 970 cm^{-1}. ^1H NMR δ 4.20 (q, 2H, J=7.1), 3.28 (s, 2H), 1.47 (s, 9H), 1.29 (t, 3H, J=7.1). ^{13}C NMR δ 166.99, 165.80, 81.96, 61.27, 42.95, 27.89, 14.06. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.55; H, 8.61.

5.5. Ethyl α-hydroxymethyl acrylate (15)[13]

In a three-necked 1-L round-bottomed flask fitted with an efficient overhead stirrer and a 250-mL dropping funnel was placed triethylphophonoacetate, **14**, (63.96 g, 285 mmol) and an aqueouos solution of formaldehyde (37%, 150 mL, 2.0 mol). The dropping funnel was charged with a saturated solution of K_2CO_3 (69.00 g, 500 mmol in ca. 110 mL of H_2O). This basic solution was added to the vigorously stirring contents of the flask over 20 min. The flask became noticeably warmer during this addition. Vigorous stirring was continued for 1 h. The dropping funnel was next charged with a 50% saturated aqueous solution of NH_4Cl (150 mL); the contents of the flask were stirred gently and the NH_4Cl solution was added dropwise. The contents of the flask were extracted into Et_2O (3×100 mL) and the pooled organic extracts were washed with brine and dried. Filtration and removal of solvent gave a colorless oil, which was distilled to give 25.21 g (68%) of a colorless oil (0.55 mmHg, bp 58–63 °C; lit.[13] 1 mmHg, 65–70 °C). IR (film) 3460, 2995, 1740, 1455, 1390, 1310, 1275, 1160, 1060, 955 cm^{-1}. ^1H NMR δ 6.25 (d, 1H, J=0.9), 5.82 (d, 1H, J=1.3), 4.32 (s, 2H), 4.24 (q, 2H, J=7.1), 2.36 (bs, 1H), 1.31 (t, 3H, J=7.1). ^{13}C NMR δ 166.33, 139.50, 125.55, 62.52, 60.85, 14.12.

5.6. Ethyl α-bromomethyl acrylate (16)[13]

In a dry, 250-mL round-bottomed flask was placed ethyl α-hydroxymethylacrylate, **15**, (25.21 g, 194 mmol) and a magnetic stir bar. The flask was sealed and the ester was dissolved in dry Et_2O (100 mL). The solution was cooled to 0 °C and PBr_3 (13.6 mL, 38.8 g, 143 mmol) was added dropwise via syringe. The solution was allowed to warm with stirring over 14 h the flask was again cooled to 0 °C and H_2O (30 mL) was slowly added via syringe. After returning to ambient temperature, the contents of the flask were extracted into hexanes (4×100 mL). The pooled organic extracts were washed with 50% saturated aq $NaHCO_3$, brine, and dried. Filtration and removal of solvents gave a yellow oil. This material was carefully distilled to give 26.65 g (70%) of a colorless, lachramatory oil (2 mmHg, bp 55–61 °C; lit.[13] 1.7 mmHg, 44–45 °C). IR (film) 3110, 2985, 1720, 1630, 1480, 1330, 1310, 1180, 1020, 955, 810, 720 cm^{-1}. ^1H NMR δ 6.34 (d, 1H, J=0.6), 5.95 (d, 1H, J=0.9) 4.28 (q, 2H, J=7.1), 4.19 (s, 2H), 1.34 (t, 3H, J=7.1). ^{13}C NMR δ 164.83, 137.56, 128.88, 61.29, 29.36, 14.12. Anal. Calcd for $C_6H_9O_2Br$: C, 37.33; H, 4.70; Br, 41.40. Found: C, 37.15; H, 4.69; Br, 41.55.

5.7. (±) *tert*-Butyl-2,4-(bisethoxycabonyl)pent-4-enoate (17)

In a dry 1-L round-bottomed flask was placed NaH (60% oil dispersion, 3.740 g, 93.5 mmol) and a large magnetic stir bar. The NaH was rinsed with hexanes (2×10 mL) under positive N_2 pressure, the flask was sealed, and the NaH was suspended in dry THF (250 mL). The suspension was cooled to 0 °C, and a solution of *tert*-butyl ethyl malonate, **13**, (17.60 g, 93.5 mmol) in dry THF (50 mL) was added via cannula.

After a brief induction period, gas evolution commenced and within 30 min, a homogeneous, colorless solution was formed. To this solution was added as rapidly as possible ethyl α-bromomethyl acrylate, **16**, (18.05 g, 93.5 mmol) in dry THF (50 mL). A copious white precipitate formed immediately upon addition. After warming to room temperature, triethylamine (26.1 mL, 18.92 g, 93.5 mmol) was added, the flask was fitted with a reflux condensor, and the mixture was gently refluxed for 13 h. The contents of the flask were cooled, a 50% aqueous solution of NH_4Cl (200 mL) was added, and the pH of the solution was adjusted to <3 with H_2SO_4 (0.5 M) as indicated by *pH* paper. The contents of the reaction flask were extracted with Et_2O (3×200 mL), and the organic extracts were pooled, washed with 50% aqueous $NaHCO_3$, brine, and dried. Filtration and removal of solvent gave a light-yellow oil. This material was distilled with a Kugelrohr apparatus (0.35 mmHg, oven temperature 115–130 °C) from MgO in a base-rinsed and oven-dried apparatus to yield 27.02 g (96%) of the triester as a colorless oil. Purification of an earlier small scale reaction by flash chromatography (20% EtOAc/hexanes) afforded the analytically pure material. IR ($CDCl_3$ solution) 2980, 1745, 13275, 1310, 1145 cm^{-1}. ^1H NMR δ 6.21 (d, 1H, J=1.3), 5.64 (d, 1H, J=1.3), 4.23 (q, 2H, J=7.1), 4.19 (q, 2H, J=7.1), 3.62 (t, 1H, J=7.8), 1.45 (s, 9H), 1.31 (t, 3H, J=7.1), 1.26 (t, 3H, J=7.1). ^{13}C NMR δ 168.83, 167.62, 161.07, 136.88, 127.06, 81.69, 60.99, 60.61, 51.49, 37.91, 31.18, 27.68, 13.98, 13.91. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.83; H, 8.04.

5.8. (±) *tert*-Butyl α,1-di(ethyoxycarbonyl)-3-cyclohexene-propanoate (18)

In a dry base-rinsed glass Parr vessel liner was placed dienophile, **17**, (26.17 g, 87 mmol). The headspace of the vessel was swept with nitrogen, the vessel was cooled in a dry ice/acetone bath, and butadiene (ca. 200 mL, 140 g, 2.5 mol) was condensed into the vessel. Condensation was removed from the outside of the liner, and the Parr bomb assembled. After coming to room temperature behind a blast shield, the vessel was cautiously heated in an oil bath to 115 °C (290 psi). The vessel was held at 110–115 °C for 8 days with a concomitant pressure drop (final pressure 100 psi). The vessel was brought to room temperature (40 psi) and carefully vented. The liner was removed and the pale-yellow oil was transferred to a 1-L flask. This material was extracted with refluxing acetone (6×100 mL). The combined acetone extracts were cooled and filtered through a Celite® pad. The solvent was removed in vacuo, and the residue was passed through a SiO_2 plug with acetone (2 L). Solvent was again removed in vacuo and the resultant yellow oil was purified by chromatography (10% EtOAc/hexanes) to give 22.88 g (78%) of the colorless monocyclic triester **18** as a 1:1 mixture of diastereomers. An analytical sample was prepared in an identical fashion from an earlier, smaller scale reaction. IR ($CDCl_3$ solution) 2590, 1725, 1450, 1370, 1300, 1150, 1095, 1025, 850 cm^{-1}. ^1H NMR δ 5.63 (m, 2H), 4.16 (m, 2H), 4.10 (m, 2H), 3.33 (m, 1H), 2.52 (m, 1H), 2.28–2.16 (m, 2H), 2.05 (bs, 2H), 2.01 (m, 1H), 1.92 (m, 1H), 1.58 (m, 1H), 1.45 (s, 4.5H), 1.44 (s, 4.5H), 1.28–1.22 (m, 6H). ^{13}C NMR δ 175.50, 169.86, 168.56, 126.20, 126.17, 124.71, 124.65, 81.85, 61.28, 60.53, 49.10, 44.23, 44.15, 36.63, 36.52, 32.75, 32.37, 30.10, 29.62, 27.82, 22.66, 22.63, 14.08, 14.03. Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.27; H, 8.52.

5.9. (±) 2-Ethoxycarbonyl-3-(1-ethoxycarbonylcyclohex-3-ene)-propanate (19)[14]

In a dry 250-mL round-bottomed flask was placed monocylic triester, **18**, (4.967 g, 14.0 mmol) and a magnetic stir bar. The flask was sealed and the triester was dissolved in 1,2-DCE (14.0 mL). To this solution was added freshly distilled trifluoroacetic acid (TFA; 10.8 mL, 16.0 g, 140 mmol).[14] The reaction was monitored by TLC and was complete within 10 h. Volatile components were removed in vacuo to give a yellow oil (4.33 g) that was immediately subjected to Curtius rearrangement (vide infra). An analytical sample was prepared by flash chromatography (97:2:1:CH_2Cl_2:MeOH:HOAc) of an earlier reaction product. IR ($CDCl_3$ solution) 2985, 2570, 1740, 1445, 1370, 1300, 1190, 1175, 1090, 1020, 860 cm^{-1}. ^1H NMR δ 9.95 (bs, 1H), 5.63 (m, 2H), 4.19 (m, 2H), 4.09 (m, 2H), 3.50 (m, 1H), 2.54 (m, 1H), 2.34–2.11 (m, 2H), 2.05 (bs, 2H), 2.02 (bs, 1H), 1.94–1.90 (m, 1H), 1.60 (m, 1H), 1.29–1.22 (m, 6H). ^{13}C NMR δ 175.48, 174.90, 169.08, 128.28, 126.20, 126.18, 124.42, 124.39, 61.85, 60.73, 47.91, 47.88, 44.03, 44.00, 36.38, 32.70, 32.41, 29.83, 22.50, 22.49, 13.97, 13.88. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.17; H, 7.37.

5.10. (±) Ethyl 2-(*N*-2-trimethylsilylethoxycarbonyl)-amino-3-(1-ethoxycarbonylcyclohex-3-ene)-propanate (20)

In a dry 250-mL round-bottomed flask containing freshly prepared monocyclic half-ester, **19**, (4.33 g, ⩽14.0 mmol, vide supra) and a magnetic stir bar was added benzene (50 mL). The flask was fitted with a reflux condensor and sealed; the contents were cooled in an ice bath. Diphenylphosphorylazide[15] 3.32 mL, 4.23 g, 15.4 mmol) and triethylamine (3.90 mL, 2.83 g, 28.0 mmol) were added sequentially by syringe. The contents of the flask were diluted with additional benzene (20 mL) and the solution was allowed to warm with stirring to ambient temperature over 3 h. During this period, a brilliant yellow color developed. The solution was slowly heated to reflux (gas evolution during warming) and after 1.5 h, 2-trimethylsilylethanol (2.41 mL, 1.99 g, 16.8 mmol) was added. The reaction mixture was allowed to gently reflux for 12 h, cooled and poured into Et_2O (300 mL). This solution was extracted with NaOH (1.0 M, 3×50 mL), H_2SO_4 (0.5 M, 3×50 mL), 50% saturated aqueous $NaHCO_3$, brine, and dried. Solvents were removed in vacuo and the product purified by flash chromatography (10% EtOAc/hexanes) to give 4.15 g (72% from **18**) of the pale-yellow monocyclic urethane **20** as a 1:1 mixture of diastereomers. A small amount (6%) of the half-ester decarboxylation product was also obtained. IR (film) 3360, 2980, 1730, 1525, 1455, 1250,

1210, 1070, 855, 835 cm^{-1}. ^1H NMR (*d-6* PhD referenced to δ 7.15) δ 5.57–5.45 (m, 2H), 5.25 (d, 0.5H, $J=9.2$), 5.20 (d, 0.5H, $J=9.3$), 4.72 (m, 1H), 4.20 (m, 2H), 4.02 (m, 2H), 3.90 (m, 2H), 2.74 (d, 0.5H, $J=17.4$), 2.42 (d, 0.5H, $J=14.3$), 2.11–1.79 (m, 6H), 1.47 (m, 0.5H), 1.03 (m, 2H), 0.91 (m, 6H), −0.12 (bs, 9H). ^{13}C NMR (50 °C in *d-6* PhD referenced to δ 128.00) δ 177.58, 176.15, 175.48, 175.39, 156.23, 155.39, 126.61, 125.89, 125.26, 124.49, 63.29, 61.15, 60.61, 51.77, 51.54, 43.62, 43.21, 40.61, 38.65, 34.71, 32.16, 31.58, 27.97, 22.78, 22.48, 18.05, 12.40, −1.61. Anal. Calcd for $C_{20}H_{35}O_6NSi$: C, 58.08; H, 8.53; N, 3.39. Found: C, 58.05; H, 8.25; N, 3.32.

5.11. (±) Diethyl (1*R**,3*R***S**,5*S**,7*R**)-2-(*N*-2-trimethylsilylethoxycarbonyl)-8-phenylselenyl-2-aza-bicyclo-[3.3.1]nonane-3,5-dicarboxylate (21)

In a dry 250-mL round-bottomed flask was placed monocylic urethane, **20**, (4.149 g, 10.0 mmol) and a magnetic stir bar. While sweeping with nitrogen, the flask was charged with CH_2Cl_2 (50 mL) followed by *N*-PSP (4.546 g, 15.1 mmol)[16] and (±)-camphorsulfonic acid (0.466 g, 2.01 mmol).[17] The flask was fitted with a reflux condensor, additional CH_2Cl_2 (50 mL) was added and reflux initiated. Analysis of the reaction mixture by TLC after 12 h indicated no starting urethane remained. The reaction mixture was cooled, poured into Et_2O (200 mL), and evaporated to give a brown oil. This material was purified by flash chromatorgraphy (20% EtOAc/hexanes) to yield 4.676 g (82%) of the deep orange bicyclic adduct as an undetermined mixture of diastereomers. IR ($CDCl_3$ solution) 3065, 2965, 1725, 1690, 1460, 1405, 1315, 1295, 1255, 1200, 1080, 1025, 865, 840 cm^{-1}. ^1H NMR (60 °C in *d-6* PhD referenced to 7.15) δ 7.85–7.50 (m, 2H), 7.10–6.85 (m, 3H), 5.00–4.85 (m, 1.5H), 4.43 (dd, 0.5H, $J=9.8$, 7.1), 4.30–3.70 (m, 6H), 3.60–2.80 (m, 1H), 2.65–2.45 (m, 2H), 2.40–1.15 (m, 6H), 1.15–0.60 (m, 8H), 0.20 to −0.20 (m, 9H). ^{13}C NMR (60 °C in *d-6* PhD referenced to δ 128.00) δ 176.16, 175.96,173.24, 172.70, 172.40, 156.51, 156.40, 156.23, 135.31, 134.82, 133.23, 130.59, 130.45, 129.35, 129.23, 129.12, 129.07, 128.29, 127.91, 127.61, 127.42, 126.99, 66.35, 63.80, 61.18, 60.96, 60.72, 60.68, 53.30, 53.12, 52.63, 52.27, 45.79, 44.85, 43.79, 43.33, 39.02, 38.88, 32.92, 32.79, 32.65, 32.26, 32.09, 31.82, 28.93, 28.15, 28.01, 26.41, 24.33, 24.14, 22.88, 18.79, 18.27, 18.20, 18.09, 14.22, 14.12, 14.11, 14.07, 14.03, −1.14, −0.43, −0.57, −1.61, −1.63, −1.82. Anal. Calcd for $C_{26}H_{39}O_6NSiSe$: C, 54.91; H, 6.91; N, 2.46. Found: C, 55.16; H, 6.86; N, 2.22.

5.12. (±) Diethyl (1*R**,3*R***S**,5*S**)-2-(*N*-2-trimethylsilylethoxycarbonyl)-2-azabicyclo[3.3.1]non-7-ene-3, 5-dicarboxylate (22)

In a 250-mL round-bottomed flask was placed the [3.3.1] adduct, **21**, (4.676, 8.22 mmol), CH_2Cl_2 (10 mL), pyridine (10 mL), and a *large* magnetic stir bar. The solution was cooled to 0 °C with stirring and cold *tert*-butyl peroxide (10 mL) and 30% hydrogen peroxide (100 mL) were added sequentially. The flask was sealed and vented with a fine needle; the two-phase mixture was vigorously stirred a 0 °C until no color remained from the bicyclic starting material. This cold, two-phase mixture was poured into 300 mL of vigorously refluxing CCl_4 and heated for 3 min after returning to reflux. The cooled solution was partitioned between Et_2O (400 mL) and NaOH (1.0 M, 3×50 mL), H_2SO_4 (0.5 M, 4×20 mL), 50% saturated aqueous $NaHCO_3$, and brine. The solution was dried, filtered and solvents evaporated to give a yellow oil. This material was purified by flash chromatography (20% EtOAc/hexanes) to yield 3.140 g (93%) of the pale-yellow bicyclic aza nonene as a 1:1 mixture of diastereomers. IR ($CDCl_3$ solution) 2970, 1730, 1690, 1530, 1420, 1300, 1255, 1215, 1110, 1070, 865, 845 cm^{-1}. ^1H NMR 6.00–5.50 (m, 2H), 4.91 (d, 0.5H, $J=7.2$), 4.87 (m, 0.5H), 4.75–4.72 (m, 1H), 4.58 (bs 0.5H), 4.28–3.98 (m, 6.5H), 2.68 (dd, 0.5H, $J=14.2$, 6.9), 2.44–2.34 (m, 1.5H), 2.21–2.08 (m, 1H), 2.06–1.95 (m, 2H), 1.90–1.72 (m, 2H), 1.27–1.17 (m, 6H), 1.07–0.91 (m, 2H), 0.40–0.00 (m, 9H). ^{13}C NMR (70 °C in *d-6* PhD referenced to δ 128.00) δ 175.91, 175.82, 172.48, 171.82, 156.22, 155.82, 155.77, 129.92, 129.61, 129.29, 126.61, 125.95, 125.95, 125.47, 125.24, 124.57, 120.56, 63.69, 63.27, 61.11, 60.94, 60.63, 60.51,52.59, 51.28, 46.23,44.82,43.74, 43.37, 39.31, 38.49, 36.73, 35.22, 34.67, 33.00, 32.88, 32.33, 31.51, 30.69, 28.28, 22.83, 22.57, 18.22, 18.14, 14.12, 14.10, 14.08, 14.05, 14.02, −1.60. Anal. Calcd for $C_{20}H_{33}O_6NSi$: C, 58.36; H, 8.08; N, 3.40. Found: C, 58.65; H, 7.94; N, 3.15.

5.13. (±) Diethyl (1*R**,2*S**,4*R**,6*S**,8*S**)-9-(*N*-2-trimethylsilylethoxycarbonyl)-9-azaoxatricyclo-[4.3.1.$0^{2,4}$]-decane-6, 8-dicarboxylate and (±) diethyl (1*R**,2*S**,4*R**,6*S**,8*R**)-9-(*N*-2-trimethylsilylethoxycarbonyl)-9-azaoxatricyclo-[4.3.1.$0^{2,4}$]-decane-6,8-dicarboxylate (23a and 23b)

In a dry 100-mL round-bottomed flask was placed the bicyclic olefin, **22**, (632 mg, 1.54 mmol), *m*CPBA (ca. 85% purity, 663 mg, 3.07 mmol) and a magnetic stir bar. The flask was sealed and CH_2Cl_2 (15.0 mL) was added. The reaction mixture was stirred for 10 h at ambient temperature, at which time TLC analysis showed only a trace of the staring olefin. The reaction suspension was cooled to 0 °C, and dimethyl sulfide (1.13 mL, 975 mg, 15.7 mmol) was added. After stirring 1 h, hexanes (60 mL) were added to the suspension. The reaction mixture was filtered through a Celite® pad, and the retained material washed with minimal cold hexanes. The combined filtrate and washings were evaporated and the residue purified by flash chromatography (20% EtOAc/hexanes, SiO_2 (8 cm×20 cm; base-rinsed and oven dried collection tubes) to give first 272 mg (41%) of *endo* epoxide **23a** followed by 291 mg (44%) of *exo* epoxide **23b**.

endo Epoxide **23a**: IR ($CDCl_3$ solution) 2990, 2970, 1730, 1695, 1415, 1330, 1295, 1250, 1210, 1100, 1050, 1030, 860, 840 cm^{-1}. ^1H NMR (90 °C, *d-8* PhMe referenced to Me at δ 2.09) δ 4.87 (bs, 2H), 4.23 (m, 2H), 3.87 (m, 4H), 3.28 (dd, 1H, $J=3.6$, 3.6), 2.74 (dd, 1H, $J=3.9$, 3.9), 2.49 (ddd, 1H, $J=14.1$, 2.3, 1.6), 2.30 (m, 1H), 2.11 (m, 1H), 1.91 (ddd, 1H, $J=16.0$, 4.4, 2.1),

1.87 (ddd, 1H, 14.2, 8.5, 1.4), 1.35 (m, 1H), 1.02–0.91 (m, 2H, 0.96 (t, 3H, $J=7.1$), 0.95 (t, 3H, $J=7.1$), −0.06 (s, 9H). ^{13}C NMR (90 °C, *d-8* PhMe referenced to Me at δ 20.40) δ 175.36, 171.96, 155.99, 64.22, 61.23, 60.79, 52.10, 51.82, 50.79, 47.15, 37.55, 34.15, 31.05, 27.90, 18.49, 14.22, 14.18, −1.42. Anal. Calcd for $C_{20}H_{33}O_7NSi$: C, 56.18; H, 7.78; N, 3.28. Found: C, 56.30; H, 7.82; N, 3.14.

exo Expoxide **23b**: IR ($CDCl_3$ solution) 2990, 2965, 1735, 1700, 1415, 1330, 1295, 1255, 1195, 1110, 1080, 1030, 860, 840 cm^{-1}. ^{1}H NMR (90 °C, *d-8* PhMe referenced to Me at δ 2.09) δ 4.67 (dd, 1H, $J=2.5$, 1.1), 4.42 (dd, 1H, $J=6.4$, 4.7), 4.21 (m, 2H), 4.02 (q, 2H, $J=7.1$), 3.87 (m, 2H), 3.06 (m, 1H), 2.75 (dd, 1H, $J=5.3$, 3.7), 2.70 (dd, 1H, $J=14.9$, 4.7), 2.06 (d, 1H, $J=15.3$), 2.04 (ddd, 1H, $J=14.0$, 3.4, 1.1), 1.89 (dd, 1H, $J=14.0$, 3.4), 1.72 (dd, 1H, $J=14.9$, 6.4), 1.62 (ddd, 1H, $J=15.3$, 5.3, 2.6), 1.06 (t, 3H, $J=7.1$), 0.95 (t, 3H, $J=7.1$), 0.95–0.76 (m, 2H), −0.06 (s, 9H). ^{13}C NMR (90 °C, *d-8* PhMe referenced to Me at δ 20.40) δ 175.45, 172.09, 156.26, 64.12, 61.20, 60.89, 53.57, 52.67, 50.21, 48.10, 37.36, 36.38, 35.08, 32.03, 26.22, 23.03, 18.55, 14.24, 14.17, −1.43. Anal. Calcd for $C_{20}H_{33}O_7NSi$: C, 56.18; H, 7.78; N, 3.28. Found: C, 56.35; H, 7.70; N, 3.23.

5.14. Large-scale preparation and procedure for epoxide diastereomer separation using medium-pressure liquid chromatography (MPLC)

All glassware used in this preparation was base-rinsed and oven-dried prior to use. In a dry 250-mL round-bottomed flask was placed bicyclic olefin **21** (906 mg, 2.20 mmol), *m*CPBA (ca. 85% purity, 894 mg, 4.40 mmol), $NaHCO_3$ (370 mg, 4.40 mmol), and a magnetic stir bar. The flask was sealed and CH_2Cl_2 (22.0 mL) was added. TLC analysis indicated no starting olefin remained after 16 h. The contents of the flask were cooled to 0 °C and dimethyl sulfide (1.62 mL, 1.37 g, 22.0 mmol) was added. After stirring for 1 h, hexanes (120 mL) were added and the suspension was allowed to stand at 0 °C for 1 additional hour. The reaction mixture was filtered through a Celite® pad and the retained material was washed with cold hexanes (2×60 mL). Solvents were removed in vacuo to give a yellow/white semi-solid. This material was dissolved in 15% EtOAc/hexanes containing 0.25% (v/v) of freshly distilled triethylamine (solvent A) and passed through a SiO_2 plug (6 cm×8 cm) with the same solvent. Solvents were evaporated and the residue was loaded and eluted from and MPLC column (LoBar, 37 mm×440 mm) with solvent A to yield 334 mg of *endo* epoxide **23a** (36%) as a pale-yellow oil and 360 mg *exo* epoxide **23b** (38%) as a pale-yellow oil. The spectral and physical properties of these epoxides were identical to those listed above.

5.15. (±) Diethyl (1*R**,3*R**,5*S**,7*S**,8*S**)-2-(*N*-2-trimethylsilylethoxycarbonyl)-8-hydroxy-7-phenylselenyl-2-azabicyclo[3.3.1]-nonane-3,5-dicarboxylate (24)

In a dry 50-mL round-bottomed flask was placed *exo* epoxide, **23b**, (232.1 mg, 0.543 mmol), diphenyldiselenide (339 mg, 1.09 mmol), sodium borohydride (86 mg, 2.28 mmol) and a small magnetic stir bar. The flask was fitted with a reflux condensor and sealed. Anhydrous ethanol (10.0 mL) was added and vigorous evolution of hydrogen commenced. After the solution became colorless, the flask's contents were heated to reflux. No starting material was evident by TLC analysis after 14 h. The contents of the flask were cooled, diluted with H_2O (10 mL) and poured into Et_2O (50 mL). Layers were separated and the diluted reaction mixture was extracted with H_2O (3×10 mL), treated with brine, and dried. Filtration and removal of solvents left a yellow oil that was purified by flash chromatography (50% EtOAc/hexanes) to yield 297 mg (94%) of the *exo* selenohydrin, **24**, as a brilliant yellow gum. IR (film) 3480, 3000, 2970, 1740, 1715, 1690, 1460, 1340, 1310, 1260, 1200, 1100, 1080, 1030, 870, 850 cm^{-1}. ^{1}H NMR δ 7.54 (bs, 2H), 7.29 (m, 3H), 4.59 (dd, 1H, $J=9.5$, 3.1), 4.43 (bs, 0.5H), 4.26–4.10 (m, 8.5H), 3.40 (m, 1H), 2.78–2.72 (m, 1H), 2.59–2.47 (m, 2H), 2.28–2.16 (m, 2H), 1.99–1.78 (m, 3H), 1.26 (t, 3H, $J=7.1$), 1.21 (t, 3H, $J=7.1$), 1.07–1.03 (m, 2H), 0.50 (bs, 9H). ^{13}C NMR δ 176.26, 173.62, 173.52, 156.75, 156.59, 133.57, 133.36, 131.38, 131.02, 130.51, 129.09, 129.05, 127.40, 71.90, 70.44, 64.25, 61.39, 60.93, 60.30, 52.96, 52.51, 52.15, 41.92, 41.57, 38.17, 38.12, 35.08, 34.64, 33.10, 32.81, 24.98, 17.87, 17.67, 14.07, 13.95, −1.60. Anal. Calcd for $C_{26}H_{39}O_7NSiSe$: C, 53.41; H, 6.72; N, 2.40. Found: C, 53.36; H, 6.62; N, 2.12.

5.16. (±) Diethyl (1*R**,3*R**,5*S**,8*S**)-2-(*N*-2-trimethylsilylethoxycarbonyl)-8-hydroxy-2-azabicyclo-[3.3.1]non-6-ene-3,5-dicarboxylate (25)

In a dry 100-mL round-bottomed flask was placed *exo* selelnohydrin, **24**, (135.4 mg, 0.232 mmol) and a large stir bar. The selenohydrin was dissolved in CH_2Cl_2 (5 mL) and pyridine (0.25 mL) and the solution was cooled to 0 °C. *tert*-Butyl hydrogen peroxide (0.25 mL, 90%) and hydrogen peroxide (2.0 mL, 30%) were added sequentially and the two-phase mixture was stirred vigorously at 0 °C for 6 h. The cold mixture was poured into refluxing CCl_4 (50 mL) and held at reflux for 5 min. The mixture was partitioned between Et_2O (100 mL) and aqueous NaOH (1.0 M, 3 20 mL), aqueous H_2SO_4 (0.5 M, 3×20 mL), 50% aqueous $NaHCO_3$, and brine. The organic solution was dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (50% EtOAc/hexanes) to give 79.6 mg (80%) of **25** as a light-yellow gum. IR ($CDCl_3$ solution) 3590, 3450, 2940, 1730, 1690, 1400, 1290, 1250, 1190, 1070, 1020, 860, 830 cm^{-1}. ^{1}H NMR δ 6.08–5.90 (m, 2H), 4.36 (bs, 1H), 4.26–4.13 (m, 6H), 4.00–3.84 (m, 2H), 2.40–1.90 (m, 4H), 1.27 (t, 6H, $J=7.1$), 1.10–0.90 (m, 2H), 0.03 (s, 9H). ^{13}C NMR δ 174.01, 172.72, 172.37, 157.00, 156.58, 130.92, 129.32, 129.01, 65.55, 64.62, 64.35, 61.23, 60.98, 53.55, 53.27, 52.65, 40.98, 34.21, 26.85, 26.47, 17.67, 17.34, 13.91, 13.89, −1.75. Anal. Calcd for $C_{20}H_{33}O_7NSi$: C, 56.18; H, 7.78; N, 3.28; found: C, 56.35; H, 7.77; N, 3.02.

5.17. (±) Diethyl (1*R**,3*R**,5*S**,8*S**)-8-hydroxy-2-azabicyclo[3.3.1]non-6-ene-3,5-dicarboxylate (26)

In a dry 50-mL round-bottomed flask was placed allylic alcohol, **25**, (41.5 mg, 0.097 mmol), anhydrous KF (22.6 mg, 0.388 mmol), and a small magnetic stir bar. The flask was sealed and CH_3CN (1.5 mL) and TBAF (0.290 mL, 1.0 M in THF) were sequentially added. The flask was placed in a preheated oil bath (70 °C) for 20 min. Analysis of the reaction mixture by TLC showed only a trace of starting material. Solvents were removed in vacuo and the residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to give 20.2 mg (77%) of **26** as a light-yellow gum. IR ($CDCl_3$ solution) 3600, 3340, 2980, 2930, 1725, 1450, 1370, 1235, 1070, 1020 cm^{-1}. ^1H NMR δ 6.15 (ddd, 1H, J = 10.0, 3.9, 1.2), 6.08 (d, 1H, J = 9.9), 4.18 (q, 2H, J = 7.1), 4.16 (q, 2H, J = 7.1), 3.99 (d, 1H, J = 3.7), 3.61 (dd, 1H, J = 12.0, 3.8), 3.41 (s, 1H), 2.50 (bs, 2H), 2.04 (m, 1H), 1.95 (m, 1H), 1.87 (m, 1H), 1.76 (dd, 1H, J = 12.5, 12.4), 1.27 (t, 3H, J = 7.1), 1.25 (t, 3H, J = 7.1). ^{13}C NMR δ 174.58, 173.08, 131.56, 131.38, 67.97, 61.26, 61.19, 52.94, 51.28, 42.70, 33.58, 29.07, 14.11 (2C). Anal. Calcd for $C_{14}H_{21}O_5N$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.27; H, 7.41; N, 4.77.

5.18. (±)-Diethyl (1*R**,2*S**,4*R**,6*S**,8*S**)-9-aza-3-oxatricyclo[4.3.1.0^{2,4}]decane-6,8-dicarboxylate (27)

In a dry 50-mL round-bottomed flask was placed *endo* epoxide, **23a**, (103.8 mg, 0.243 mmol), anhydrous KF (56.4 mg, 0.971 mmol) and a magnetic stir bar. The flask was sealed and CH_3CN (2.0 mL) and TBAF (1 M in THF, 0.730 mL, 0.73 mmol) were added sequentially via syringe. The flask was immersed in a preheated (60 °C) oil bath. Analysis of the reaction mixture by TLC showed no starting material remained after 20 min. Solvents were quickly removed in vacuo and the residue suspended in EtOAc. Flash chromatography (EtOAc) afforded 67.5 mg (95%) of aminoepoxide, **27**, as a light-yellow gum. IR ($CDCl_3$ solution) 2995, 1730, 1260, 1220, 1205, 1165, 1070, 1030 cm^{-1}. ^1H NMR δ 4.16 (m, 2H), 4.08 (q, 2H, J = 7.1), 3.63 (dd, 1H, J = 7.5, 1.5), 3.53 (m, 1H), 3.03 (m, 1H), 2.91 (dd, 1H, J = 4.3, 4.2), 2.46 (m, 2H), 2.23 (m, 1H), 2.11–1.89 (m, 3H), 1.57 (m, 1H), 1.27 (t, 3H, J = 7.1). ^{13}C NMR δ 176.09, 174.81, 61.21, 60.71, 53.93, 51.78, 50.96, 46.44, 36.75, 32.85, 30.85, 27.62, 14.91, 14.01. Anal. Calcd for $C_{14}H_{21}O_5N$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.07; H, 7.12; N, 4.90.

5.19. (±)-Diethyl (1*R**,3*S**,5*S**,7*S**,8*S**)-8-hydroxy-7-phenylselenyl-2-azabicyclo[3.3.1]nonane-3,5-dicarboxylate (28)

In a dry 10-mL round-bottomed flask was placed diphenyldiselenide (71.4 mg, 0.229 mmol), sodium borohydride (18.2 mg, 0.480 mmol), 15-crown-5 (0.012, 12.6 mg, 0.057 mmol), powdered molecular sieves (3 Å, ca. 40 mg) and a magnetic stir bar. The flask was sealed and 1,2-DME (0.90 mL) was added via syringe. Hydrogen evolution occurred and the yellow color of diphenyldiselenide had disappeared within 1 h. To this solution was added *endo* aminoepoxide, **27**, (32.4 mg, 0.114 mmol) in 1,2-DME (0.20 mL followed by 0.10 mL rinse). After 15 min, TLC analysis showed none of the aminoepoxide remained. The reaction mixture was cooled to 0 °C and trimethylsilyl chloride (0.145 mL, 124.4 mg, 1.14 mmol) was added dropwise; thirty min later, MeOH (0.50 mL) was added to the solution. The solution was allowed to warm to room temperature and loaded directly (**STENCH!!!** This operation must be performed in a well-ventilated hood) onto a SiO_2 column and eluted with 2% MeOH/CH_2Cl_2) to yield 36.3 mg (72%) of *endo* selenohydrin, **28**, as a bright yellow gum. IR ($CDCl_3$ solution) 3680, 3590, 2990, 1730, 1600, 1435, 1220 cm^{-1}. ^1H NMR δ 7.58 (m, 2H), 7.37–7.26 (m, 3H), 5.30 (bs, 1H), 4.26–4.15 (m, 4H), 3.96 (dd, 1H, J = 7.9, 2.6), 3.63–3.60 (m, 2H), 3.28 (ddd, 1H, J = 8.0, 8.0, 8.0), 2.66–2.58 (m, 2H), 2.25–1.95 (m, 2H), 1.90–1.50 (m, 3H), 1.30 (t, 2H, J = 7.1), 1.27 (t, 3H, J = 7.1). ^{13}C NMR 175.25, 171.12, 135.59, 129.61, 128.87, 126.93, 72.77, 62.60, 61.68, 61.58, 59.18, 42.91, 38.40, 37.32, 33.72, 23.56, 14.09, 14.03. FABHRMS: calcd $C_{20}H_{28}O_5N^{78}Se$, $[MH]^+$: 441.113090; found: 441.114052; calcd: $C_{20}H_{28}O_5N^{80}Se$, $[MH]^+$: 443.114140; found: 443.113269.

5.20. (±) Diethyl (1*R**,3*S**,5*S**,8*S**)-8-hydroxy-2-azabicyclo[3.3.1]non-6-ene-3,5-dicarboxylate (29)

In a dry 10-mL round-bottomed flask was placed *endo* selenohydrin, **28**, (19.7 mg, 0.045 mmol), (±)-(camphorsulfonyl)oxaziridine ((±)-CSOA, 20.5 mg, 0.089 mmol),[23] a spatula tip of powdered 3 Å molecular sieves (ca. 40 mg), and a small magnetic stir bar. The flask was fitted with a reflux condensor, sealed, and purged with nitrogen; 1,2-DME (0.500 mL) was added and the suspension stirred at ambient temperature. After 2 h, *d*-5 pyridine (0.036 mL, 36.2 mg, 0.450 mmol) and additional 1,2-DME (1.00 mL) were added and the contents of the flask heated to reflux for 1 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to yield 8.5 mg (67%) of the *endo* allylic alcohol, **29**, as a colorless gum. IR ($CDCl_3$ solution) 3600, 2990, 2940, 1745, 1460, 1370, 1260, 1215, 1190, 1075, 1030 cm^{-1}. ^1H NMR δ 5.97 (dd, 1H, J = 10.0, 1.2), 5.84 (ddd, 1H, J = 10.0, 4.4, 1.3), 4.19 (q, 2H, J = 7.1), 4.16–4.06 (m, 2H), 3.61 (d, 1H, J = 6.0), 3.35 (bs, 1H), 2.50 (m, 1H), 2.18 (dd, 1H, J = 13.6, 6.9), 2.10–1.80 (m, 4H), 1.28 (t, 3H, J = 7.1), 1.27 (t, 3H, J = 7.1). ^{13}C NMR δ 175.06, 174.94, 132.42, 130.15, 67.73, 61.10, 60.97, 52.51, 52.04, 41.56, 30.57, 28.62, 14.16 (2C). FABHRMS: calcd: $C_{14}H_{22}O_5N$, $[MH]^+$: 284.149798; found: 284.149370.

5.21. (±) Diethyl (1*R**,3*R**,5*S**,8*S**)-2-(*N*-trimethylsilylethoxycarbonyl)-8-methylsulfonlyloxy-2-azabicyclo-[3.3.1]non-6-ene-3,5-dicarboxylate (30)

In a dry 25-mL round-bottomed flask was placed fully protected *exo* allylic alcohol, **25**, (78.0 mg, 0.182 mmol), mesyl anhydride (38.1 mg, 0.219 mmol), and a small magnetic stir bar. The flask was sealed, cooled to 0 °C, and the contents dissolved in CH_2Cl_2 (2.0 mL). After 5 min, TEA (0.051 mL, 36.8 mg, 0.364 mmol) and DMAP (4.5 mg, 0.036 mmol) were added sequentially.

Analysis of the reaction mixture at 1 h indicated some starting allylic alcohol remained; additional mesyl anhydride (17.0 mg, 0.110 mmol) was added. After an additional 20 min, only a trace of the starting material was evident by TLC. A cold (0 °C) aqueous solution (2 mL) of 50% $NaHCO_3$ was added and the mixture was stirred vigorously at 0 °C for 20 min. The contents of the flask were portioned between Et_2O and $NaHCO_3$ (50% saturated aqueous, 3×10 mL), H_2SO_4 (0.5 M, 2×10 mL), saturated bicarbonate solution and brine. The organic solution was dried, filtered, and concentrated in vacuo. Purification by flash chromatography (50% EtOAc/hexanes) provided 91.9 mg (quantitative) of allylic mesylate, **30**, as a light-yellow gum. IR ($CDCl_3$ solution) 2960, 1735, 1700, 1400, 1360, 1290, 1250, 1180, 1080, 860 cm^{-1}. ^1H NMR δ 6.28 (m, 1H), 6.00 (dd, 1H, J=9.3, 4.2), 4.90–4.65 (m, 1H), 4.60–4.40 (m, 1H), 4.35–3.80 (m, 7H), 3.22 (bs, 1.5H), 3.07 (bs, 1.5H), 2.40–1.90 (m, 4H), 1.29 (t, 3H, J=7.1), 1.28 (t, 3H, J=7.1), 1.20–1.00 (m, 1H), 1.00–0.90 (m, 1H), 0.03 (bs, 9H). ^{13}C NMR δ 173.23, 172,40, 172.01, 170.99, 156.46, 135.34, 135.09, 124.61, 72.41, 71.87, 65.14, 64.84, 61.61, 61.29, 61.04, 60.24, 53.35, 52.89, 50.63, 40.64, 40.32, 38.83, 37.94, 34.31, 33.92, 33.70, 29.55, 27.03, 26.65, 20.91, 17.46, 14.08, 13.98, −1.70. Anal. Calcd for $C_{21}H_{35}O_9NSSi$: C, 49.88; H, 6.98; N, 2.77. Found: C, 50.27; H, 6.81; N, 2.83.

5.22. (±) Diethyl (1*R**,3*R**,5*S**,8*R**)-2-azatricyclo-[3.3.1.0^{1,8}]non-6-ene-3,5-dicarboxylate (31)

In a dry 10-mL pear-shaped flask was placed **30** (24.3 mg, 0.048 mmol), potassium fluoride (11.2 mg, 0.192 mmol), and a small magnetic stir bar. The flask was sealed; the contents were suspended in CH_3CN (1.0 mL) and TBAF (1.0 M, 0.144 mL, 0.144 mmol) was added. The flask was immersed in a preheated (60 °C) oil bath, and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 0.036 mL, 37 mg, 0.240 mmol) added. Analysis of the reaction mixture after 30 min by TLC showed no remaining mesylate, **30**. The solvents were removed in vacuo and the residue purified by flash chromatography (50% EtOAc/hexanes) to yield 10.7 mg (84%) of **31** as a light-yellow gum. IR ($CDCl_3$ solution) 2995, 1730, 1370, 1250, 1195, 1180, 1120, 1070, 1030 cm^{-1}. ^1H NMR δ 6.18 (d, 1H, J=9.6), 6.01 (dd, 1H, J=9.6, 4.9), 4.21 (q, 2H, J=7.1), 4.17 (q, 2H, J=7.1), 3.43 (dd, 1H, J=12.3, 7.5), 2.87 (m, 1H), 2.67 (m, 1H), 2.27 (dd, 1H, J=13.2, 2.7), 1.96 (ddd, 1H, 13.1, 7.4, 2.4), 1.70 (dd, 1H, J=13.0, 1.3), 1.67 (dd, 1H, 12.8, 12.7), 1.28 (t, 3H, J=7.0), 1.27 (t, 3H, J=7.1). ^{13}C NMR δ 174.18, 173.44, 129.57, 123.76, 61.18, 61,16, 55.02, 41.89, 34.26, 34.21, 31.05, 27.96, 14.20, 14.11. FABHRMS: calcd: $C_{14}H_{20}O_4N$, $[MH]^+$: 266.139050; found: 266.139233.

5.23. (±) Diethyl (1*R**,3*S**,5*S**,7*S**,8*S**)-7-((methoxycarbonyl)-sulfamyloxy)-2-azatricyclo-[3.3.1.1^{2,8}]nonane-3,5-dicarboxylate (32)

In a dry 5-mL round-bottomed flask was placed the corresponding aziridine alcohol (12.9 mg, 0.046 mmol), Burgess reagent[24] (16.3 mg, 0.068 mmol), and a small magnetic stir bar. The flask was sealed and the contents dissolved in *d*-6 PhD (0.700 mL). The flask was heated to 50 °C and held at this temperature for 3 h; at this time no change was evident by ^1H NMR analysis. Solvent was removed in vacuo and the residue redissolved in *d*-6 Ph-D (0.700 mL) and heated to a brisk reflux for 20 min. Purification by flash chromatography yielded 3.1 mg (16%) of the Burgess adduct, **32**, as a colorless gum. ^1H NMR (400 MHz) δ 7.55 (bs, 1H), 4.90 (d, 1H, J=8.0), 4.57 (d, 1H, J=5.0), 4.25 (m, 2H), 4.13 (q, 2H, J=7.1), 3.80 (s, 3H), 3.34 (m, 1H), 2.99 (m, 1H), 2.59 (m, 1H), 2.18 (m, 1H), 2.10 (m, 2H), 1.50 (m, 1.33 (t, 3H, J=7.1), 1.25 (t, 3H, J=7.1). FAB-HRMS: calcd: $C_{16}H_{25}O_9N_2S$, $[MH]^+$: 421.128710; found: 421.128078.

5.24. (±) Ethyl (1*R**,2*S**,3*S**,5*S**,7*S**)-8-(*N*-2-trimethylsilylethoxycarbonyl)-aza-2-hydroxy-9-oxo-10-oxatricyclo-[3.3.2.1]-undecanene-5-carboxylate (33)

In a dry 10-mL round-bottomed flask was placed *endo* epoxide, **23a**, (98.7 mg, 0.231 mmol), triphenylphosphine (15.1 mg, 0.058 mmol) and a small magnetic stir bar. The flask was sealed and CH_2Cl_2 (2.5 mL) was added. The resulting solution was cooled in a dry ice/acetone bath and trimethylsilyl bromide (0.061 mL, 70.7 mg, 0.462 mmol) was added dropwise. The cold solution was allowed to warm overnight. Solvent was removed in vacuo and the residue was dissolved in THF (5.0 mL); H_2O (0.200 mL) and HCl (0.200 mL, 12 M) were sequentially added. After stirring 2 h, the reaction mixture was poured into Et_2O (30 mL) and extracted with 50% saturated $NaHCO_3$ (3×10 mL), treated with brine and dried. After filtration and concentration, the residue was purified by flash chromatography (50% EtOAc/hexanes) to give 65.0 mg (70%) of the tricyclic lactone, **33**, as a colorless gum. IR ($CDCl_3$ solution) 3600, 3440, 2980, 1725, 1680, 1415, 1385, 1340, 1315, 1255, 1160, 1110, 1055, 1055, 990, 870, 840 cm^{-1}. ^1H NMR (70 °C, *d-6* PhH referenced to δ 7.15) δ 5.21 (bs, 1H), 4.56 (bs, 1H), 4.24 (m, 2H), 4.04 (bs, 1H), 3.84 (q, 2H, J=7.1), 3.74 (bs, 1H), 2.40–2.34 (m, 2H), 2.10 (bs, 1H), 1.85–1.74 (m, 3H), 1.49 (ddd, 13.3, 3.1, 3.0), 0.98 (dd, 2H, J=3.7, 3.7), 0.90 (t, 3H, J=7.1), −0.05 (s, 9H). ^{13}C NMR (70 °C, *d-6* PhH referenced to δ 128.00) δ 174.37, 171.17, 155.54, 75.30, 62.27, 64.90, 60.82, 55.59, 49.82, 38.68, 32.61, 31.63, 28.44, 18.11, 13.96, −1.63. Anal. Calcd for $C_{18}H_{29}O_7NSi$: C, 54.11; H, 7.31; N, 3.51. Found: C, 54.14; H, 7.30; N, 3.20.

5.25. (±) Ethyl (1*S**,4*S**,6*R**,8*S**,10*S**)-5-(N-2-trimethyl-)-10-hydroxy-3-oxo-5-aza-2-oxabicyclo[4.3.1.1^{4,8}]undecane-8-carboxylate (34)

In a dry 10-mL round-bottomed flask was placed lactone, **33**, (56.5 mg, 0.141 mmol), anhydrous KF (32.9 mg, 0.566 mmol), and a small magnetic stir bar. The flask was sealed, and CH_3CN (1.4 mL) and TBAF (0.425 mL, 1.0 M in THF) were sequentially added. The flask was placed in a preheated oil bath (60 °C) for 1 h; no starting material was detected by TLC analysis at this time. Solvents were removed in vacuo, and the residue was purified by flash chromatography

(EtOAc) to yield 30 mg (83%) of **34** as a white crystalline material, mp 154–155 °C. IR ($CDCl_3$ solution) 3600, 2950, 1760, 1460, 1390, 1260, 1160, 1080, 1055 cm^{-1}. ^1H NMR δ 4.40 (m, 1H), 4.17 (q, 2H, J=7.1), 4.07 (dd, 1H, J=6.9, 1.3), 3.96 (bs, 1H), 3.30 (d, 1H, J=2.9), 2.53 (ddd, 1H, J=15.4, 5.1, 2.4), 2.31–2.28 (m, 1H), 2.18 (ddd, 1H, J=14.1, 6.9, 2.4), 2.07 (m, 1H), 1.96–1.93 (m, 1H), 1.83–1.80 (m, 1H), 1.27 (t, 3H, J=7.1). ^{13}C NMR δ 176.44, 175.22, 75.52, 69.90, 61.15, 56.11, 50.04, 38.55, 32.78, 31.49, 28.94, 14.08. Anal. Calcd for $C_{12}H_{17}O_5N$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.36; H, 6.71; N, 5.53.

5.26. (±) Ethyl (1*R**,4*S**,6*S**,8*S**,10*S**)-5-(*N*-trimethylsilylethoxycarbonyl)-10-methylsulfonyloxy-3-oxo-5-aza-2-oxatricyclo[4.3.1.1^{4,8}]undecane-8-carboxylate (35)

In a 10-mL pear-shaped flask was placed lactone, 33 (98.6 mg, 0.274 mmol), mesyl anhydride (86.0 mg, 0.494 mmol) and a small magnetic stir bar. The flask was sealed, the solids dissolved in CH_2Cl_2 (2.5 mL), and the resulting solution cooled in an ice bath. After 5 min, TEA (0.072 mL. 52 mg, 0.518 mmol) and DMAP (6.0 mg, 0.049 mmol) were sequentially added. The reaction mixture was stirred for 2.5 h at 0 °C, at which time no starting lactone was evident by TLC. A 50% saturated solution of $NaHCO_3$ was added (ca. 5 mL) and the contents of the flask stirred an additional 30 min. The contents of the flask were portioned between Et_2O and $NaHCO_3$ (50% saturated aqueous, 3×10 mL), H_2SO_4 (0.5 M, 2×10 mL), saturated bicarbonate solution, and brine. The organic solution was dried, filtered, and the solvents removed in vacuo. The residue was purified by flash chromatography (50% EtOAc/hexanes) provided 112.0 mg (95%) of the lactone mesylate, **35**, as a colorless gum. IR ($CDCl_3$ solution) 2980, 1730, 1460, 1370, 1260, 1250, 1180, 1150, 1100, 1060, 990, 900, 860, 830 cm^{-1}. ^1H NMR (60 °C, *d*-8 PhMe referenced to Me at δ 2.09) δ 5.15 (bs, 1H), 4.67 (bs, 1H), 4.62 (bs, 1H), 4.35 (bs, 0.7H), 4.20 (m, 2H), 4.10 (bs, 0.3H), 3.89 (q, 2H, J=7.1), 2.42 (s, 3H), 2.25–2.15 (m, 1H, 2.15–2.05 (m, 2H), 1.90–1.70 (m, 2H), 1.55–1.45 (m, 1H), 0.98 (m, 6H), −0.06 (m, 9H). ^{13}C NMR (60 °C, *d*-8 PhMe referenced to Me at δ 20.4) δ 174.47, 173.81, 171.16, 170.33, 75.43, 73.14, 72.65, 65.35, 64.78, 61,20, 60.88, 60.03, 55.36, 49.85, 48.12, 38.76, 38.10, 37.50, 32.65, 31.71, 31.31, 28.74, 28.54, 18.16, 18.09, 14.27, 14.10, −1.52, −1.58. FABHRMS: calcd $C_{22}H_{40}O_9NSi_2S$, $[MH]^+$: 550.195700; found: 550.196236.

5.27. (±) Ethyl (1*S**,4*S**,6*R**,8*S**,10*S**)-3-Oxo-5-aza-2-oxatetracyclo[4.3.1.1^{4,8}1.^{6,10}]undecane-8-carboxylate (36)

In a dry 10-mL round-bottomed flask was placed lactone mesylate, **35**, (74.6 mg, 0.156 mmol), anhydrous potassium fluoride (36.6 mg, 0.625 mmol), and a small magnetic stir bar. The flask was sealed and CH_3CN (1.6 mL) and TBAF (1.0 M, 0.469 mL, 0.469 mmol) were sequentially added via syringe. The flask was placed in a preheated (60 °C) oil bath; analysis of the reaction mixture by TLC at 1 h showed none of the lactone mesylate remained. Solvents were removed in vacuo; the residue was purified by flash chromatography (50% EtOAc/hexanes → EtOAc) to give 34.1 mg (94%) of the tetracycle **36** as a light-yellow gum. IR ($CDCl_3$ solution) 2995, 1750, 1730, 1470, 1380, 1260, 1240, 1170, 1160, 1090, 1070, 1010 cm^{-1}. ^1H NMR δ 5.13 (ddd, 1H, J=7.4, 5.7, 1.6), 4.27 (d, 1H, J=8.5), 4.14 (q, 2H, J=7.1), 2.70 (m, 1H), 2.66 (m, 1H), 2.22 (ddd, 1H, J=13.9, 3.0, 1.8), 2.15–2.09 (m, 3H), 2.06 (ddd, 1H, J=7.9, 5.8, 2.0), 1.88 (dd, 1H, J=14.6, 2.3), 1.24 (t, 3H, J=7.1). ^{13}C NMR δ 174.07, 172.39, 71.82, 61.32, 53.97, 38.24, 35.92, 35.55, 32.30, 29.90, 27.76, 14.02. FABHRMS: calcd $C_{12}H_{16}O_4N$, $[MH]^+$: 238.107630; found: 238.107933.

5.28. (±) (1*R**,3*S**,5*S**,8*S**)-8-Hydroxy-2-azabicyclo[3.3.1]non-6-ene-3,5-dicarboxylate, disodium salt (4)

In a 10-mL round-bottomed flask was placed *endo* aminodiester, **29**, (7.2 mg, 0.025 mmol) and a small magnetic stir bar. The material was dissolved in EtOH (0.5 mL) and H_2O (0.051 mL). Sodium hydroxide (2.0 M, 0.051 mL) was added and the solution stirred 18 h at ambient temperature. The volatile solvents were removed in vacuo, and the residual solution was diluted with D_2O (ca. 2 mL), frozen, and lyophilized to give a quantitative yield of a white powder. IR (KBr pellet) 3400, 1580, 1460, 1390, 1030, 880 cm^{-1}. ^1H NMR (D_2O referenced to residual HDO at δ 4.60) δ 5.74 (d, 1H, J=10.0), 5.50 (ddd, 1H, J=10.0, 4.4, 1.3), 3.99 (d, 1H, J=3.8), 3.04 (m, 1H), 2.98 (bs, 1H), 2.09 (m, 1H), 1.77–1.70 (m, 2H), 1.50 (m, 1H). ^{13}C NMR (D_2O referenced to a 1,4-dioxane (ca. 0.1% v/v) co-solvent δ 66.50) δ 184.57, 181.89, 134.99, 127.47, 67.04, 52.73, 51.85, 42.63, 31.19, 28.53. FABHRMS: calcd for $C_{10}H_{11}O_5NNa$ $[M-H]^-$: 248.053470; found: 248.053492.

5.29. (±) (1*R**,3*R**,5*S**,8*S**)-8-Hydroxy-2-azabicyclo[3.3.1]non-6-ene-3,5-dicarboxylate, disodium salt (5)

In a 5-mL round-bottomed flask was placed *exo* aminodiester, **26**, (39.8 mg, 0.140 mmol) and a small magnetic stir bar. The material was dissolved in EtOH (1.0 mL) and H_2O (0.574 mL). Sodium hydroxide (1.0 M, 0.426 mL) was added and the solution stirred 5 h at ambient temperature. The volatile solvent was removed in vacuo, and the residual solution was diluted with H_2O (ca. 2 mL), frozen and lyophilized to give 37.5 mg (quantitative) of a white powder. IR (KBr pellet) 3400, 1630, 1460, 1400, 1080, 1010, 880, 830 cm^{-1}. ^1H NMR (D_2O referenced to residual HDO at 4.60) δ 5.86–5.80 (m, 2H), 3.70 (d, 1H, J=2.9), 3.03 (dd, 1H, J=12.1, 3.6), 2.99 (s, 1H), 1.65 (m, 1H), 1.56 (m, 1H), 1.45 (dd, 1H, J=12.5, 3.0), 1.29 (dd, 1H, J=12.6, 12.6). ^{13}C NMR (D_2O referenced to a 1,4-dioxane (ca. 0.1% v/v) co-solvent δ 66.50) δ 186.42, 183.76, 136.59, 131.75, 69.84, 55.72, 54.90, 46.73, 37.46, 32.12. FABHRMS: calcd $C_{10}H_{11}O_5NNa$ $[M-H]^-$: 248.053470; found: 248.053492.

5.30. (±) (1*R**,3*R**,5*S**,8*R**)-2-Azatricyclo[3.3.1.0^{1,8}]-non-6-ene-3,5-dicarboxylate, disodium salt (7)

In a 10-mL pear-shaped flask was placed *exo* unsaturated aziridine, **31**, (6.6 mg, 0.25 mmol) and a small

magnetic stir bar. The diester was dissolved in D_2O (0.250 mL) and a solution of NaOH (2.0 M in D_2O, 0.30 mL, 0.060 mmol) was added. The resulting solution was stirred at ambient temperature for 20 h. The contents of the flask were diluted with H_2O (ca. 2 mL), frozen, and lyophilized to give a white powder in quantitative yield. IR (KBr pellet) 3400, 1600, 1400, 1120, 1010, 860, 840 cm^{-1}. ^1H NMR (D_2O referenced to residual HDO at δ 4.60) δ 5.93 (d, 1H, J = 9.6), 5.78 (dd, 1H, J = 9.6, 5.0), 3.02 (dd, 1H, J = 12.3, 7.3), 2.59 (m, 1H), 2.30 (dd, 1H, J = 5.0, 5.0), 1.90 (dd, 1H, J = 13.2, 1.9), 1.70 (ddd, 1H, J = 12.7, 7.3, 1.2), 1.45 (d, 1H, J = 13.2), 1.18 (dd, 1H, J = 12.7, 12.6). ^{13}C NMR (D_2O referenced to a 1,4-dioxane (ca. 0.1% v/v) co-solvent δ 66.50) δ 183.51, 182.08, 132.59, 121.98, 57.28, 43.40, 34.39, 33.51, 32.77, 28.29. FABHRMS: calcd for $C_{10}H_9O_4N$, $[M\text{-}H]^-$: 230.042700; found: 230.042928.

5.31. (±) (1*R**,2*S**,3*S**,5*S**,7*S**)-10-Hydroxy-3-oxo-2-oxa-5-azatricyclo[4.3.1.1^{4,8}]undecane-8-carboxylate, sodium salt (8)

In a 10-mL pear-shaped flask was placed amino ester, **34**, (11.4 mg, 0.045 mmol) and a small magnetic stir bar. The material was dissolved in D_2O (0.425 mL) and an aqueous solution of sodium hydroxide in D_2O added (2.0 M, 0.050 mL). After stirring 4 h at ambient temperature, the solution was frozen and lyopholyzed to give a white powder. ^1H NMR analysis of this material indicated the lactone had opened. The hydroxy acid salt was dissolved in HCl (1.0 M, 0.500 mL) and warmed to 50 °C for 3 days. After cooling, the volatile components were removed in vacuo, and the residual solution was diluted with H_2O (ca. 2 mL), frozen, and lyophilized to give 11.8 mg (quantitative) of a white powder. IR (KBr pellet) 3160, 1730, 1465, 1440, 1390, 1250, 1170, 1140, 1050 cm^{-1}. ^1H NMR (D_2O referenced to residual HDO at δ 4.60) δ 4.53 (bs, 1H), 4.47 (d, 1H, J = 6.4), 4.11 (s, 1H), 3.83 (bs, 1H), 2.40 and 2.08 (AB q, 2H, J = 15.8), 2.40 (ddd, J = 15.8, 4.7, 1.8), 2.31 and 1.87 (AB q, 2H, J = 14.6) 2.24 and 2.16 (AB q, 2H, J = 15.3), 2.24 (ddd, 1H, J = 15.3, 6.8, 1.8). ^{13}C NMR (D_2O referenced to a 1,4-dioxane (ca. 0.1% v/v) co-solvent δ 66.50) δ 177.14, 169.58, 75.40, 64.03, 54.57, 50.24, 36.47, 31.03, 28.66, 25.45. FABHRMS: calcd $C_{10}H_{13}O_5NNa$ $[M-H]^-$: 226.071840; found: 226.071548.

5.32. (±) (1*S**,4*S**,6*R**,8*S**,10*S**)-3-Oxo-5-aza-2-oxa-tetracyclo[4.3.1^{4,8}.0^{6,10}]undecane-8-carboxylate, sodium salt (9)

In a 10-mL pear-shaped flask was placed aziridine lactone, **36** (14.1 mg, 0.059 mmol) and a small magnetic stir bar. This material was suspended in H_2O (0.480 mL) and an aqueous solution of NaOH (1.0 M, 0.120 mL, 0.120 mmol) was added; EtOH (0.500 mL) was added to the turbid solution to effect dissolution. After 2 h, the volatile solvents were removed in vacuo and the residual solution was diluted with H_2O (ca. 5 mL), frozen and lyophilized to give 16.4 mg (quantitative) of a white powder. ^1H NMR (D_2O referenced to residual HDO at δ 4.60) δ 4.31 (m, 1H), 3.74 (dd, 1H, J = 10.0, 9.1), 2.38 (m, 1H), 2.32 (m, 1H), 2.03 (m, 1H), 1.87 (d, 1H, 14.1), 1.59 (m, 4H). FABHRMS: calcd $C_{10}H_{10}O_4N$, $[M-H]^-$: 208.060580; found: 208.060983.

5.33. Enzyme assays

The standard buffer used in all assays consisted of 50 mM *N*-ethylmorpholine, 0.5 mM dithioerythritol, 0.5 mM ethylenediaminetetraacetic acid, 10 mM trisodium citrate, 0.1 mg/mL of bovine serum albumin, 10% (v/v) glycerol in doubly distilled water. This buffer solution was adjusted to the required pH with concentrated HCl.[10] Bifunctional chorismate mutase/prephenate dehydrogenase (T-protein) was derived from *E. coli* strain JFM-30 as was a generous gift of Prof. Jeremy Knowles' research group at Harvard University. The enzyme had been purified by ammonium sulfate fractionation and was stored at −78 °C. Concentrated enzyme was stored in a stabilizing buffer, which consisted of 100 mM *N*-ethylmorpholine, 1.0 mM dithioerythritol, 1.0 mM ethylenediaminetetraacetic acid, 21 mM trisodium citrate, 10% (v/v) glycerol in doubly distilled water adjusted to pH 7.0 with concentrated HCl. Prior to assaying, stock enzyme solutions were allowed to reactivate at 0 °C for 2 h and then centrifuged. Chorismic acid was used as obtained from Sigma. All buffer, substrate and inhibitor solutions were filtered (0.45 μm) prior to use. Inhibitor solutions were prepared by initial dilution of analytically weighed samples corrected for residual salts with stabilizing buffer. Subsequent dilutions were made with assay buffer at the appropriate pH.

Assays were performed at 30 °C using a Lauda Model RM 20 circulating bath connected to a water-jacketed cell holder in a Uvikon 860 spectrophotometer. The conversion of chorismate to prephenate was directly monitored by following the decrease in absorbance at λ = 274 nm ($\Delta\varepsilon$ = 2630). Assays at pH 7.5 were conducted in a 1.00 cm cell with a total reaction volume of 1.00 mL; assays at pH 9.0 were conducted in a 0.200 cm cell with a total reaction volume of 0.500 mL. Reactions were initiated by addition of enzyme (gas-tight syringe) to a solution of substrate with or without inhibitor in the appropriate buffer. Enzyme concentrations were adjusted to give approximately 15% conversion of chorismate to prephenate at the lowest substrate concentrations over 8 min. Data were analyzed with EnzFitter,[33] IC_{50} values were generated with Kincalc.[34] Inhibitor and substrate solutions were routinely stored for several days at −78 °C; chorismate concentrations fell approximately 1% for each day of such storage.

Acknowledgements

Professor Paul A. Bartlett's insistence upon independent submission of this manuscript is graciously acknowledged. This work was supported in part by Grant No. GM-28965 from the National Institute of Health (PAB). Thanks to the laboratories of Professor Jeremy Knowles (Harvard University) for the generous gift of chorismate mutase used in these experiments. Sincerest appreciation is extended to the staff of the University

of California, Berkeley, Mass Spectrometry and NMR Facilities for their professional expertise and assistance in the face of compound characterization challenges.

References and notes

1. (a) Haslam, E. *Shikimic Acid Metabolism and Metabolites*; John Wiley and Sons: New York, 1993; (b) Ganem, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 936; (c) Knaggs, A. R. *Nat. Prod. Rep.* **2001**, *18*, 334.
2. Gibson, F. *Biochem. J.* **1964**, *90*, 248.
3. (a) Cotton, R. G. H.; Gibson, F. *Biochem. Biophys. Acta* **1965**, *100*, 76; (b) Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* **1972**, *12*, 3492.
4. (a) Hilvert, D.; Carpenter, S. H.; Nared, K. D.; Auditor, M.-T. M. *Proc. Nat. Acad. Sci. U.S.A.* **1988**, *85*, 4953; (b) Jackson, D. Y.; Jacobs, J. W.; Sligaswara, R.; Reich, S. H.; Bartlett, P. A.; Schultz, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 4841; (c) Schultz, P. G.; Lerner, R. A.; Benkovic, S. J. *Chem. Eng. News* **1990**, *68*, 26; (d) Lemer, R. A.; Benkovic, S. J.; Schultz, P. G. *Science* **1991**, *252*, 659.
5. (a) Chook, Y. M.; Gray, J. V.; Ke, H.; Lipscomb, W. N. *J. Mol. Biol.* **1994**, *240*, 476; (b) Lee, A. Y.; Karplus, P. A.; Ganem, B.; Clardy, J. *J. Am. Chem. Soc.* **1995**, *117*, 3627; (c) Xue, Y.; Libscomb, W. N.; Gray, R.; Schnappauf, G.; Braus, G.; Libscomb, W. N. *Proc. Nat. Acad. Sci. U.S.A.* **1994**, *91*, 10814; (d) Sträter, N.; Håkansson, K.; Schnappauf, G.; Braus, G.; Lipscomb, W. N. *Proc. Nat. Acad. Sci. U.S.A.* **1996**, *93*, 3330; (e) Sträter, N.; Schnappauf, G.; Braus, G.; Lipscomb, W. N. *Structure (London)* **1997**, *5*, 1437.
6. Guo, H.; Cui, Q.; Lipscomb, W. N.; Karplus, M. *Proc. Nat. Acad. Sci. U.S.A.* **2001**, *98*, 9032.
7. Hur, S.; Bruice, T. C. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 1176.
8. Aemissegger, A.; Jaun, B.; Hilvert, D. *J. Org. Chem.* **2002**, *67*, 6725.
9. Pawlak, J. L.; Padykula, P. E.; Kronis, J. D.; Aleksejczyk, R. A.; Berchtold, G. A. *J Am. Chem. Soc.* **1989**, *111*, 3374.
10. (a) Johnson, C. R. Ph. D. Dissertation. *Transition State Analog Inhibitors of Chorismate Mutase*. University of California at Berkeley, 1986; (b) Bartlett, P. A.; Johnson, C. R. *J. Am. Chem. Soc.* **1985**, *107*, 7792; (c) Bartlett, P. A.; Nakagawa, Y.; Johnson, C. R.; Reich, S. H.; Luis, A. *J. Org. Chem.* **1988**, *53*, 3195, For an improved preparation of *endo* ether, **3**, see: Smith, W. W.; Bartlett, P. A. *J. Org. Chem.* **1993**, *58*, 7308.
11. Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5008.
12. Strube, R. E. *Organic Syntheses CoII* **1963**, *IV*, 417. The overall yield for this three-step sequence was improved to 70% as compared to the 48% yield reported by these authors. Improved yields in both the saponification and esterification steps were contributing.
13. Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.
14. Conditions were optimized using the criteria outlined by Lukas, T. J.; Prystowsky, M. B.; Erickson, B. W. *Proc. Nat. Acad. Sci. U.S.A.* **1981**, *78*, 2791.
15. (a) Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203; (b) Yamada, S.; Ninomiya, K.; Shiori, T. *Tetrahedron Lett.* **1973**, *26*, 2343.
16. Commercially available *N*-PSP was less effective in effecting cyclization than the freshly prepared material Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.
17. Webb, R. R., II; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 1357.
18. Schwartz, N. N.; Blumbergs, J. M. *J. Org. Chem.* **1964**, *29*, 1916.
19. Through the modification of the COMOE2PH experiment originally co-written by Drs. R. Nunlist and D. Meyerhoff, University of California, Berkeley. For background see: (a) Dodenhasen, G.; Kogler, H.; Ernst, E. E. *J. Mag. Res.* **1984**, *58*, 370; (b) Gurevich, A. Z.; Barsukov, I. L.; Arseniev, A. S.; Bystrov, V. F. *J. Mag. Res.* **1984**, *56*, 471.
20. For a similar procedure see: Stevens, R. V.; Albizati, K. F. *J. Org. Chem.* **1985**, *50*, 632.
21. Presumably steric compression made *endo* epoxide **23a** prone to ready epimerizaion. Nonepimerizing conditions for this deprotection were developed from the report of Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514, Successful deprotection of the *endo* epoxide amine was determined by preparation of the authentic *exo* aminoepoxide (generated directly from **23b** with KF and TBAF deprotection) and comparison of ^{1}H NMR (500 MHz) spectra. Genuine samples of both diastereomers allowed limits of detection better than 0.5% in this ^{1}H NMR experiment.
22. (a) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: New York, 1990; (b) Gokel, G. W.; Durst, H. D. *Aldrichim. Acta* **1976**, *9*, 3; (c) *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley Interscience: New York, 1990.
23. (a) Bartlett, P. D.; Knox, L. H. *Organic Syntheses CoII.* **1973**, *V*, 196; (b) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774; (c) Davis, F. A.; Charropadhyay, S.; Towson, J. T.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087; (d) Davis, F. A.; Towson, I. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477; (e) Davis, F. A.; McCauley, J. P., Jr.; Chattopadhyay, S.; Harakal, M. E.; Towson, J. C.; Watson, W. H.; Tavanaiepour, I. *J. Am. Chem. Soc.* **1987**, *109*, 3370.
24. Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A.; Williams, W. M. *Org. Synth.* **1973**, *53*, 175.
25. Andrews, G. C.; Crawford, T. C.; Contillo, L. G., Jr. *Tetrahedron Lett.* **1981**, *22*, 3803.
26. Chao, H. S.-I.; Berchtold, G. A. *Biochemistry* **1982**, *21*, 2778.
27. Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1993**, *114*, 10966.
28. Curran, D. P.; Suh, Y. G. *J. Am. Chem. Soc.* **1984**, *106*, 5002.
29. (a) Wiest, O.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 7582; (b) Wiest, O.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 11628.
30. Bruice, T. C.; Pandit, U. K. *Proc. Nat. Acad. Sci. U.S.A.* **1960**, *46*, 402.
31. (a) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966; (b) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1983**, *48*, 2420.
32. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
33. Elsevier-Biosoft, 68 Hills Road, Cambridge CB2 1LA, United Kingdom.
34. Generously provided by Dr. A. Rendina.