Articles

Is There Another Common Intermediate beyond Chorismic Acid in the Shikimate Pathway? Synthesis of *trans*-3-[(1-Carboxyvinyl)oxy]-6-hydroxycyclohexa-1,4-diene-1-carboxylic Acid

Karen Marie Mattia and Bruce Ganem*

Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

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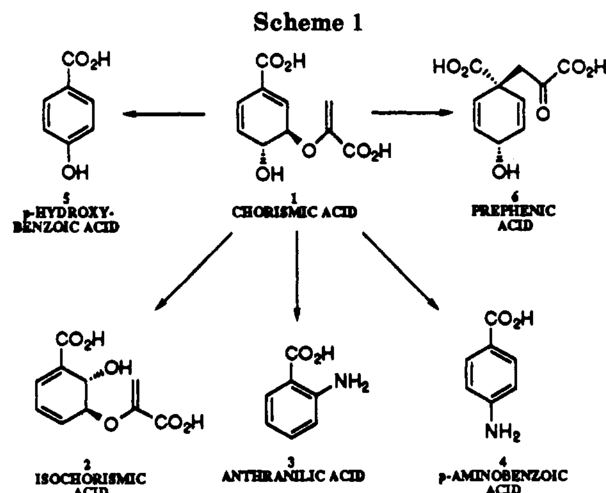
As part of a search for mechanistic commonalities uniting the three chorismate-processing enzymes of anthranilate, PABA, and isochorismate biosynthesis, the title compound **9a**, a highly labile allylic isomer of chorismic acid, was prepared by total synthesis. The synthetic route featured a new, Lewis-acid promoted opening of epoxides by diselenides leading to *trans*-hydroxy selenides. This remarkable reaction obviates the need to handle unpleasant selenols and simplifies the usual two-step anionic process involving *in situ* generation of alkali metal selenides. Diene **9a** underwent rapid acid-catalyzed aromatization and [3,3]-sigmatropic rearrangement. Claisen rearrangement of **9a** ($t_{1/2} \ll 10$ min at 4 °C) was much faster than that of chorismate, isochorismate, aminodeoxychorismate, or aminodeoxyisochorismate, making conventional kinetic assays in the presence of shikimate branchpoint pathway enzymes impossible. Nevertheless, the rapid and regioselective Claisen rearrangement of **9a** led to an alternative mechanistic rationale for the biosynthesis of aromatic amino acids such as *m*-carboxyphenylalanine and *m*-carboxytyrosine.

Introduction

The transformations of chorismic acid (1) into isochorismic, anthranilic, and *p*-aminobenzoic acids (2–4, respectively; Scheme 1) represent three of the five known branchpoint processes by which plants and microorganisms biosynthesize an extraordinary variety of aromatic metabolites.[1-3] Of those three, the unusual 1,5-dienol rearrangement of **1** to **2** is catalyzed by isochorismate synthase in a process eventually leading to the production of catechol-containing molecules such as enterobactin, as well as the menaquinones, vitamin K, and salicylic acid.[4-6] The biosynthesis of anthranilic acid **3** from **1** represents the first committed step in the formation of the amino acid tryptophan and has also been implicated in the production of phenazines and phenoxazinones.[7] Third, the transformation of **1** into *p*-aminobenzoic acid (PABA) (**4**) leads ultimately to the formation of di- and tetrahydrofolic acids which are essential coenzymes for one-carbon metabolism.[8] While the formation of *p*-hydroxybenzoic acid **5** and prephenic acid **6** are also of considerable independent interest, the genesis of the present work lay in recent findings that the transformations leading to **2–4** share certain intriguing mechanistic and enzymological similarities.

Scheme 1



The pathways which convert chorismate into **3** and **4** both proceed by regioselective aminations and subsequent aromatization. Both pathways have been shown to involve discrete intermediates whose structural relationship to isochorismic acid is readily apparent.[8] To probe anthranilate biosynthesis, 2-amino-2-deoxyisochorismate (**7**) (ADIC, Scheme 2) was synthesized and shown to be a kinetically viable intermediate on the pathway to **3**.[9,10] Recently, Bauerle *et al.* have isolated and identified **7** as it accumulates in the *Escherichia coli* auxotrophic mutant TrpE^{H398M}.[11,12] In the case of PABA biosynthesis, 4-amino-

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Scheme 2

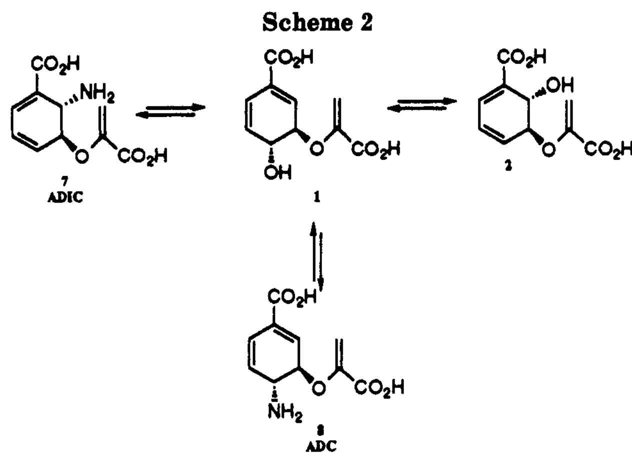

Table 1. Branchpoint Enzymes Involved in the Biosyntheses of 2–4

enzyme	composition	MW (Da)	gene
anthranilate synthase	Co I(AS-I)	57 000	*trpE*
	Co II (AS-II)	21 000	*trpG*
PABA synthase	Co I (PABS-I)	53 400	*pabB*
	Co II	21 700	*pabA*
	Co III	50 000	*pabC*
isochorismate synthase	monomer	43 000	*entC*

4-deoxychorismate (ADC) (8) was synthesized, and its ammonia-independent conversion to PABA was established using crude enzyme extracts.[13] Since then, Anderson *et al.* have reported definitive evidence for the formation of 8 during enzyme turnover both by rapid chemical quench techniques and by direct NMR spectroscopic observation.[14] Remarkably, both ADIC and ADC have been shown to undergo reversible interconversion with chorismate under physiological conditions, with $K_{eq} \cong 4$ favoring ADIC[12] and $K_{eq} = 6.1$ favoring ADC.[14]

Further relationships between these pathways are evident at both the enzymatic and genetic level (Table 1). Anthranilate synthases from a number of bacteria,[15] *Neurospora crassa*,[16] and *Euglena*[17] have been purified to homogeneity. The enzyme consists of two nonidentical subunits designated component I (AS-I, MW ca. 57 kDa) and component II (AS-II, MW 21 kDa). The former catalyzes the NH_3-dependent conversion of 1 to 3 and is encoded by the *trpE* gene,[18,19] while the latter is a glutamine amidotransferase encoded by the *trpG* gene. In fact, AS-I can function in the absence of AS-II when ammonia is provided.[18]

The organization of the genes encoding anthranilate synthase may vary.[20] For example, in *Serratia marcescens*, anthranilate synthase is encoded by two, separate, unfused genes. However, in *E. coli* and *Salmonella typhimurium*, *trpG* is fused with *trpD*, which encodes anthranilate phosphoribosyltransferase. In *Euglena* and *Rhizobium meliloti*, *trpE* and *trpG* are fused, resulting in a single gene that encodes both AS-I and AS-II activities.[17,20]

The biosynthesis of PABA from 1 has been shown to involve a three-protein complex.[21] In *E. coli*, a 53.4-kDa protein encoded by *pabB* transforms 1 and ammonia into ADC 8. In addition to a glutaminase (21.7 kDa), which is encoded by the *pabA* gene, a third protein (active as a dimer; M_r 30 kDa) is encoded by *pabC* and catalyzes aromatization of 8 to PABA.[22–24] Isochorismate synthase (IS) consists of a monomeric, 43 kDa protein encoded by the *entC* gene.[25] Alone, it catalyzes the reversible interconversion of 1 and 2, with $K_{eq} = 0.56$ favoring chorismate.[26] Overexpression and purification of this enzyme has recently been achieved,[26] and labeling experiments with $H_2{}^{18}O$ have established that the incoming hydroxyl group is derived from bulk water.[26,27]

Besides sharing organizational similarities, the enzyme systems which biosynthesize anthranilate, PABA, and isochorismate each employ a comparably sized chorismate-binding protein that requires divalent magnesium for catalysis. Moreover, antibodies raised against AS-I cross-react with PABS-I.[28] In addition, AS-I from *E. coli* shows a 26% similarity in amino acid sequence with PABS-I (40% similarity at the nucleotide level).[29,30] Comparable similarity (19%) is found in the respective amino acid sequences of AS-I and IS (45% similarity at the nucleotide level). Isochorismate synthase is also structurally related to PABS-I (26% at the amino acid level, 46% at the nucleotide level).[6] For all three proteins, areas of homology are most heavily concentrated in the carboxyl termini.[6]

Such structural relationships cannot simply be explained by the fact that all three proteins utilize chorismate. Both chorismate mutase and chorismate lyase use 1 as substrate; however, neither shares significant sequence similarity with the three proteins discussed above.[8,31] Alternatively, it has been suggested that the chorismate-binding proteins involved in the biosynthesis of 2–4 represent a closely related family whose genes may have evolved from a common ancestor.[6,29]

The premise that evolutionary relationships in the genetic code may be manifested as functional similarities in the resulting proteins led us in this case to search for mechanistic commonalities in the three chorismate-processing enzymes of anthranilate, PABA, and isochorismate biosynthesis. As a group, the transformations depicted in Scheme 2 represent reversible, nucleophilic substitution reactions of 1 either with water (leading to 2) or with ammonia (leading to 7 and 8). Substitution could occur either as a concerted 1,5-addition–elimination

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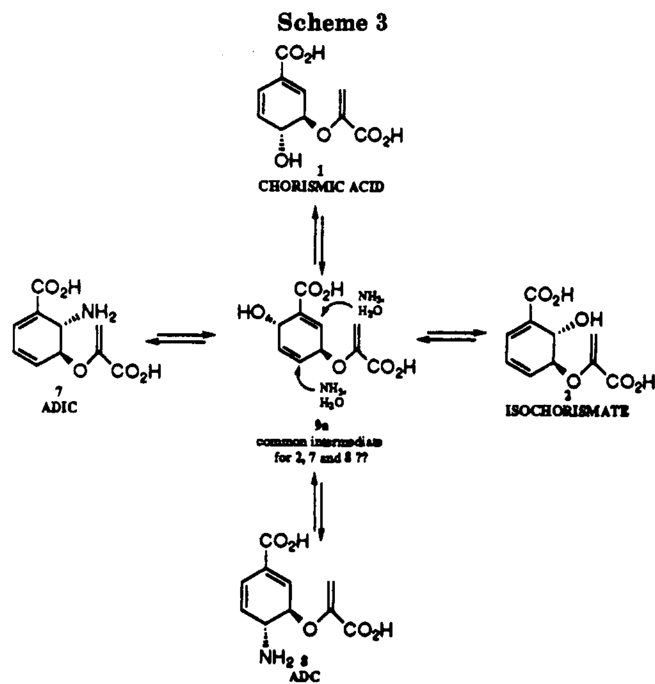
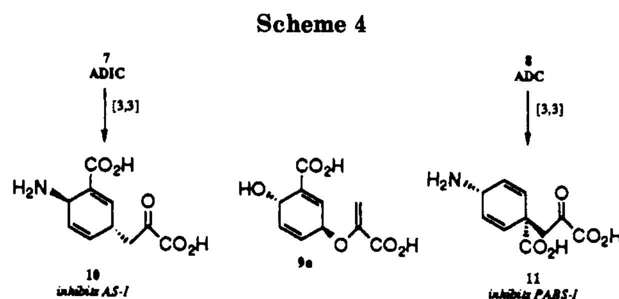
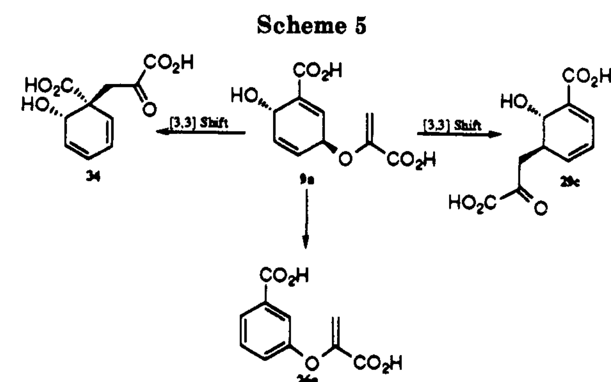
Scheme 3



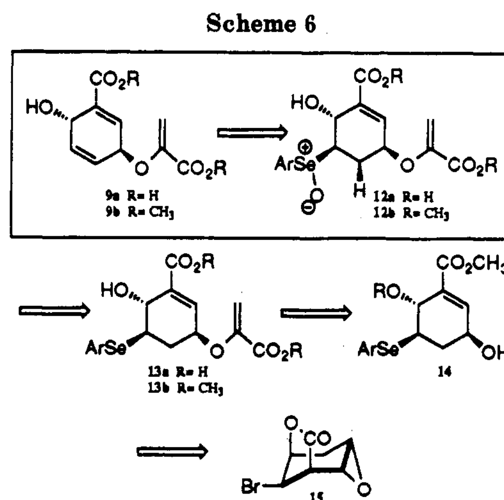
Scheme 4



Scheme 5



Scheme 6



reaction leading to **2** and **7** or as a series of stepwise, 1,3-addition/eliminations.[30]

The latter possibility led us to consider whether 1,4-diene **9a** (Scheme 3), the product of initial *syn*-allylic rearrangement of **1**, might be a transient, though as yet undetected, intermediate in the biosynthesis of **2**–**4**. The common intermediacy of **9a** (or its *cis*-isomer) would also explain the observed protein sequence similarities in AS-I, PABS-I, and IS. Rearrangement of **1** to **9a** might take place in those active site domains of the chorismate-binding proteins which are bounded by sequences of similar C-terminal amino acid residues noted earlier. Once formed, pseudosymmetric diene **9a** might then undergo any of four possible, enzyme-catalyzed, *syn*-stereoselective 1,3-nucleophilic addition reactions of water or ammonia at either allylic terminus. A related double-S_N2' proposal, using either a nucleophile from the enzyme's active site or the enolpyruvyl carboxylate group as an internal nucleophile, has been proposed independently by Walsh *et al.*[8a]

The close mechanistic relationships shared by such allylic substitutions are consistent with the "common ancestral gene" hypothesis and may be seen to furnish each of the three diene intermediates **2**, **7**, and **8**. Moreover, the experimentally observed chemical equilibria noted above between chorismate and **2**, **7**, and **8** might also invoke **9a** as a transient intermediate, subject to the usual thermodynamic driving forces. Finally, not the least enticing feature of this hypothesis was that it shed light on our earlier observation[9,13] that *trans*-substituted 1,4-dienes **10** and **11**, the Claisen rearrangement products of **7** and **8**, inhibited AS-I and PABS-I, respectively (Scheme 4).

Taken as a whole, these observations led us to select the *trans*-stereoisomer of (±)-**9a** as our primary synthetic target. In planning its synthesis, we expected **9a** to be extremely labile, perhaps more so than chorismic acid itself. Like **1**, diene **9a** may undergo acid- or base-catalyzed dehydration to stable aromatic structures. However, in contrast to **1**, where only a single [3,3]-sigmatropic rearrangement is possible, **9a** may undergo two competing pericyclic rearrangements (Scheme 5), probably via dissociative pathways established in earlier work.[32] Because the ground state free energy of an unconjugated diene like **9a** would be higher than for conjugated dienes like **1**, [3,3]-rearrangement of the former may be expected to be more rapid. Moreover, since the rate of rearrangement would be enhanced in polar aqueous media,[32] the prospects of conducting enzymatic bioassays to establish the intermediacy of **9a** and obtaining the desired kinetic parameters, not to mention chromatographic purification, clearly merited special consideration.

With these concerns in mind, we decided to elaborate the 1,4-diene system of **9a** in the final step of the synthesis by elimination of a *trans*-hydroxyselenoxide such as **12a** (Scheme 6). In view of Sharpless' finding that electron-withdrawing aryl substituents on alkyl aryl selenoxides dramatically increased the rate of elimination of areneselenenic acid,[33] we reasoned that an appropriately configured nitrophenyl or halophenyl selenoxide might undergo elimination to produce **9a** well below rt, thus improving the prospects for product survival.

Selenoxide **12a** would be derived from the corresponding seleno diester **13b** by saponification to **13a** and oxidation.

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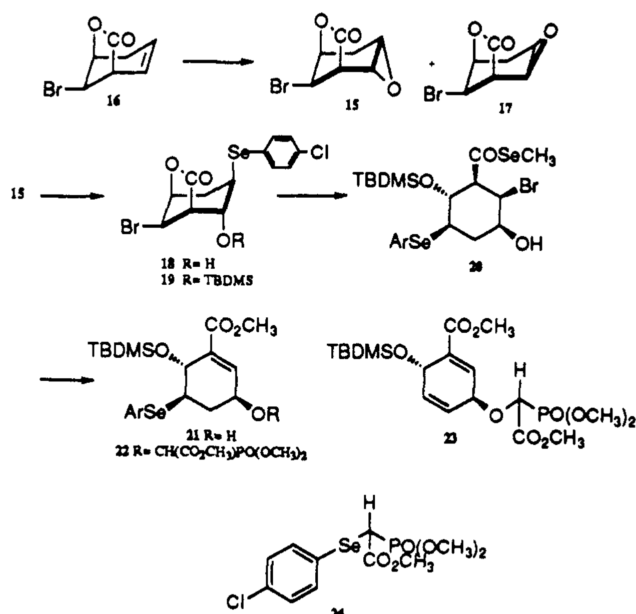
Scheme 7



This analysis considerably eased the synthetic problem by suggesting two further simplifications. First, construction of the enol pyruvate side chain in **13b** might be achieved from hydroxy enoate **14** using now-familiar rhodium–carbenoid insertion methodology developed independently by us[34] and by the Berchtold group at MIT[35] for the total synthesis of chorismate and its congeners. Second, nucleophilic opening of an appropriate epoxide with ArSeNa or its equivalent is well-known to afford *trans*-hydroxy selenides,[36] although to ensure the proper regiochemical outcome in **14**, the alkene group would have to be temporarily masked. The bridged ring system of bromo lactone **15**, developed earlier by our group as a synthetically useful precursor of γ-hydroxy enoic acids,[37] here provided an attractive solution to both issues of regio- and stereocontrol in hydroxy selenide formation.

Results and Discussion

The synthesis began with the known unsaturated halo lactone **16** (Scheme 7), readily available from benzoic acid in three steps.[37] Epoxidation using trifluoroperoxyacetic acid (CH_2Cl_2, rt) furnished a 5:1 mixture of **15**:**17** from which pure **15** could be obtained in 62–70% yield. Nucleophilic opening of the hindered oxirane ring in **15** failed under a variety of conditions[38] using PhSeNa generated either from $NaBH_4$ reduction of PhSeSePh in alcohol or from sodium metal reduction of PhSeSePh in THF/HMPA. Hydroxyselenation of **16** using (phenylseleno)trifluoroacetate[39] was briefly explored but gave a 3:2 stereoisomeric mixture of the corresponding *trans-vic*-(phenylseleno) alcohols.

In view of the report of alumina-promoted epoxide openings with benzeneselenol published by Posner *et al.*,[40] we investigated the effect of stronger Lewis acids on reactions of **15**. Addition of catalytic amounts of $BF_3{\cdot}Et_2O$ to a solution of **15** and excess *p*-chlorobenzeneselenol furnished the desired hydroxy selenide **18** (72%), whose structure was confirmed by oxidative elimination to the corresponding known allylic alcohol.[41] Although the scope and generality of this new process has not been explored, it provides an alternative to the usual selenide anion procedures. It should be noted that no reaction was observed under the same conditions using the less nucleophilic and more hindered *o*-nitrobenzeneselenol.

We noted that *p*-chlorobenzeneselenol underwent facile air oxidation, even during handling, so that formation of **18** was always accompanied by significant amounts of bis(4-chlorophenyl) diselenide. It occurred to us that diselenides should also exhibit considerable nucleophilicity towards **15** in the presence of acid. To test this idea, $BF_3{\cdot}Et_2O$ was added to a mixture of **15** and 4 equiv of bis(4-chlorophenyl) diselenide. Gratifyingly, the same hydroxy selenide **18** was obtained in 46% yield. This remarkable reaction, if general, would obviate the need to handle unpleasant selenols and would also simplify the usual two-step anionic process involving *in situ* generation of alkali metal selenides.[36]

Protection of **18** as its *tert*-butyldimethylsilyl (TBDMS) ether **19** was carried out under neutral conditions,[42] in preparation for lactone opening and concomitant HBr elimination to elaborate the conjugated allylic alcohol in **14**. Hydrolysis and methanolysis of **19** proved difficult using conventional methods, and forcing conditions only caused aromatization. Clearly, the axial aryl selenide substituent retarded nucleophilic attack by enhancing steric congestion around the incipient tetrahedral intermediate.

Both dialkylaluminum thiolates[43] and selenolates[44] have proven to be effective nucleophiles in transforming lactones to hydroxy thioesters and selenoesters, respectively. These aluminum reagents were appealing because complexation of oxygen to aluminum would activate the lactone carbonyl toward nucleophilic attack; moreover, the resulting activated thio- or selenoesters might easily be transformed into the corresponding carboxylic acid or some readily cleavable ester. With its weak carbon–selenium bond,[45] the selenoester seemed the more versatile target for subsequent refunctionalization. Treatment of lactone **19** with dimethylaluminum methylselenolate[44] at ambient temperatures afforded the hydroxy selenoester **20** in 70–86% yield. Upon exposure to 2.1 equiv of $NaOCH_3$ in methanol, transesterification and β-elimination resulted in formation of unsaturated methyl ester **21** in 36–44% yield.

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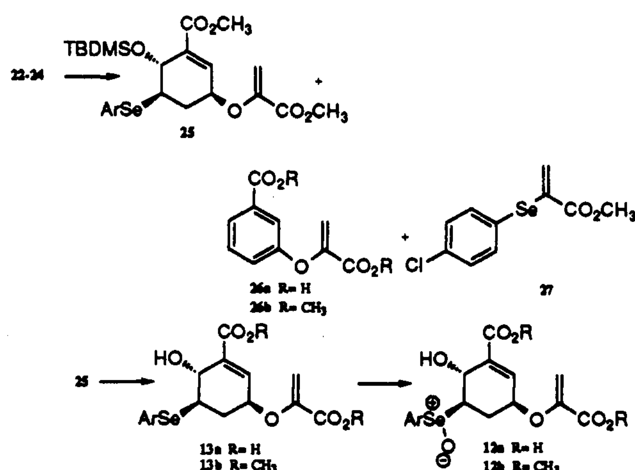
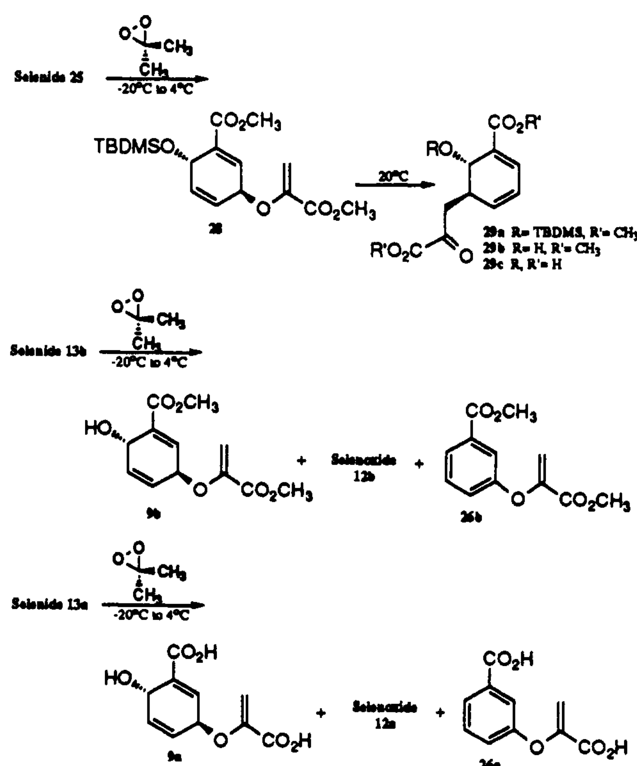
Scheme 8



Scheme 9



Several protocols were explored to functionalize **21** with the requisite carboxyvinyl ether side chain. In the past, rhodium acetate-catalyzed carbenoid insertions of dimethyl diazomalonate or trimethyl diazophosphonoacetate proved most successful in attaching alkoxy malonate or alkoxy phosphonoacetate substituents to γ-hydroxyenoates like **21**. Enol pyruvates have been constructed from those groups by straightforward Mannich or Horner–Emmons reactions, respectively.[34,35] However, the presence of an aryl selenide clearly complicated the situation. Electrophilic additions of rhodium carbenoids to amines, ethers, and sulfides leading to ylides have been well-documented,[46] and the resulting zwitterionic species may undergo [2,3]-sigmatropic rearrangements or cycloelimination.[47] In the case of **21**, reaction with $Rh_2(OAc)_4$ and trimethyl diazophosphonoacetate furnished the desired phosphonoacetate **22** (Scheme 7), diene **23**, and selenophosphonoacetate **24**, along with some recovered **21**. Diene **23** likely arose from competing electrophilic attack at selenium and cycloelimination of the resulting seleno ylide to produce the remaining observed byproduct **24**.

Chromatography could not completely resolve compounds **22–24**; therefore, impure phosphonoacetate was subjected to the Horner–Emmons methylenation procedure. The mixture containing **22** was deprotonated with LDA/THF and then condensed with formaldehyde. The desired enol pyruvate **25** (Scheme 8), obtained in 30–36% yield from **21**, was now easily purified by flash column chromatography. In addition, the known[48] aromatic diester **26b** was obtained in low yield (15%), most likely from elimination during olefination of diene **23**. Interestingly, vinyl selenide **27**, the product of phosphonate **24**, was also isolated in 42% yield.

The TBDMS ether in **25** was removed (60–70%) using tetra-n-butylammonium fluoride at −40 °C. Regular TLC monitoring of this deprotection was required, since extended reaction times led to lower yields. The product, hydroxy seleno diester **13b**, was saponified (NaOH, THF–H_2O, 4 °C) and hydroxy seleno diacid **13a** isolated in 70–80% yield after careful acidification with Amberlite IR-120H resin. With **13a** in hand, the next objective was to find conditions for its transformation into the corresponding selenoxide **12a** and thence to target diene **9a**.

Initial model studies on the oxidative elimination of silyl-protected seleno diester **25** were encouraging (Scheme 9). When **25** was treated with dimethyldioxirane in THF at −20 °C and the reaction mixture warmed to 4 °C, low-temperature NMR spectroscopic analysis after 30 min indicated the presence of one compound whose spectroscopic characteristics were consistent with 1,4-diene **28**. The diene showed little change after 2.5 h at 4 °C, judging from ^{1}H-NMR spectroscopy. However, upon warming to rt, **28** rearranged cleanly (approximate half-life at 20 °C = 2 h) to a new silyloxy diene whose structure was consistent with **29a**. Apparently, [3,3]-rearrangement of the enol pyruvate side chain in **28** occurred selectively with the nonconjugated alkene. Despite its short half-life at rt, results with **28** suggested that enzymological studies might be possible at subambient temperatures, for which special techniques are available.[49]

Results with hydroxy seleno diester **13b** were less clearcut (Scheme 9). After dimethyldioxirane oxidation at −20 °C, the THF solution of **13b** was warmed to 4 °C and monitored by ^{1}H-NMR spectroscopy. Spectra obtained after 35 min revealed a mixture of selenoxide **12b**, the desired 1,4-diene **9b**, and a new aromatic compound whose spectrum was consistent with structure **26b**, described earlier as a byproduct of enol pyruvate synthesis. Elimination of selenoxide **12b** was only complete after warming to 10 °C, by which point only 1,4-diene **9b** and arene **26b** were observable. Warming to 20 °C caused the disappearance of **9b** and concomitant formation of the expected Claisen rearrangement product **29b**.

While both **28** and **9b** underwent [3,3]-rearrangement at similar rates in THF, the latter hydroxy diene formed more slowly and aromatized more rapidly than its silyloxy counterpart, a finding of considerable concern to us, since

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(47) (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919–939. (b) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348–356. (c) Adams, J.; Spero, D. M.; *Tetrahedron* **1991**, *47*, 1765–1808.

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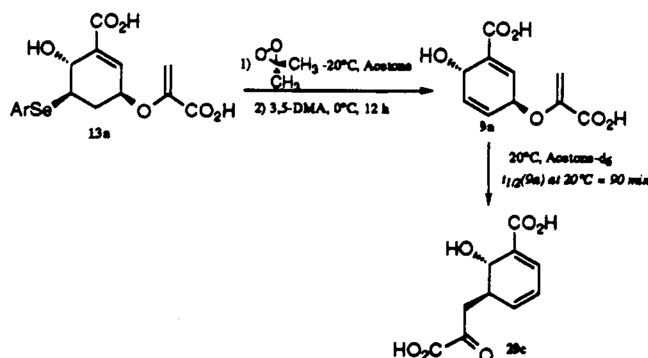
Scheme 10



9b closely resembled the target hydroxy diacid 9a. With these results in hand, it was not surprising when preliminary attempts to oxidize 13a with dimethyldioxirane, monitored spectroscopically as before, afforded a mixture of 9a and 12a (Scheme 9), along with 26a. Since 9a obtained this way required purification, which would almost surely accelerate its decomposition, some more controlled method for the oxidative elimination of 13a would have to be developed in which aromatization, at least, was suppressed.

Aryl selenoxide eliminations produce arylselenenic acids (ArSeOH), which are in equilibrium with diaryl diselenides and arylseleninic acids ($ArSeO_2H$).[50] The acidity of C_6H_5-SeOH is not known, since it is not an isolable substance, but the pK_a of $C_6H_5SeO_2H$ has been reported to be 4.70.[51] The pK_a of *p*-chlorobenzeneseleninic acid would be expected to be even lower. Since such acidic byproducts could catalyze the aromatization of 9a and its congeners, the use of an appropriate acid scavenger was investigated.

The presence of 3,5-dimethoxyaniline (DMA) in selenoxide eliminations has been reported to suppress the aromatization of sensitive dienes[52] as well as the electrophilic addition of organoselenium byproducts to sensitive alkenes.[53] Therefore, seleno diacid 13a was oxidized in the usual way (dimethyldioxirane, acetone, −20 °C) and a stoichiometric amount of DMA added in the cold. The reaction mixture was warmed to 4 °C and stirred for 12 h and the bulk of solvent removed *in vacuo* at 4 °C. After extraction with ice-cold CH_2Cl_2 to remove selenated DMA adducts, the residue was dissolved in ice-cold acetone-d_6 (Scheme 10). Analysis by ^{1}H-NMR spectroscopy revealed the formation of 9a along with traces of selenated DMA; however, no significant levels of arene 26a were detectable in the spectrum. Small quantities of Claisen rearrangement product 29c were also observed but could be minimized with careful temperature control during extractive workup.

Not surprisingly, diene 9a was considerably more stable under these conditions. It could be kept in acetone-d_6 solution at 0 °C for up to 12 h with little detectable decomposition. When warmed to ambient temperatures, 9a underwent [3,3]-sigmatropic rearrangement to 29c with a half-life of 90 min at 20 °C (Scheme 10). However, rearrangement was considerably accelerated in an aqueous environment. In 1:1 acetone-d_6/D_2O, the half-life of 9a was 100 min at 4 °C. With pure D_2O as solvent (pH = 7), the Claisen rearrangement of 9a to 29c was too rapid to follow by ^{1}H-NMR spectroscopy and was complete within 10 min at 4 °C. Because of its exceedingly rapid rate of rearrangement, conventional kinetic assays of 9a in the presence of shikimate branchpoint pathway enzymes were impossible. Nevertheless, several attempts were made to examine the biological involvement of this diene in the biosynthesis of anthranilic acid.

In one approach, freshly prepared 9a was incubated with a large quantity of anthranilate synthase–anthranilate-5-phosphorylribose 1-pyrophosphate phosphoribosyltransferase (AS–PRT) complex isolated from *Salmonella typhimurium*.[54] The AS–PRT enzyme system converts chorismate 1 to anthranilate 3 in the presence of ammonia and magnesium. Control experiments demonstrated reasonable catalytic activity at 4 °C, and the strong fluorescence of 3 provided a sensitive assay (10^{-9} M detection limit) for product. Since the presence of trace amounts of selenium-containing byproducts in 9a could not be ruled out, additional controls were performed which demonstrated that low concentrations of selenated DMA adducts or rearrangement product 29c had no inhibitory effects on AS–PRT. Nevertheless, low-temperature assays of 9a with AS–PRT failed to produce any detectable levels of 3. In view of these negative findings, no assays with PABS-I and IS were attempted.

Although 9a showed no evidence of acting as a substrate toward AS–PRT, such negative evidence does not preclude the involvement of 9a in the enzymatic reaction mechanism. In general, such ambiguous situations arise when binding of an intermediate to an enzyme is not part of the normal enzymatic reaction pathway.[55,56] If, for instance, turnover of 1 to 9a were to involve a conformational change in the protein, the resting enzyme's conformation might not recognize 9a, in which case binding of the putative intermediate might be negligible.

It should further be noted that the idea of a pseudosymmetric common intermediate may instead be manifested as an enzyme-bound diene species, in which case turnover of 9a would not be observed. Such an enzyme-bound intermediate has been independently suggested.[8]

In realizing our synthetic objective, we discovered the rapid and regioselective Claisen rearrangement of 9a. This finding unexpectedly led us to recognize an alternative mechanistic rationale for the biosynthesis of aromatic amino acids such as *m*-carboxyphenylalanine (33) (Scheme 11) and *m*-carboxytyrosine, which contain the unusual 1,3-pattern of aromatic substituents. These nonproteinaceous amino acids are made by certain higher plants (e.g., iris) as secondary metabolites.[57] Studies with labeled shikimic acid (30) (Scheme 11) have established that the ring carboxyl group in 33 originates from the carboxylic acid group of shikimate and that the *pro*-6*S* hydrogen in 30 is retained. Consistent with those findings, Larsen *et al.* have suggested isochorismate 2 as a key biosynthetic intermediate. Indeed, when 2 is heated at 100 °C (10 min, pH 7) (*m*-carboxyphenyl)pyruvic acid (32) is produced.

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(54) Samples of the AS–PRT complex were kindly provided by Dr. Ronald Bauerle, University of Virginia.

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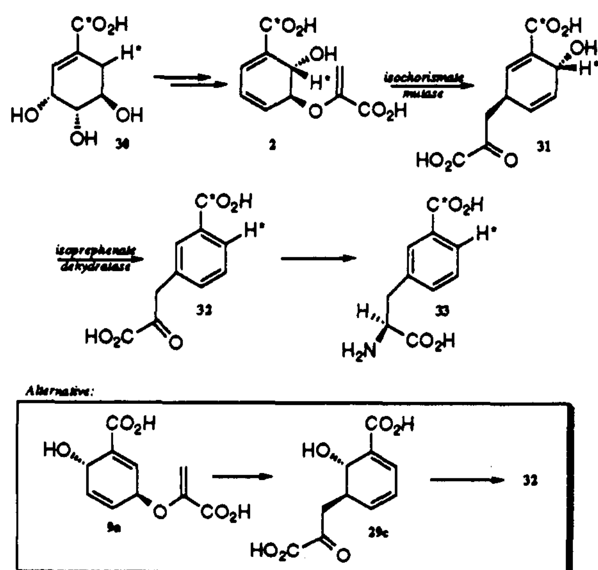
Scheme 11



Formation of **32** presumably involves rearrangement to isoprephenate **31** with accompanying dehydration, although **31** has never been isolated or synthesized.[58] Indeed, the putative *in vivo* biogenesis shown in Scheme 9 would appear to require at least two as-yet-undiscovered enzymes, which have hypothetically been named isochorismate mutase and isoprephenate dehydratase.[59,60]

An alternative biosynthetic pathway to the *meta*-substituted aromatics may now be envisioned based on the chemical properties of **9a**. Rapid, uncatalyzed [3,3]-rearrangement would lead to **29c** which could subsequently aromatize to **32**. As a test of this hypothesis, **29c** was exposed briefly to acid, whereupon (*m*-carboxyphenyl)-pyruvic acid (**32**) was produced whose NMR spectrum was consistent with that of an authentic sample.[61]

In summary, a new, highly labile chorismate isomer **9a** has been prepared which undergoes rapid [3,3]-sigmatropic rearrangement and acid-catalyzed aromatization. The Claisen rearrangement of **9a** (complete within 10 min at 4 °C, D_2O, pH = 7.0) was much faster than that of chorismic acid (**1**) ($t_{1/2}$ = 16 h at 30 °C),[62] isochorismic acid (**2**) ($t_{1/2}$ = 6 h at 30 °C),[26] or the trifluoroacetate salts of ADC (**8**) ($t_{1/2}$ ~5 d at 23 °C)[62] or ADIC (**7**) (complete within 20 h at 23 °C).[63] Even allowing for the presence of trace impurities in **9a**, the data at hand still indicate the extraordinary lability of this 1,4-diene and suggest at least one rationale why such a perilously unstable intermediate might never be released from the enzyme and why it has never been directly observed or isolated *in vitro*. The observed experimental behavior of putative intermediate **9a** also suggests a novel biosynthetic pathway from chorismate to the *meta*-substituted aromatic amino acids found in higher plants.[64]

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(62) (a) Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* **1973**, *12*, 3492–3498. (b) Pawlak, J. L.; Padykula, R. E.; Kronis, J. D.; Aleksejczyk, R. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 3374–3381.
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Experimental Section

Epoxidation of Lactone 16. To a solution of trifluoroacetic anhydride (9.3 g, 44.4 mmol, 6.0 equiv) in CH_2Cl_2 (20 mL) at 0 °C was added 70% H_2O_2 (1.8 mL, 36.9 mmol, 5.0 equiv). The reaction mixture was then warmed to rt and stirred for 1.5 h. To this was added lactone **16** (1.5 g, 7.4 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture was stirred at rt for 6 h. Water (40 mL) was added, and the biphasic mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with 10% $NaHSO_3$ (40 mL) and saturated $NaHCO_3$ (40 mL), dried with $MgSO_4$, and concentrated *in vacuo*. Flash chromatography of the crude mixture (2:1 hexanes/EtOAc) afforded epoxide **15** (1.0 g, 62%, mp 156–158 °C) and epoxide **17** (0.2 g, 12%, mp 149–150 °C).

15: R_f = 0.35 (2:1 hexanes/EtOAc); ^{1}H-NMR ($CDCl_3$) 4.71 (m, 1H), 4.50 (s, 1H), 3.48 (t, J = 4.1 Hz, 1H), 3.39 (d, J = 4.2 Hz, 1H), 3.15 (m, 1H), 2.35 (m, 2H); ^{13}C-NMR ($CDCl_3$) 172.1, 81.0, 51.7, 48.1, 46.6, 46.0, 30.2 ppm; IR (film) 3100–2900, 1780, 1240, 940, 820 cm^{-1}; CIMS *m/e* 221 (92), 219 (100), 203 (12), 201 (12), 159 (30), 157 (32), 139 (23), 95 (58), 67 (38).

17: R_f = 0.11 (2:1 hexanes/EtOAc); ^{1}H-NMR ($CDCl_3$) 4.70 (m, 1H), 4.39 (s, 1H), 3.59 (m, 1H), 3.42 (d, J = 6.8 Hz, 1H), 3.18 (m, 1H), 2.62 (d, J = 16.1 Hz, 1H), 2.17 (dt, J = 16.4, 3.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) 170.6, 81.5, 51.9, 49.8, 48.4, 47.8, 29.3 ppm; IR (film) 3100–2900, 1780, 1100, 970, 840 cm^{-1}; CIMS *m/e* 221 (96), 220 (18), 219 (100), 218 (11), 107 (25), 95 (11).

Synthesis of Seleno Alcohol 18. Method A. To a solution of epoxide **15** (2.0 g, 9.13 mmol) and 4-chlorobenzeneselenol (7.0 g, 36.5 mmol, 4.0 equiv) in CH_2Cl_2 (100 mL) cooled to 0 °C was added boron trifluoride etherate (1.2 g, 8.2 mmol, 1 mL, 0.9 equiv). The reaction mixture was warmed to room temperature and stirred for 1.5 h. NaOH (10%, 100 mL) was added, and the mixture was extracted. The aqueous layer was washed with CH_2Cl_2 (3 × 100 mL), and the organic extracts were pooled, dried with $MgSO_4$, and concentrated *in vacuo* to afford a crude yellow solid. The yellow solid was chromatographed (40:1 CH_2Cl_2/CH_3CN) to yield 2.7 g of hydroxy selenide **18** as a white foam (72%): R_f = 0.37 (40:1 CH_2Cl_2/CH_3CN); ^{1}H NMR ($CDCl_3$) 7.48 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 4.94 (dt, J = 4.5, 1.32 Hz, 1H), 4.79 (s, 1H), 4.31 (m, 1H), 3.48 (dq, J = 8.0, 1.5 Hz, 1H), 3.1 (dm, J = 4.4 Hz, 1H), 2.67 (ddd, J = 16.0, 8.0, 1.3 Hz, 1H), 2.45 (ddt, J = 15.9, 4.5, 1.5 Hz, 1H), 2.22 (d, J = 3.9 Hz, –OH, 1H); ^{13}C NMR ($CDCl_3$) 173.1, 135.6, 134.7, 129.7, 127.8, 83.1, 71.7, 54.2, 48.9, 39.2, 32.5 ppm; IR (film) 3200, 3000, 2900, 1770, 1460, 1150, 750 cm^{-1}; EIMS *m/e* 414 (17), 412 (50), 410 (54), 409 (13), 408 (24), 194 (22), 193 (25), 192 (54), 191 (54), 190 (36), 189 (34), 188 (20), 187 (10), 156 (31), 121 (25), 112 (39), 65 (43), 55 (100), 39 (93).

Method B. To a solution of epoxide **15** (20 mg, 0.091 mmol) and bis(4-chlorophenyl) diselenide (139 mg, 0.365 mmol, 4 equiv) in CH_2Cl_2 (1 mL) cooled to 4 °C was added boron trifluoride etherate (12 mg, 0.082 mmol, 10 μL, 0.9 equiv). The reaction mixture was warmed to rt and stirred for 2 h. Water (1 mL) was added, and after shaking, the aqueous layer was washed with CH_2Cl_2 (3 × 1 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (CH_2Cl_2 to 40:1 CH_2Cl_2/CH_3CN) to afford 8.9 mg of hydroxy selenide **18** as a clear oil (46% based on recovered starting material) whose spectral data were identical to those described above in the reaction of **15** with ArSeH/BF_3.

Synthesis of Seleno Ether 19. To a solution of hydroxy selenide **18** (6.1 g, 14.9 mmol) in DMF (28 mL) was added *tert*-butyldimethylsilyl chloride (5.4 g, 35.7 mmol, 2.4 equiv) and imidazole (5.1 g, 74.9 mmol, 5.0 equiv). The solution was stirred for 24 h at rt. The reaction mixture was acidified (1% H_2SO_4, 28 mL) and then diluted with H_2O (120 mL) and extracted with Et_2O (4 × 150 mL). The combined ether layers were washed with saturated NaCl (600 mL), dried with $MgSO_4$, and concentrated *in vacuo* to afford a yellow oil. Chromatography (CH_2Cl_2) yielded **19** (6.6 g, 84%) as a white solid: mp 100–102 °C: R_f = 0.63 (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) 7.52 (d, J = 8.15 Hz, 2H), 7.25 (d, J = 8.50 Hz, 2H), 4.92 (d, J = 4.66 Hz, 1H), 4.75 (s, 1H), 4.22

(64) For general experimental procedures, see: Wood, H. B.; Buser, H.-P.; Ganem, B. *J. Org. Chem.* **1992**, *57*, 178–184.

(d, J = 4.76 Hz, 1H), 3.35 (d, J = 7.55 Hz, 1H), 2.96 (d, J = 4.79 Hz, 1H), 2.63 (dd, J = 15.9, 4.79 Hz, 1H), 2.48 (dd, J = 15.9, 4.76 Hz, 1H), 0.84 (s, ^{t}Bu, 9H), -0.17 (s, $-CH_3$, 3H), -0.32 (s, $-CH_3$, 3H); ^{13}C-NMR ($CDCl_3$) 172.3, 136.9, 135.1, 129.6, 127.7, 82.7, 72.1, 54.7, 49.5, 40.7, 32.5, 25.4, 17.7, -5.4, -5.5 ppm; IR (film) 3000–2800, 1800, 1460, 1240, 1150, 1080, 840 cm^{-1}; FABMS m/e 524 (6.3), 467 (100), 445 (11.6), 395 (47.6).

Synthesis of Selenoester 20. To a solution of **19** (3.9 g, 7.4 mmol) in deaerated CH_2Cl_2 (19 mL) at 0 °C was added a solution of dimethylaluminum methyl selenolate (1.8 g, 11.8 mmol, 1.6 equiv) in toluene (5.9 mL). The dimethylaluminum methyl selenolate was generated by addition of trimethylaluminum (1.08 g, 15.0 mmol) in toluene (7.5 mL) to powdered gray selenium metal (1.2 g, 15.3 mmol) followed by a 2 h reflux. After the addition of the selenolate, the mixture was warmed to rt and stirred for 16 h. The solution was then cooled to 0 °C and quenched by slow addition of wet Na_2SO_4 until gas evolution ceased. Ether (50 mL) was added to the resulting gel, and the suspension was suction filtered. The residue was rinsed repeatedly with Et_2O (5 × 100 mL), and the filtrate was concentrated *in vacuo* to yield a yellow oil. Column chromatography (CH_2Cl_2) afforded 3.8 g (82%) of the selenoester **20** as a white foam: R_f = 0.28 (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) 7.48 (d, J = 8.31 Hz, 2H), 7.24 (d, J = 8.57 Hz, 2H), 4.63 (m, 1H), 4.38 (t, J = 9.16 Hz, 1H), 3.60 (m, 1H), 3.17 (dd, J = 8.73, 3.03 Hz, 1H), 3.03 (m, 1H), 2.27 (s, $-CH_3$, 3H), 1.95 (m, 2H), 0.85 (s, ^{t}Bu, 9H), 0.23 (s, $-CH_3$, 3H), 0.05 (s, $-CH_3$, 3H); ^{13}C-NMR ($CDCl_3$) 198.0, 137.1, 134.7, 129.3, 125.6, 71.1, 69.8, 65.3, 59.5, 45.2, 37.1, 26.4, 18.7, 5.6, -3.5, -4.3 ppm; IR (film) 3600–3200, 3000–2800, 1800, 1720, 1470, 1240, 1180, 1010, 840, 760 cm^{-1}; FABMS m/e 621 (5.6), 605 (4.5), 563 (52.9), 393 (38.6).

Synthesis of Methyl Ester 21. To a solution of the seleno ester **20** (2.7 g, 4.35 mmol) in anhydrous methanol (218 mL) at 0 °C was added 7.2 mL (2.1 equiv) of 1.28 M $NaOCH_3$ over 2 h. The reaction mixture was then warmed to rt and stirred for 16 h. The mixture was quenched with saturated NH_4Cl (82 mL), and the clear yellow solution was concentrated *in vacuo*. The resulting slurry was extracted with EtOAc (5 × 150 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Flash chromatography (40:1–20:1–5:1 CH_2Cl_2/CH_3CN) gave **21** (0.84 g, 40%) as a white solid: mp 89–90 °C; R_f = 0.38 (40:1 CH_2Cl_2/CH_3CN); ^{1}H-NMR ($CDCl_3$) 7.52 (d, J = 8.40 Hz, 2H), 7.27 (d, J = 8.56 Hz, 2H), 7.03 (d, J = 3.14 Hz, 1H), 4.72 (d, J = 2.14 Hz, 1H), 4.36 (m, 1H), 3.77 (s, $-CH_3$, 3H), 3.43 (m, 1H), 2.67 (dm, J = 12.4 Hz, 1H), 2.49 (d, J = 8.83 Hz, OH, 1H), 2.16 (dm, J = 17.5 Hz, 1H), 0.77 (s, ^{t}Bu, 9H), -0.085 (d, 2-CH_3, 6H); ^{13}C-NMR ($CDCl_3$) 166.6, 139.4, 136.4, 134.6, 131.6, 129.4, 127.6, 65.3, 63.3, 51.9, 43.4, 30.0, 25.6, 17.9, -4.9, -5.3 ppm; IR (film) 3500–3200, 3000–2700, 1720, 1460, 1250, 1050, 840 cm^{-1}; FABMS m/e 475 (2.4), 459 (5.8), 419 (83.5), 345 (34.3), 327 (10.3), 307 (60.5), 289.2 (40.6).

Synthesis of Seleno Phosphonate 22. To a solution of methyl ester **21** (300 mg, 0.628 mmol) in benzene (16 mL) was added rhodium acetate (14 mg, 0.031 mmol, 0.05 equiv), and the mixture was brought to reflux. Trimethyl diazophosphonoacetate (144 mg, 0.690 mmol, 1.1 equiv) in benzene (6 mL) was added by syringe pump over 50 min. The mixture was refluxed for an additional 2 h, and another aliquot of rhodium acetate dimer (14 mg, 0.031 mmol, 0.05 equiv) was added. The mixture was refluxed for an additional 4 h, cooled to rt, and concentrated *in vacuo* to yield a green oil. Flash chromatography (2:1 hexanes/EtOAc to EtOAc) afforded 291 mg of a purple oil containing **22** as a mixture of diastereomers along with small quantities of **23** and **24**. This oil was used without further purification or characterization.

Synthesis of Silyloxy Seleno Diester 25. To a solution of insertion product **22** (291 mg, 0.444 mmol) in THF (36 mL) cooled to -20 °C was added 575 μL (0.5 mmol, 1.1 equiv) of a 0.85 M THF solution of lithium diisopropylamide. The solution was stirred at -20 °C for an additional 20 min. Gaseous formaldehyde (0.13 g, 4.44 mmol, 10 equiv) was bubbled through the mixture, and the solution was warmed to rt. Saturated NH_4Cl (36 mL) was added followed by H_2O (8 mL), and the aqueous layer was separated and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a dark oil containing **25**, the known[48] aromatic diester **26b**, and **27**. Flash chromatography (hexanes to 9:1 hexanes/EtOAc) gave the following compounds:

25 (78 mg, 31% from methyl ester **21**): mp 82–83 °C; R_f = 0.30 (9:1 hexanes/EtOAc); ^{1}H-NMR ($CDCl_3$) 7.55 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 7.7 Hz, 2H), 6.98 (d, J = 4.2 Hz, 1H), 5.53 (d, J = 2.8 Hz, 1H), 4.75 (d, J = 2.8 Hz, 1H), 4.70 (m, 1H), 4.65 (d, J = 2.5 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.35 (dd, J = 6.6, 3.8 Hz, 1H), 2.62 (dt, J = 15.1, 4.7 Hz, 1H), 2.34 (d, J = 15.0 Hz, 1H), 0.73 (s, ^{t}Bu, 9H), -0.18 (s, $-CH_3$, 3H), -0.26 (s, $-CH_3$, 3H); ^{13}C-NMR ($CDCl_3$) 166.5, 163.4, 149.3, 136.9, 134.5, 134.0, 129.3, 128.7, 96.8, 68.1, 66.0, 52.5, 52.0, 43.0, 27.1, 25.6, 17.9, -5.0, -5.5 ppm; IR ($CHCl_3$) 3000, 2980, 2880, 1740, 1650, 1500, 1460, 1270, 940, 740 cm^{-1}; FABMS m/e 503 (25.8), 459 (5.0), 429 (6.8), 307 (15.9), 289 (11.9), 267 (30.6).

26b (15%): R_f = 0.35 (9:1 hexanes/EtOAc); ^{1}H-NMR ($CDCl_3$) 7.82 (d, J = 8.0 Hz, 1H), 7.68 (bs, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 5.80 (d, J = 3.3 Hz, 1H), 4.99 (d, J = 3.4 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H). These data matched reported values.[48]

27 (42%): R_f = 0.55 (9:1 hexanes/EtOAc); ^{1}H-NMR ($CDCl_3$) 7.53 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 6.68 (s, 1H), 5.34 (s, 1H), 3.80 (s, 3H).

Synthesis of Hydroxy Seleno Diester 13b. To a solution of **25** (78 mg, 0.139 mmol) in THF (5 mL) cooled to -30 °C was added tetra-*n*-butylammonium fluoride (0.153 mmol, 1.1 equiv) in THF (153 μL). The reaction mixture was further cooled to -40 °C and was then stirred for 2 h. Water (2.5 mL) was added, and the mixture was warmed to rt. The biphasic mixture was concentrated *in vacuo* to remove THF, and the remaining aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give a brown oil. Flash chromatography (2:1 hexanes/EtOAc) yielded diester **13b** (38 mg, 62%) as a clear oil: R_f = 0.25 (2:1 hexanes/EtOAc); ^{1}H-NMR ($CDCl_3$) 7.57 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 7.8 Hz, 2H), 6.90 (s, 1H), 5.50 (d, J = 3.0 Hz, 1H), 4.73 (m, 1H), 4.66 (d, J = 3.0 Hz, 1H), 4.50 (d, J = 8.3 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.23 (m, 1H), 2.53 (dm, J = 13.2 Hz, 1H), 1.92 (m, 1H); ^{13}C-NMR ($CDCl_3$) 166.6, 163.2, 149.1, 137.8, 137.51, 137.47, 135.0, 134.2, 129.4, 97.1, 72.1, 69.6, 52.6, 52.3, 41.9, 34.6 ppm; IR (film) 3500–3200, 2900, 1720, 1570, 1420, 1300, 1200, 1150, 1000, 950, 750 cm^{-1}; CIMS m/e 446 (12.1), 429 (8.6), 345 (10.2), 327 (23.2), 292 (9.4).

Synthesis of Hydroxy Seleno Diacid 13a. To an ice-cold solution of diester **13b** (18.4 mg, 0.041 mmol) in THF (0.5 mL) containing water (0.27 mL) was added alkali (0.23 mL of 0.5 M NaOH) and the reaction mixture stirred for 5 h at 4 °C. Amberlite IR-120H pellets were carefully added to pH 4. The mixture was filtered to remove the pellets, and the resin was rinsed with EtOAc (4 × 1 mL). The resulting biphasic mixture was separated, and the aqueous portion was extracted with EtOAc (5 × 1 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield diacid **13a** (13 mg, 76%) as a clear oil: R_f = 0.37 (1:1 $MeOH/CH_2Cl_2$); ^{1}H-NMR (acetone-d_6) 7.61 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.62 Hz, 1H), 5.44 (d, J = 2.54 Hz, 1H), 4.95 (m, 1H), 4.91 (d, J = 2.53 Hz, 1H), 4.59 (d, J = 6.3 Hz, 1H), 3.49 (m, 1H), 2.62 (dt, J = 13.2, 4.9 Hz, 1H), 2.04 (m, 1H); ^{13}C-NMR (acetone-d_6) 167.6, 163.8, 150.4, 137.2, 137.1, 135.9, 134.2, 129.9, 128.8, 97.0, 71.8, 69.0, 43.5, 33.2 ppm; IR (film) 3600–2900, 1700, 1650, 1200, 1120, 1080, 900, 850 cm^{-1}; CIMS m/e 381.8 (5.4), 192.9 (15.8), 141.0 (18.1), 123.0 (100).

Oxidative Elimination of Silyloxy Seleno Diester 25. Selenide **25** (3.7 mg, 0.007 mmol) in THF-d_8 (0.5 mL) was cooled in a NMR tube to -20 °C, and dimethyldioxirane (0.007 mmol, 64 μL, 0.104 M solution, prepared by the method of Adam *et al.*[65]) was added. The solution was warmed to 4 °C, and the solvents were evaporated using a stream of argon. The residue was dissolved in ice-cold THF-d_8 (1 mL), and subsequent reactions were monitored by ^{1}H-NMR at 0 and 20 °C. Selenoxide elimination to form **28** was complete within 30 min at 0 °C. For **28**: ^{1}H-NMR (THF-d_8, 300 MHz) δ 6.98 (bs, 1H), 6.09 (bs, 2H), 5.44 (d, J = 2.7 Hz, 1H), 5.23 (bs, 1H), 5.04 (bs, 1H), 4.95 (d, J = 2.6 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 0.84 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H).

The product 1,4-diene was stable over 2.5 h at 0 °C but underwent Claisen rearrangement to **29a** at rt, with a half-life of ca. 2 h at 20 °C. For **29a**: ^{1}H-NMR (THF-d_8, 300 MHz) δ 7.06

(65) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* 1987, *52*, 2800–2803.

(d, J = 5.7 Hz, 1H), 6.25 (m, 1H), 6.12 (m, 1H), 4.49 (s, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.04 (dd, J = 13.3, 8.0 Hz, 1H), 2.81 (dd, J = 18.7, 8.0 Hz, 1H), 2.68 (dd, J = 18.7, 7.9 Hz, 1H), 0.83 (s, 9H), 0.19 (s, 3H), 0.05 (s, 3H).

Oxidative Elimination of Hydroxy Seleno Diester 13b. To a −20 °C solution of selenide **13b** (3.2 mg, 0.007 mmol) in THF-d_8 (0.5 mL) in a NMR tube was added dimethyldioxirane (0.007 mmol, 82 μL, 0.088 M solution). The solution was warmed to 4 °C, and the solvents were removed *in vacuo* at this temperature. The residue was dissolved in ice-cold THF-d_8 (1 mL). Selenoxide elimination and subsequent rearrangements were monitored by 300-MHz ^{1}H-NMR at 0, 10, and 20 °C. Selenoxide elimination was complete after the mixture was warmed to 10 °C. At temperatures below 20 °C, diene diester **9b** decomposed to aromatic **26b** exclusively. Claisen rearrangement to **29b** occurred only at 20 °C. The final ratio of rearranged diene **29b** to aromatic **26b** was 1:4. The ^{1}H-NMR spectrum of **26b** matched that described previously.

9b: ^{1}H-NMR (THF-d_8, 300 MHz) δ 6.96 (bs, 1H), 6.12 (dd, J = 10.0, 3.0 Hz, 1H), 6.04 (d, J = 12.0 Hz, 1H), 5.44 (d, J = 2.5 Hz, 1H), 5.20 (bs, 1H), 4.92 (d, J = 3.0 Hz, 1H), 4.82 (t, J = 3.0 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H).

29b: ^{1}H-NMR (THF-d_8, 300 MHz) δ 7.02 (d, J = 6.0 Hz, 1H), 6.22 (dd, J = 10.0, 4.3 Hz, 1H), 6.10 (m, 1H), 4.31 (d, J = 2.0 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.05 (m, 1H), 2.81 (dd, J = 18.0, 7.9 Hz, 1H), 2.65 (dd, J = 18.0, 7.8 Hz, 1H).

Oxidative Elimination of Hydroxy Seleno Diacid 13a. Without 3,5-Dimethoxyaniline. Selenide **13a** (8.6 mg, 0.021 mmol) was dissolved in acetone-d_6 (0.5 mL), and a reference NMR spectrum was obtained. This solution was cooled to -20 °C, and dimethyldioxirane (0.021 mmol, 234 μL, 0.088 M solution, prepared *via* the method of Adam *et al.*[65]) was added. The mixture was warmed to 4 °C and concentrated *in vacuo* at this temperature. The resulting white residue was taken up in ice-cold acetone-d_6 and transferred to an ice-cooled NMR tube. Selenoxide elimination and subsequent rearrangements were monitored using 300-MHz ^{1}H-NMR at 0 and 20 °C. Selenoxide elimination was complete after warming to 20 °C. At 20 °C, diene **9a** aromatized and Claisen rearranged rapidly ($t_{1/2}$(**9a**) at 20 °C = 40 min). The final product ratio of Claisen diene **29c** to aromatic **26a** was 1:2. The THF case study was performed as described above except that THF-d_8 was used in place of acetone-d_6. In this case, aromatization to produce **26a** was observed at 0 °C. Selenoxide elimination was complete after warming to 10 °C. At 20 °C, aromatization and Claisen rearrangement of **9a** occurred readily ($t_{1/2}$(**9a**) at 20 °C = 35 min). The final ratio of Claisen diene **29c** to aromatic **26a** was 1:10. The structure of aromatic **26a** was confirmed by comparison of its spectra with that of an authentic sample independently synthesized according to a published method.[66]

9a: ^{1}H-NMR (acetone-d_6, 300 MHz) δ 7.02 (bs, 1H), 6.17 (dm, J = 10.0 Hz, 1H), 6.11 (bd, J = 10.5 Hz, 1H), 5.50 (d, J = 2.7 Hz, 1H), 5.25 (m, 1H), 5.04 (d, J = 2.5 Hz, 1H), 4.39 (t, J = 5.0 Hz, 1H); (THF-d_8, 300 MHz) 6.99 (bs, 1H), 6.10 (d, J = 10.3 Hz, 1H), 6.03 (d, J = 10.5 Hz, 1H), 5.44 (d, J = 2.1 Hz, 1H), 5.13 (m, 1H), 4.86 (d, J = 2.1 Hz, 1H), 4.81 (m, 1H); (DMSO-d_6, 300 MHz) 6.81 (bs, 1H), 6.10 (d, J = 10.5 Hz, 1H), 6.01 (d, J = 10.7 Hz, 1H), 5.38 (d, J = 4.0 Hz, 1H), 5.21 (m, 1H), 5.01 (d, J = 4.0 Hz, 1H), 4.72 (m, 1H).

29c: ^{1}H-NMR (acetone-d_6, 300 MHz) δ 7.09 (d, J = 5.5 Hz, 1H), 6.26 (dd, J = 10.0, 5.0 Hz, 1H), 6.15 (dd, J = 10.0, 5.5 Hz, 1H), 4.44 (d, J = 3.2 Hz, 1H), 3.11 (m, 1H), 2.94 (dd, J = 18.0, 6.8 Hz, 1H), 2.82 (dd, J = 18.0, 7.7 Hz, 1H); (DMSO-d_6, 300 MHz) 6.95 (d, J = 6.0 Hz, 1H), 6.15 (m, 2H), 4.19 (s, 1H), 2.91 (dd, J = 15.0, 7.5 Hz, 1H), 2.73 (dd, J = 16.0, 7.5 Hz, 1H), 2.61 (dd, J = 16.0, 7.5 Hz, 1H); (D_2O, 300 MHz, HOD = 4.65 ppm) 7.11 (d, J = 6.0 Hz, 1H), 6.22 (m, 1H), 6.12 (dd, J = 10.0, 6.0 Hz, 1H), 4.31 (s, 1H), 2.98 (dd, J = 15.5, 6.0 Hz, 1H), 2.58 (dd, J = 7.5, 4.5 Hz, 2H); IR (film) 3600–2800, 1710, 1590, 1450, 1400, 1250, 1100, 1000 cm^{-1}; MS (electrospray) 227 (39), 208 (58), 180 (35), 135 (45); UV (H_2O) λ_{max} = 268 nm.

With 3,5-Dimethoxyaniline. Selenide **13a** (5.0 mg, 0.012 mmol) was dissolved in acetone-d_6 and cooled to −20 °C. Dimethyldioxirane (0.012 mmol, 136 μL, 0.088 M solution, prepared according to the method of Adam *et al.*[65]) was added, and the mixture was stirred at −20 °C for 1 h. At this point, 3,5-dimethoxyaniline[52,53] (4.0 mg, 0.024 mmol, 2.0 equiv) was added, and the mixture was warmed to 0 °C and stirred for 12 h. The mixture was concentrated *in vacuo* at 4 °C to give an orange-green slurry. This slurry was washed with ice-cold CH_2Cl_2 (3 × 2 mL) and concentrated *in vacuo* to remove traces of solvents. The resulting yellow residue was dissolved in acetone-d_6 (4 °C), and 300-MHz ^{1}H-NMR spectra were obtained at 0 °C. These spectra showed 1,4-diene **9a** contaminated with minor amounts of DMA–selenide species and Claisen product **29c**. This sample of diene **9a** was stable at 0 °C over 2.5 h. After this time, the mixture was warmed to 20 °C. At this temperature, diene **9a** rearranged to Claisen product **29c** ($t_{1/2}$(**9a**) at 20 °C = 1.5 h) exclusively. ^{1}H-NMR spectra for diene **9a** and Claisen product **29c** were identical to those obtained in the unbuffered selenoxide elimination.

Solvent Effects on Elimination and Rearrangement of 1,4-Diene 9a in the Presence of 3,5-Dimethoxyaniline. Diene **9a** was prepared according to the procedure for selenoxide elimination in the presence of stoichiometric amounts of 3,5-dimethoxyaniline. Formation of the diene was confirmed by ^{1}H NMR, and solvents were removed by concentration *in vacuo* at 4 °C. The deuterated solvent system under consideration was added at 4 °C, and subsequent reactions were monitored by NMR at 4 °C and 20 °C. Half-lives of diene **9a** were determined by monitoring its disappearance with time. Product ratios were determined by comparison of the appropriate integration values.

3-[(1-Carboxyvinyl)oxy]benzoic Acid (26a). Chorismic acid **1** (54.0 mg, 0.239 mmol) was dissolved in pyridine (0.6 mL), and acetic anhydride (0.65 g, 6.36 mmol, 0.6 mL) was added.[66] This mixture was stirred at room temperature for 16 h, diluted with CH_2Cl_2 (4.0 mL), and concentrated *in vacuo* to afford a brown oil. Acetone (2.0 mL) was added to this oil, and a precipitate formed. The solid material was filtered off, and the filtrate was concentrated *in vacuo* to yield **26a** (26.3 mg, 53%) as an off-white solid: R_f = 0.75 (10:2:1 MeCN/H_2O/AcOH); ^{1}H NMR (acetone-d_6) 7.81 (d, J = 7.5 Hz, 1H), 7.62 (s, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.29 (dd, J = 8.0, 2.5 Hz, 1H), 5.90 (d, J = 1.8 Hz, 1H), 5.26 (d, J = 1.8 Hz, 1H); ^{13}C NMR (acetone-d_6) 167.0, 163.4, 157.5, 150.6, 133.2, 130.9, 125.4, 123.2, 119.1, 108.5 ppm; IR (film) 3200–2850, 2600, 1710, 1650, 1600, 1460, 1320, 1250, 950, 900 cm^{-1}. These spectra were consistent with the reported literature spectra for **26a**[66] and match that of crude **26a** obtained by aromatization of diene **9a**.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of new compounds (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(66) Ife, R. J.; Ball, L. F.; Lowe, P.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1776–1783 and references cited therein.