Improved Synthesis of Racemic Chorismic Acid. Claisen Rearrangement of 4-*epi*-Chorismic Acid and Dimethyl 4-*epi*-Chorismate

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Abstract: The total synthesis of racemic chorismic acid (**1**) in eleven steps (6% overall yield) from methyl cyclohex-1-ene-4-carboxylate (**9**) is described. Dimethyl 4-*epi*-chorismate (**8**) and 4-*epi*-chorismic acid (**6**) are prepared by similar procedures, and their rate of Claisen rearrangement is investigated. A convenient preparation of disodium prephenate (**2**) and disodium 4-*epi*-prephenate (**5**) from dimethyl chorismate (**7**) and **8**, respectively, is described.

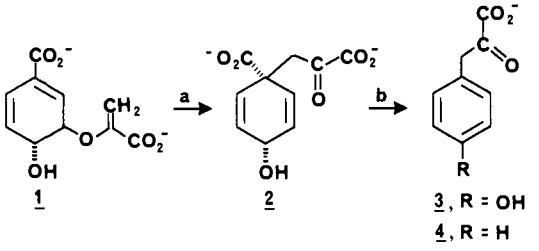
The classic work of Gibson and co-workers has established chorismic acid (**1**) as the last common intermediate in the biosynthesis of aromatic amino acids and growth factors in bacteria, fungi, and higher plants.[1] One of the more intriguing enzyme-catalyzed reactions of chorismate (**1**, Scheme I) is the rearrangement to prephenate (**2**), which serves as a precursor to tyrosine and phenylalanine via **3** and **4**, respectively. The total synthesis of racemic **1** has been accomplished in our laboratory[2] and in Ganem's laboratory.[3] Danishefsky[4] and Plieninger[5] have completed the total synthesis of disodium prephenate (**2**) and disodium 4-*epi*-prephenate (**5**). The free acids are unstable.

In view of our interest in the design of substances that act as pseudosubstrates or inhibitors of chorismate mutase or prephenate dehydrogenase, we have continued synthetic efforts in this area. Described below are (1) an improved procedure for our synthesis of racemic **1**, (2) investigations of the synthesis and stability of 4-*epi*-chorismic acid (**6**), and (3) the synthesis of **2** and **5** from dimethyl chorismate (**7**) and dimethyl 4-*epi*-chorismate (**8**).

Recently we described the preparation of **12** in poor yield as outlined in Scheme II.[6] The procedure has been improved to obtain **12** from **9** in an overall yield of 47%. Bis allylic bromination of **9** with *N*-bromosuccinimide (NBS) in CCl_4 gave a mixture of epimeric dibromides that were dehalogenated to **10** with either tri-*n*-butyltin hydride in benzene or NaI in acetone. The latter procedure was more convenient for large-scale preparation.[7] Although **10** was contaminated with 10–20% methyl benzoate, it was satisfactory for further transformations. Epoxidation of **10** with *m*-chloroperoxybenzoic acid (mCPBA) in CH_2Cl_2 gave **11**, which was isomerized to **12** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2.

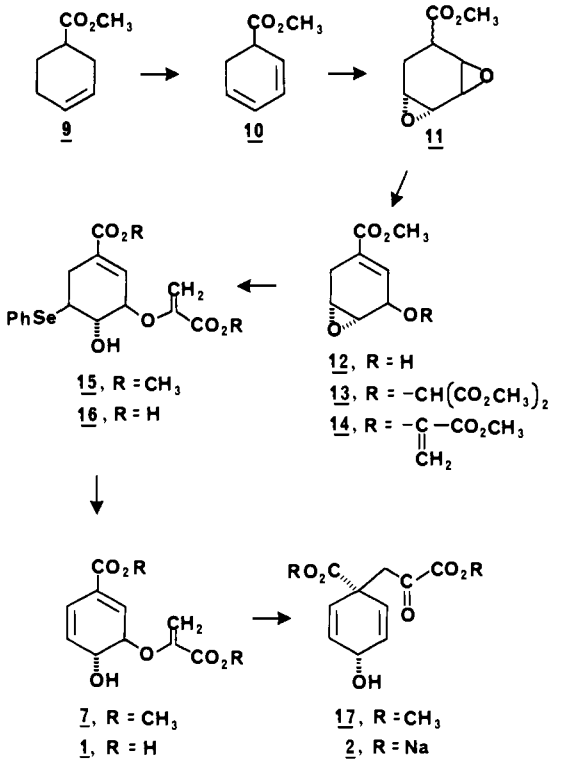
Alcohol **12** was converted to malonate **13** (82% yield) by the Ganem procedure[3] with dimethyl diazomalonate and a catalytic amount of $Rh_2(OAc)_4$. Alternatively, malonate **13** could be prepared from **12** by a three-step procedure similar to that described previously for related systems.[2] The procedure involves reaction of **12** with dimethyl oxomalonate to give the hemiketal, conversion to the chloromalonate with $SOCl_2$/pyridine, and reduction to **13** with Zn/HOAc buffered with NaOAc to prevent cleavage of the epoxide moiety. The sequence is carried out without purification of intermediates beyond **12**, and **13** is obtained in 62% yield from **12**. Malonate **13** was converted to **14** (25% yield) by formation of the Mannich base $[(CH_3)_2N^+{=}CH_2I^-/(C_2H_5)_3N]$, methylation ($CH_3I$), and fragmentation in dimethyl sulfoxide (Me_2SO) at 80 °C.[2]

Scheme I



a- chorismate mutase
b- prephenate dehydrogenase, NAD→3
- prephenate dehydratase→4

Scheme II



(1) For detailed reviews, see: (a) Weiss, U.; Edwards, J. M. "The Biosynthesis of Aromatic Compounds"; Wiley: New York, 1980. (b) Haslam, E. "The Shikimate Pathway"; Wiley: New York, 1974. (c) Ganem, B. *Tetrahedron* **1978**, *34*, 3353–3383.

(2) McGowan, D. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 1153–1154, 7036–7041.

(3) Ganem, B.; Ikota, N.; Muralidharan, V. B.; Wade, W. S.; Young, S. D.; Yukimoto, Y. *J. Am. Chem. Soc.* **1982**, *104*, 6787–6788.

(4) Danishefsky, S.; Hirama, M. *J. Am. Chem. Soc.* **1977**, *99*, 7740–7741. Danishefky, S.; Hirama, M.; Fritsch, N.; Clardy, J. *Ibid* **1979**, *101*, 7013–7018.

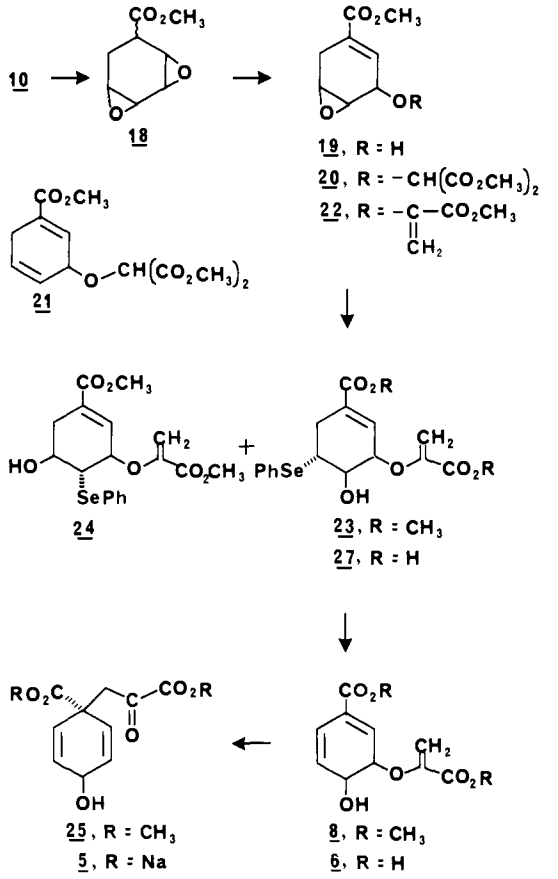
(5) Gramlich, W.; Plieninger, H. *Tetrahedron Lett.* **1978**, 3619–3622; *Chem. Ber.* **1979**, *112*, 1550–1570, 1571–1584.

(6) McGowan, D. A.; Berchtold, G. A. *J. Org. Chem.* **1981**, *46*, 2381–2383.

(7) Other reported preparations of **10** are less convenient or more expensive. See ref 9–11 of ref 6. The NaI in acetone procedure was developed by George Sigel.

0002-7863/83/1505-6264$01.50/0

Scheme III



The present sequence is a shorter, more convenient route to **14** which, in our original synthesis, was converted to **1** by a three-step sequence involving reaction with $PhSe^-$ to give **15**, selenoxide elimination to dimethyl chorismate (**7**), and hydrolysis to provide **1**. Although hydrolysis of **7** gave 60% of **1** in the crude product mixture (40% aromatic product from dehydration), purification by recrystallization gave only 11% of analytically pure racemic **1**.[8]

Modification of conditions (see Experimental Section) for conversion of **14** to **15** has resulted in significant improvement in yield. In order to circumvent the problem of aromatization during hydrolysis of **7** and the difficulty in purification of **1**, **15** was hydrolyzed to provide diacid **16** (81%). Selenoxide elimination from **16** in the presence of 3,5-dimethoxyaniline (DMA) as a scavenger for PhSeOH[9] afforded **1** with almost no aromatization, and pure **1** was obtained in 65% yield. The present sequence is a much simpler route to **1** than our original synthesis,[2] and it provides **1** in overall yield of 6% from **9**.

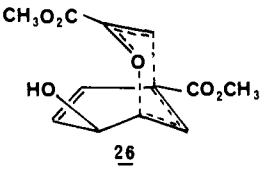
Thermal rearrangement of **7** at 55 °C in Me_2SO gave dimethyl prephenate (**17**). Saponification of **17** afforded disodium prephenate (**2**), the IR and ^1H NMR of which were identical with those of **2** obtained from natural sources.[10]

The synthesis of 4-*epi*-chorismic acid (**6**) and 4-*epi*-prephenate (**5**) was investigated with **10** as the starting material (Scheme III). The endoperoxide from reaction of **10** with singlet oxygen rearranged to **18** in high yield with 0.5 mol % $RuCl_2(PPh_3)_3$ in CH_2Cl_2 at room temperature.[11] Base-catalyzed isomerization of **18** with $NaOCH_3/CH_3OH$ gave **19** (34% yield from **9**). Application of the Ganem procedure to prepare malonate **20** from **19** was not satisfactory since it gave a mixture of **20** (30%) and diene **21** (15%) from deoxygenation of the syn epoxide group. Although **20** and **21** could be separated by chromatography on silica gel, the alternate three-step procedure described above was more convenient and provided **20** in 45% yield from **19**. Malonate **20** was converted to **22** (43% yield) by the procedure described above (**13** → **14**). Nucleophilic addition of $PhSe^-$ to **22** gave regioisomers **23** (39%) and **24** (13%), which were separated by chromatography on a silica gel plate. Selenoxide elimination from **23** afforded dimethyl 4-*epi*-chorismate (**8**), which was not a stable substance due to its propensity to undergo Claisen rearrangement. Isomerization of **8** to dimethyl 4-*epi*-prephenate (**25**) was complete after 24 h in $CHCl_3$ at room temperature. Hydrolysis of **25** afforded **5**, the IR and ^1H NMR spectral data of which were identical with those reported by Danishefsky and co-workers.[4,12]

Comparison of the relative ease of Claisen rearrangement of esters **7** and **8** is most interesting. Claisen rearrangement requires that either isomer adapt a conformation in which the enol pyruvate side chain is quasi-axial. The H_3–H_4 coupling constant in the ^1H NMR spectrum of **7** in $CDCl_3$ is 13.2 Hz indicating the preferred conformation is that in which the trans C-4 hydroxyl and C-3 enol pyruvate substituents are quasi-equatorial. Presumably, as reported for **1**,[13] this conformation is more stable due to intermolecular hydrogen bonding between the C-3 and C-4 substituents. Disruption of the internal hydrogen bonding is necessary for the molecule to adapt the conformation required for the chairlike transition state in the Claisen rearrangement.[14] On the other hand, Dreiding models indicate that ester **8** can adapt the conformation necessary for the chairlike transition state (**26**) with retention of intramolecular hydrogen bonding between the C-3 and C-4 substituents.

Ester **7** showed no tendency to undergo Claisen rearrangement at 30 °C in $CDCl_3$. It was necessary to heat **7** in Me_2SO, a solvent that disrupts the intramolecular hydrogen bonding,[13] at 55 °C for 36 h to effect complete reaction of **7**. The thermal reaction gave dimethyl prephenate (**17**, Scheme II) in poor yield (34%) and a mixture of aromatic products. In contrast, the half-life for Claisen rearrangement of ester **8** to **25** was 2.3 h at 30 °C in $CDCl_3$. The rearrangement was quantitative; no aromatic products were observed.

Efforts to prepare 4-*epi*-chorismic acid in pure form were not successful. Hydrolysis of **23** gave diacid **27** (Scheme III) which underwent selenoxide elimination (DMA as scavenger) at −35 → 0 °C to provide crude **6**, which was contaminated with aromatic impurities. The estimated purity was ~60% (see Experimental Section). Attempts to obtain pure **6** by low-temperature recrystallization met with failure. It was possible, however, to follow the Claisen rearrangement of the dianion of **6** to **5** in D_2O (pH 7, acetate buffer) at 30 °C. The half-life for the rearrangement was 40 min, and no aromatization occurred under these conditions.[15]



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In summary, our approach to the synthesis of racemic chorismic acid has been improved significantly. Inversion of configuration

(8) The Ganem group has been able to obtain pure **1** in 30% yield by a similar procedure.

(9) Tietze, L. F.; Kiedrowski, G.; Berger, B. *Synthesis* **1982**, 683–684. Selenoxide elimination without scavenger resulted in addition of PhSeOH to **1**.

(10) We thank Dr. J. F. Morrison for a sample of **2**: Dudzinski, P. K.; Morrison, J. F. *Prep. Bioch.* **1976**, *6*, 113–121.

(11) Procedure of Suzuki, M.; Noyori, R.; Hamanaka, N. *J. Am. Chem. Soc.* **1982**, *104*, 2024–2025. The uncatalyzed thermal rearrangement of the endoperoxide gave **18** that was contaminated with ketol, and purification was difficult.

(12) We thank Professor Danishefsky for providing spectral data of **5**.

(13) Batterham, T. J.; Young, I. G. *Tetrahedron Lett.* **1969**, 945–948.

(14) Inhibitor studies suggest that the enzyme-catalyzed rearrangement of **1** to **2** proceeds through a chair-like transition state: Andrews, P. R.; Cain, E. N.; Rizzardo, E.; Smith, G. D. *Biochemistry* **1977**, *16*, 4848–4852.

(15) Andrews and co-workers have investigated the rate of Claisen rearrangement and aromatization of **1** in H_2O (pH 7.5, Tris-HCl buffer) at various temperatures. The half-life for the Claisen rearrangement at 29.9 °C was 15.7 h: Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* **1973**, *12*, 3492–3498.

at C-4 of chorismate or dimethyl chorismate enhances the rate of Claisen rearrangement.

Experimental Section[16]

Methyl Cyclohexa-1,3-diene-5-carboxylate (10). A mixture of **9** (120 g, 0.86 mol, Frinton Laboratories), NBS (321 g, 1.80 mol), and azobis(isobutyronitrile) (AIBN) (500 mg) in CCl_4 (2 L) was heated at reflux for 40 min, cooled, and filtered. The filtrate was washed (aqueous Na_2SO_3, H_2O), dried ($MgSO_4$), and concentrated under reduced pressure to give 256 g of dibromide as a yellow oil.

Method A. A mixture of dibromide (254 g, 0.85 mol), tri-*n*-butyltin hydride (625 g, 2.15 mol), and AIBN (500 mg) in benzene (1.8 L) was heated at reflux under N_2 for 3 h. Solvent was removed under reduced pressure, and the residue was distilled. The distillate was distilled through a Vigreux column to obtain 88 g (75%) of **10**, bp 55 °C (0.4 mm), that was contaminated with 13% methyl benzoate.[6]

Method B. A solution of NaI (63.9 g, 0.426 mol) in acetone (550 mL) was added dropwise over a period of 20 min to a solution of dibromide (55 g, 0.18 mol) in acetone (550 mL), and stirring was continued for 5 min after addition was complete. The solution was filtered and concentrated. The residue was dissolved in ether (500 mL), filtered, and cooled in a dry ice/acetone bath. The cold solution was washed with 10% aqueous Na_2SO_3, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Distillation gave 14.1 g (57%) of **10**, bp 28 °C (0.005 mm), that was contaminated with 15% methyl benzoate.

Methyl (1β,6β)-2β-Hydroxy-7-oxabicyclo[4.1.0]hept-3-ene-4-carboxylate (12). To a solution of **10** (16.1 g, 0.117 mol) in CH_2Cl_2 (240 mL) at −78 °C was added mCPBA (47.5 g, 85%, 0.234 mol). The cooling bath was removed. After the solution came to room temperature, it was heated at reflux for 1.5 h. The mixture was washed with 10% aqueous Na_2SO_3 (100 mL), H_2O (100 mL), and saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), and filtered. Concentration under reduced pressure gave 19.9 g of epimers **11**: ^1H NMR (60 MHz) δ 3.77 (3 H, s), 3.8–2.5 (5 H, m), 2.5–1.8 (2 H, m).

A solution of **11** (19.9 g, 0.117 mol) in CH_2Cl_2 (250 mL) was cooled to −78 °C, and DBU (17.7 g, 0.116 mol) was added. The solution was allowed to warm to room temperature and was stirred for 1 h. The solution was washed with 2 M aqueous KH_2PO_4 (3 × 100 mL). The combined aqueous extracts were saturated with $(NH_4)_2SO_4$ and extracted with CH_2Cl_2 (5 × 50 mL). The CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography[17] on silica gel (1:1 ethyl acetate/hexanes) gave 12.5 g (63%) of **12**.[6]

Methyl (1β,6β)-2β-[Bis(methoxycarbonyl)methoxy]-7-oxabicyclo-[4.1.0]hept-3-ene-4-carboxylate (13). A mixture of **12** (1.07 g, 6.27 mmol), dimethyl diazomalonate[18] (1.10 g, 6.93 mmol), and $Rh_2(OAc)_4$ (51 mg) in benzene (25 mL) was heated at 65 °C under N_2 for 2.5 h. The solution was cooled, filtered, and washed (10 mL of saturated aqueous $NaHCO_3$ and 2 × 10 mL of H_2O). The solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 1.54 g (82%) of **13** as a light yellow oil: IR ($CHCl_3$) 1748, 1719 cm^{-1}; ^1H NMR (60 MHz) δ 6.72 (1 H, m), 4.70 (1 H, s), 4.60 (1 H, m), 3.82 (6 H, s), 3.73 (3 H, s), 3.37 (2 H, m), 2.82 (2 H, m); high-resolution mass spectrum, calcd for $C_{13}H_{16}O_8$, 300.0845; found, 300.0856.

Methyl (1β,6β)-5β-[[1-(Methoxycarbonyl)ethenyl]oxy]-7-oxabicyclo-[4.1.0]hept-3-ene-3-carboxylate (14). Malonate **13** (11.5 g, 38.4 mmol) was dissolved in CH_2Cl_2 (225 mL), and Eschenmoser's salt (9.25 g, 50.0 mmol) and $(C_2H_5)_3N$ (5.5 mL) were added. The solution was stirred under N_2 at room temperature for 2.5 h. The solution was washed (3 × 75 mL of H_2O), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual Mannich base was dissolved in CH_2Cl_2 (100 mL), and methyl iodide (20 mL) was added. The solution was stirred overnight at room temperature and concentrated under reduced pressure to a gummy orange solid (11 g), which was triturated with ether. The insoluble salt was dissolved in dry Me_2SO (100 mL) and heated at 80 °C for 4 h. The mixture was cooled and poured into benzene (300 mL). The solution was washed (5 × 100 mL of H_2O), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was crystallized from methanol to give 3.95 g (25%) of **14** that was identical with **14** reported previously.[2]

Improved Preparation of Selenide 15 and Dimethyl Chorismate (7). The preparation of **15** was carried out as described previously[2] except that a *minimum* amount of $NaBH_4$ was added every 12 h to decolorize the solution (requires ~5 min to decolorize), and the reaction mixture was not acidified prior to workup. Solvent was removed, and the residue was dissolved in CH_2Cl_2, washed (1 M phosphate buffer, pH 7), dried ($MgSO_4$), filtered, and concentrated to give pure **15** in quantitative yield.

The preparation of **7** from **15** was carried out as described previously except that methanol was used as the solvent. The reaction mixture was diluted with CH_2Cl_2, washed (saturated aqueous $NaHCO_3$), dried ($MgSO_4$), filtered, and concentrated to give pure **7** in quantitative yield without chromatography.

(3β,4α,5β)-3-[(1-Carboxyethenyl)oxy]-4-hydroxy-5-(phenylseleno)-1-cyclohexene-1-carboxylic Acid (16). Diester **15** (395 mg, 0.96 mmol) was dissolved in THF (2 mL) and cooled in an ice bath. Cold 1 N aqueous NaOH (2.1 mL) was added, and H_2O was added dropwise until the mixture was homogeneous. The solution was stirred at 0 °C for 4 h. After acidification to pH 4 with Amberlite IR-120, the solution was filtered and extracted with ethyl acetate (4 × 10 mL). The ethyl acetate extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Recrystallization of the residue from ethyl acetate gave 299 mg (81%) of **16** as a white solid: mp 141–143 °C; IR (nujol) 1685, 1640, 1620 cm^{-1}; ^1H NMR δ 7.68 (2 H, m), 7.35 (3 H, m), 6.77 (1 H, s), 5.52 (1 H, d, J = 4 Hz), 5.00 (1 H, d, J = 4 Hz), 4.82 (1 H, m), 3.89 (1 H, m), 3.67 (1 H, m), 2.82 (1 H, dd, J = 19 Hz, J' = 6 Hz), 2.48 (1 H, m).

(±)-Chorismic Acid (1). A solution of **16** (48 mg, 0.13 mmol) in acetone (2.3 mL) was cooled to −35 °C. Hydrogen peroxide (31.3%, 34 μL, 0.32 mmol) was added and the solution was stirred at −35 °C for 1 h. Recrystallized 3,5-dimethoxyaniline (61.5 mg, 0.40 mmol, Aldrich Chemical Co.) was added, and the solution was allowed to warm to room temperature. Stirring was continued for 30 min at room temperature during which time the solution turned orange. The solution was concentrated, dissolved in a minimum amount of methanol, and poured into cold water (7.5 mL). The aqueous solution was washed with CH_2Cl_2 (7 × 5 mL) and then extracted with ether (7 × 5 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated, leaving 18.3 mg (65%) of pure **1** that was identical with **1** prepared previously.[2]

Dimethyl Prephenate (17). A solution of **7** (99 mg, 0.39 mmol) in Me_2SO-d_6 (0.5 mL) was heated at 55 °C, and the reaction was followed by ^1H NMR. After 36 h **7** was completely consumed. Benzene (10 mL) was added. The solution was washed (H_2O), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel plate (3:7 ether/CH_2Cl_2) to separate methyl *p*-hydroxybenzoate (R_f 0.45) and *17* (33 mg, 34%, R_f 0.28): IR ($CHCl_3$) 3580, 1730 cm^{-1}; ^1H NMR δ 5.97 (4 H, m), 4.43 (1 H, m), 3.82 (3 H, s), 3.67 (3 H, s), 3.20 (2 H, s), 1.93 (1 H, br s); high-resolution mass spectrum, calcd for $C_{12}H_{14}O_6$, 254.0790; found, 254.0762.

Disodium Prephenate (2). A solution of 1 N aqueous NaOH (131 μL) was added to a solution of **17** (33 mg, 0.13 mmol) at 0 °C, and the mixture was stirred for 4 h. The mixture was concentrated under high vacuum, and the residue was triturated with ethyl acetate and with CH_2Cl_2 to give 10.5 mg (30%) of **2** an off-white solid. The IR and ^1H NMR were identical with those of an authentic sample of **2**.[10]

Methyl (1β,6β)-2α-Hydroxy-7-oxabicyclo[4.1.0]hept-3-ene-4-carboxylate (19). Diene **10** (20.0 g, 0.15 mol, contaminated with 13% methyl benzoate) was converted to the endoperoxide as described previously.[6] The solution was concentrated under reduced pressure, filtered through a short silica gel column (1:1 hexane/ether) to remove Rose Bengal, and concentrated to an oil (20 g). The oil was dissolved in CH_2Cl_2 (350 mL) and cooled to 0 °C under N_2. $Ru(Ph_3P)_3Cl_2$ (500 mg, 0.5 mol %) was added, and the mixture was stirred overnight at room temperature. Solvent was evaporated, and the black residual oil was filtered through a short silica gel column with ether. The filtrate was concentrated under reduced pressure to give 18.7 g of **18** as an oil that was dissolved in methanol (350 mL) and cooled to −5 °C. A solution of $NaOCH_3$, formed from Na (3.0 g) and methanol (125 mL), was added over a period of 5 min. After 25 min Amberlite IR-120 resin (acid form) was added with stirring to pH 7. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether, dried (K_2CO_3), filtered through Celite, and concentrated to a volume of 200 mL. On standing overnight at −20 °C, **19** (6.4 g) crystallized as white needles. Concentration of the mother liquor gave an additional 4.9 g for a total yield of 11.3 g (52%) of **19** that was identical with **19** reported previously.[6]

Methyl (1α,6α)-2β-[Bis(methoxycarbonyl)methoxy]-7-oxabicyclo-[4.1.0]hept-3-ene-4-carboxylate (20). A mixture of **19** (5.0 g, 29 mmol) and dimethyl oxomalonate (9.8 g, 67 mmol) was heated at 65 °C under N_2 for 4 h. Excess dimethyl oxomalonate was removed by vacuum distillation (0.1 mm). The residue and pyridine (4.7 mL) were dissolved in dry THF (150 mL), and the solution was cooled to −78 °C. Thionyl chloride (2.43 mL, 32 mmol) in THF (40 mL) was added dropwise over a period of 20 min. The solution was kept at −78 °C for 15 min, warmed

(16) High-resolution mass spectra were provided by the facility supported by National Institutes of Health Grant RR00317 (principal investigator Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Unless otherwise indicated, ^1H NMR spectra were obtained in $CDCl_3$ at 250 or 270 MHz.

(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(18) Ando, W.; Yagihara, T.; Tozune, S.; Imai, I.; Suzuki, J.; Toyama, T.; Nakaido, S.; Migita, T. *J. Org. Chem.* **1972**, *37*, 1721–1727.

to 0 °C, and stirred for 30 min. The mixture was diluted with ethyl acetate and filtered through a short silica gel column. Concentration under reduced pressure gave 9.0 g (92%) of crude chloro compound as a straw-colored oil: ^{1}H NMR δ 6.82 (1 H, s), 5.09 (1 H, m), 3.90 (6 H, s), 3.75 (3 H, s), 3.51 (2 H, m), 3.12 (1 H, d, J = 19 Hz), 2.48 (1 H, dd, J = 19, 2 Hz). Crude chloromalonate was dissolved in 5:1 methanol/ethyl acetate (125 mL), and the solution was cooled to 0 °C. Sodium acetate (11.0 g), acetic acid (6.6 mL), and Zn dust (18.9 g) were added with stirring. The mixture was allowed to come to room temperature over 3.5 h. It was filtered through Celite, and the Celite was washed with ethyl acetate. The combined extracts were concentrated under reduced pressure, and the resulting oily solid was triturated with ethyl acetate (100 mL). The ethyl acetate solution was filtered through a short silica gel column, and solvent was removed. The residual oil was purified by column chromatography on silica gel (3:1 CH_2Cl_2/ether) to give 3.9 g (45%) of **20** (R_f 0.38) as a colorless oil that crystallized on standing. An analytical sample was prepared by recrystallization from hexane/ethyl acetate: mp 83–84 °C; IR ($CHCl_3$) 1745, 1715, 1655 cm^{-1}; ^{1}H NMR δ 6.74 (1 H, br s), 4.88 (1 H, br s), 4.82 (1 H, s), 3.83 (6 H, s), 3.77 (3 H, s), 3.60 (1 H, br s), 3.45 (1 H, br s), 3.04 (1 H, d, J = 20 Hz), 2.45 (1 H, br d, J = 20 Hz). Anal. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.33. Found: C, 52.26; H, 5.40.

Methyl (1α,6α)-5β-[[1-(Methoxycarbonyl)ethenyl]oxy]-7-oxabicyclo-[4.1.0]hept-3-ene-3-carboxylate (22). Malonate **20** (3.24 g, 11 mmol) was converted to **22** by the same procedure for preparation of **14** from **13**. The yield of **22** was 1.21 g (43%): mp 73–75 °C; IR ($CHCl_3$) 1715, 1655, 1620 cm^{-1}; ^{1}H NMR δ 6.77 (1 H, br s), 5.63 (1 H, d, J = 2.8 Hz), 5.04 (1 H, t, J = 2.2 Hz), 4.90 (1 H, d, J = 2.8 Hz), 3.83 (3 H, s), 3.76 (3 H, s), 3.65 (1 H, m), 3.53 (1 H, m), 3.16 (1 H, br d, J = 19 Hz), 2.51 (1 H, dm, J = 19 Hz); high-resolution mass spectrum, calcd for $C_{12}H_{14}O_6$, 254.0791; found, 254.0788.

Methyl (3β,4β,5β)-3-[[1-(Methoxycarbonyl)ethenyl]oxy]-4-hydroxy-5-(phenylseleno)-1-cyclohexene-1-carboxylate (23). The procedure described for the preparation of **15** was used for the reaction of **22** (246 mg, 0.97 mmol) with $PhSe^-$. The crude product mixture was chromatographed on a silica gel plate (3:1 CH_2Cl_2/ether) to obtain 156 mg (39%) of **23** and 52 mg (13%) of **24**.

23: IR (neat) 3600–3200 cm^{-1}; ^{1}H NMR δ 7.61 (2 H, m), 7.31 (3 H, m), 6.85 (1 H, s), 5.75 (1 H, d, J = 2.9 Hz), 4.95 (1 H, br s), 4.90 (1 H, d, J = 2.9 Hz), 4.10 (1 H, m), 3.79 (3 H, s), 3.73 (3 H, s), 3.63 (1 H, m), 3.07 (1 H, dm, J = 19 Hz), 2.56 (1 H, dm, J = 19 Hz); high-resolution mass spectrum, calcd for $C_{18}H_{20}O_6{}^{80}Se$, 412.0447; found, 412.0425.

24: ^{1}H NMR δ 7.62 (2 H, m), 7.33 (3 H, m), 6.84 (1 H, br s), 5.50 (1 H, d, J = 3.1 Hz), 4.61 (1 H, br s), 4.51 (1 H, d, J = 3.1 Hz), 3.81 (3 H, s), 3.75 (3 H, s), 3.6–3.4 (2 H, m), 2.92 (1 H, dd, J = 18.2, 5.3 Hz), 2.48 (1 H, dd, J = 18.2, 7.4 Hz).

Dimethyl 4-*epi*-Prephenate (25) via Dimethyl 4-*epi*-Chorismate (8). Aqueous H_2O_2 (2%, 10 mL) was added to a solution of **23** (186 mg, 0.45 mmol) in $CHCl_3$ (15 mL), and the mixture was stirred vigorously at room temperature for 2 h. $NaHCO_3$ (200 mg) was added, and vigorous stirring was continued for 1.5 h. The layers were separated. The organic phase was washed (H_2O), dried (K_2CO_3), and allowed to stand at room temperature for 24 h to effect complete rearrangement of **8** to **25**. Evaporation of solvent gave 114 mg (99%) of pure **25** as an oil: IR (CH_2Cl_2) 3560, 1730, 1615 cm^{-1}; ^{1}H NMR δ 6.07 (2 H, dd, J = 10.2, 3.3 Hz), 5.94 (1 H, dd, J = 10.2, 1.3 Hz), 4.56 (1 H, br s), 3.88 (3 H, s), 3.70 (3 H, s), 3.35 (2 H, s), 1.05 (1 H, br s); high-resolution mass spectrum, calcd for $C_{11}H_{10}O_5$ ($M^+ - CH_3OH$) 222.0528; found 222.0505.

When the selenoxide elimination was carried out in $CDCl_3$, **8** was observed as the initial product: ^{1}H NMR δ 6.98 (1 H, br s), 6.56 (1 H, d, J = 9.9 Hz), 6.16 (1 H, dd, J = 9.9, 4.5 Hz), 5.62 (1 H, d, J = 3.0 Hz), 4.90 (1 H, d, J = 3.0 Hz), 4.73 (1 H, m), 4.40 (1 H, t, J = 5.2 Hz), 3.83 (3 H, s), 3.80 (3 H, s). Rearrangement of **8** to **25**, followed by 250-MHz ^{1}H NMR, had a half-life of 2.3 h at 30 °C.

Disodium 4-*epi*-Prephenate (5). Aqueous NaOH (1 N, 708 μL, 0.68 mmol) was added to suspension of **27** (85 mg, 0.33 mmol) in THF/H_2O (3:1, 4 mL). The mixture was stirred at room temperature for 3 h and concentrated to dryness under high vacuum. Methanol (2 mL) was added to the residue, and the resulting precipitous suspension was centrifuged. The precipitate was suspended in methanol (1 mL), cooled to 0 °C, and centrifuged. The supernatant was removed to give 26 mg of **5**. Evaporation of the combined methanolic supernatants, followed by treatment with methanol (1 mL) of 0 °C, gave an additional 12 mg of **5** for a total yield of 38 mg (43%). The IR and ^{1}H NMR of **5** were identical with the spectral data of **5** reported by Danishefsky and coworkers.[4,12]

Preparation and Rearrangement of 4-*epi*-Chorismic Acid (6). Selenide **23** (164 mg, 0.40 mmol) was dissolved in THF/H_2O (3:1, 4 mL) at 0 °C, and 1 N NaOH (1.2 mL) was added. The mixture was stirred at 0 °C for 4 h. The solution was neutralized (Amberlite IR-120), filtered, and concentrated under reduced pressure to yield 156 mg (100%) of **27** as a white powder: ^{1}H NMR (CD_3OD) δ 7.67 (2 H, m), 7.34 (3 H, m), 6.86 (1 H, br s), 5.41 (1 H, d, J = 2 Hz), 5.0–4.7 (2 H, m), 4.71 (1 H, d, J = 2 Hz), 4.10 (1 H, m), 3.88 (1 H, m), 2.98 (1 H, d, J = 19 Hz), 2.55 (1 H, d, J = 19 Hz).

Selenide **27** (69 mg, 0.18 mmol) in acetone (5 mL) was cooled to −35 °C. Aqueous hydrogen peroxide (30%, 51 μL, 2.5 equiv) was added, and the solution was stirred at −35 °C for 1 h. Solid 3,5-dimethoxyaniline (55 mg, 0.36 mmol) was added, and the solution was allowed to warm to 0 °C over 30 min. Solvent was removed under high vacuum at 0 °C. The resulting dark oil was suspended in CH_2Cl_2 (15 mL) at 0 °C, and the mixture was centrifuged. The precipitate was separated, and washing with CH_2Cl_2 (15 mL) at 0 °C was repeated several times. The precipitate was swirled with acetone (15 mL) and centrifuged. The supernatant was separated and evaporated under high vacuum below 0 °C. The residue was triturated with CH_2Cl_2 (5 mL) and dried under high vacuum at 0 °C to give 8.0 mg of crude **6**: UV (pH 7 phosphate buffer) λ_{max} 267 nm (ϵ 2600); ^{1}H NMR (acetone-d_6) δ 6.99 (1 H, br d, J = 2.2 Hz), 6.47 (1 H, br d, J = 9.8 Hz), 6.17 (1 H, dd, J = 9.8 Hz, J' = 4.8 Hz), 5.54 (1 H, d, J = 2.5 Hz), 5.08 (1 H, d, J = 2.5 Hz), 4.93 (1 H, dd, J = 6.0 Hz, J' = 3.3 Hz), 4.44 (1 H, br t, J = 5.3 Hz). The esimated purity of **6** from the ^{1}H NMR spectrum was 60%.

The rearrangement of **6** to **5** at 30 °C in D_2O at pH 7 (acetate buffer) was followed by 250-MHz ^{1}H NMR. The half-life for the rearrangement was 40 min, and no aromatization was observed under the reaction conditions.

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