cessful, so a sample of questionable quality for X-ray studies was finally used. The crystal studied was cleaved from a larger one in a nitrogen-filled glovebag and transferred under a nitrogen atmosphere to the cold stream of the goniostat. After the crystal was cooled to -161 °C, a search of a limited hemisphere of reciprocal space located reflections that were indexable as monoclinic, space group $A2/a$. The structure was in fact isomorphous with the molybdenum analogue, and the cell was chosen to agree with the latter. The cell dimensions obtained at -161 °C from 54 reflections with Mo K$\alpha$ ($\lambda$ = 0.71069 Å) were $a$ = 18.053 (19) Å, $b$ = 18.251 (17) Å, $c$ = 10.575 (8) Å, $\beta$ = 87.18 (4)°, $V$ = 3480 (2) Å, $Z$ = 4, and $d_{calcd}$ = 1.734 g cm$^{-3}$ with space group $A2/a$.

A total number of 3494 reflections was collected with use of standard moving-crystal moving-detector techniques with the following values: scan speed 4.0° min$^{-1}$, scan width 2.0 + dispersion, single background time at extremes of scan 5 s, aperture size 3.0 × 4.0 mm. The limits of data collection were 5° < 2$\theta$ < 50°. Of the 3494 reflections collected, 2294 reflections were unique. The number of reflections with $F > 2.33\sigma(F)$ was 1627.

The fractional coordinate for $Mo_2(O\text{-}i\text{-}Pr)_6(py)_2(\mu\text{-}CO)$ were used as a starting point for the refinement. As in the case of the molybdenum compound, a disorder was apparent in the bridging isopropoxy groups. Isotropic refinement converged to $R(F)$ = 0.123 and $R_w(F)$ = 0.109.

While the faces of the crystal were uneven, due to fracturing, approximate indices could be assigned. With use of these indices and the crystal dimensions, an analytical absorption correction was performed ($\mu$(Mo K$\alpha$) = 67.89 cm$^{-1}$, maximum and minimum absorption 0.61 and 0.95).

The final residuals are $R(F)$ = 0.0769 and $R_w(F)$ = 0.0584, and the maximum $\Delta/\sigma$ for the last cycle was 0.05 for the absorption-corrected data. When attempts were made to assign anisotropic thermal parameters to the light atoms of the structure, the residual did not indicate a significant improvement.

A final difference Fourier synthesis contained several peaks of intensity 1.3-2.4 e Å$^{-3}$ within 1 Å of the tungsten atoms but otherwise was featureless. The rather poor precision of the structure is undoubtedly due to a combination of the disorder and a poor absorption correction.

**Acknowledgment.** We thank the Office of Basic Sciences, Chemistry Division, U.S. Department of Energy, the Wrubel Computing Center, and the taxpayers of the state of Indiana for support of this work. M.H.C. is also grateful for a Camille and Henry Dreyfus Teacher-Scholar Grant.

**Registry No.** $W_2(O\text{-}i\text{-}Pr)_6(py)_2$, 70178-75-5; $W_2(O\text{-}i\text{-}Pr)_6(py)_2(\mu\text{-}CO)$, 83436-99-1; $Mo_2(O\text{-}i\text{-}Pr)_6(py)_2(\mu\text{-}CO)$, 83437-00-7; $Mo_2(O\text{-}i\text{-}Pr)_6$, 62509-78-8; $W_2(ONeo)_6(HNMe_2)_2(m\text{-}CO)$, 83437-01-8; $W_2(ONeo)_6(HNMe_2)_2$, 83437-02-9; $Mo_2(ONeo)_6(HNMe_2)_2(\mu\text{-}CO)$, 83437-03-0; $Mo_2(ONeo)_6(HNMe_2)_2$, 83437-04-1; $Mo_2(ONeo)_6(py)_2(\mu\text{-}CO)$, 83437-05-2; $Mo_2(ONeo)_6(py)_2$, 81987-92-0; $Mo_2(O\text{-}i\text{-}Pr)_6(i\text{-}PrOH)_2(\mu\text{-}CO)$, 83447-51-2; $Mo_2(O\text{-}i\text{-}Pr)_6(\mu\text{-}CO)$, 83437-06-3; $Mo(CO)_6$, 13939-06-5; $Ti(O\text{-}i\text{-}Pr)_4$, 546-68-9.

**Supplementary Material Available:** Tables of observed and calculated structure factors and anisotropic thermal parameters (32 pages). Ordering information is given on any current masthead page. The complete structural reports, MSC Report No. 8062, $Mo_2(O\text{-}i\text{-}Pr)_6(py)_2(\mu\text{-}CO)$, and No. 81042, $W_2(O\text{-}i\text{-}Pr)_6(py)_2(\mu\text{-}CO)$, are available, in microfiche form only, from the Indiana University Chemistry Library.

# Total Synthesis of Racemic Chorismic Acid and (-)-5-Enolpyruvylshikimic Acid ("Compound $Z_1$")

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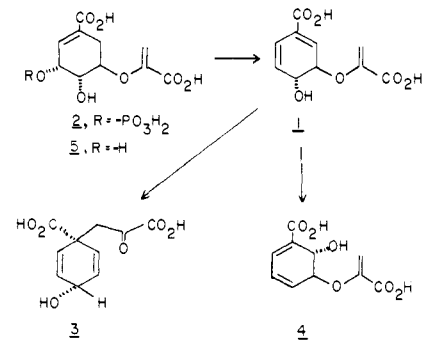
*Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.* *Received April 14, 1982*

**Abstract:** A new synthesis of methyl 4-*epi*-shikimate (**6**) is described. Ester **6** is used as the starting material for a total synthesis of racemic chorismic acid (**1**), the branch-point intermediate in the biosynthesis of aromatic amino acids and growth factors in microorganisms and higher plants. The procedure developed for the construction of the enolpyruvate functionality of **1** is applied also to the synthesis of (-)-5-enolpyruvylshikimic acid (**5**), a secondary metabolite derived from the biosynthetic precursor of chorismic acid.

The glucose-derived shikimate pathway and the acetate-derived polyketide pathway are the major routes for the biosynthesis of aromatic compounds from acyclic, nonaromatic precursors in bacteria, fungi, and higher plants. The shikimate pathway is better understood due to the successful isolation of discrete intermediates.[1] Chorismic acid (**1**, Scheme I) is the last common intermediate in aromatic biosynthesis from shikimic acid. Unambiguous proof that **1** is the intermediate between 5-enolpyruvylshikimic acid 3-phosphate (**2**) and prephenic acid (**3**) in the biosynthesis of phenylalanine and tyrosine was estabished after Gibson and collaborators developed a mutant of *A. aerogenes* from which **1** was isolated,[2] and the structure and absolute stereochemistry were determined.[3] Other work has established that **1** serves also as a biosynthetic precursor to *p*-aminobenzoic acid, anthranilic acid, tryptophan, hydroxybenzoic acids, and numerous other aromatic derivatives.[1] Of special interest from the chemical standpoint are the enzyme-catalyzed rearrangement of **1** to isochorismic acid (**4**)[4] and to **3**. The latter transformation, presumably a Claisen rearrangement, is unique to **1** and **4**, and in the case of **1**, the enzymatic reaction has been studied in detail.[5]

Scheme I




(1) (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.

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(4) Young, I. G.; Batterham, T. J.; Gibson, F. *Biochim. Biophys. Acta* **1969**, *177*, 389-400; **1968**, *165*, 567-568.

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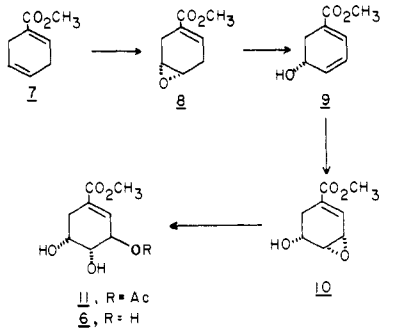
Scheme II



"Compound $Z_1$", 5-enolpyruvylshikimic acid (**5**), has been observed as a secondary metabolite from hydrolytic cleaveage of the phosphate ester group of **2**.[6] Metabolite **5** has no known biological function.

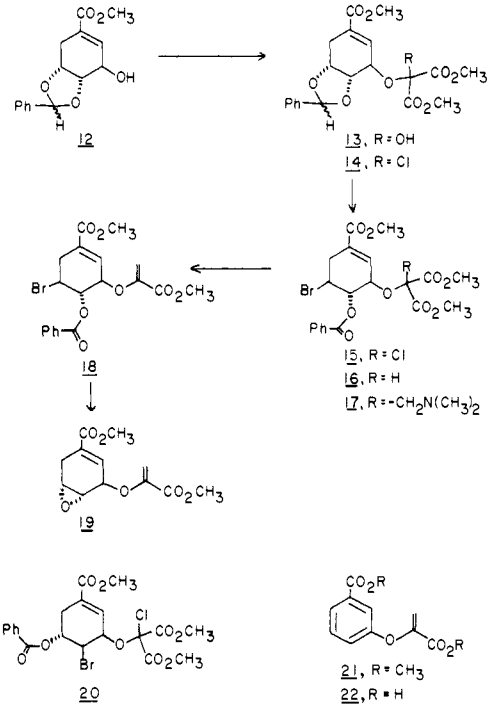
The synthesis of disodium prephenate (free acid unstable) has been accomplished in the laboratories of Danishefsky[7] and Plieninger.[8] Ikota and Ganem have developed a synthesis of norchorismic acid.[9]

Described below are (1) a new, convenient preparation of methyl 4-*epi*-shikimate (**6**), (2) the total synthesis of racemic chorismic acid from **6**,[10] and (3) a synthesis of (−)-5-enolpyruvylshikimic acid from shikimic acid.

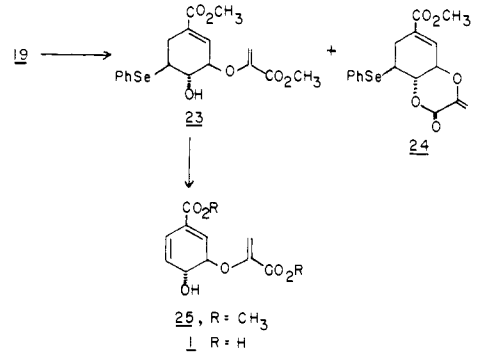
Although racemic **6**[11] and the (−) and (±) forms of the acid[11,12] have been prepared, in our hands a more convenient route to **6** was that outlined in Scheme II. Epoxidation ($CH_3CO_3H$) of diene **7**[13] afforded **8** which was isomerized to **9** with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN).[14] Epoxidation of **9** with *m*-chloroperbenzoic acid (mCPBA) gave **10** and the corresponding anti isomer[15] in a ratio of 19:1 ($^1$H NMR). Solvolysis of **10** in refluxing acetic acid gave a 3:1 mixture of acetates ($^1$H NMR) of which the major isomer (**11**) resulted from the desired mode of oxirane cleavage at $C_5$. Acetate cleavage of the mixture ($CH_3O^-$/$CH_3OH$) and acidification gave a crude syrup from which pure, crystalline **6** was obtained by treatment with hot ethyl acetate. The overall yield of **6** from **7** was ~20%, and the sequence was convenient for large-scale preparation. Triol **6** prepared in this fashion was devoid of isomeric impurities and was identical with a sample of **6** prepared by the procedure of Grewe and Kersten.[11]

For the synthesis of **1** from **6**, we envisaged transformation of the $C_3$ hydroxyl group to the enolpyruvate derivative and conversion of the $C_4$,$C_5$ diol to an oxirane to provide **19** (Scheme III) for further elaboration to **1**. Although literature procedures are available for the synthesis of enolpyruvates,[16] for a variety of reasons they were unattractive, and a new procedure was developed. The synthesis involved conversion of the $C_3$ hydroxyl to a malonate derivative by literature methods to effect similar substitution on the nitrogen atom of β-lactams.[17] Subsequent fragmentation of the Mannich base quaternary salt derivative was effected by modification of the literature procedure for the preparation of acrylic esters.[18]

Scheme III



Scheme IV



The epimeric benzylidine acetals (**12**, 4:1, Scheme III) were condensed with dimethyl oxomalonate[19] to afford **13** which, without purification, was treated with thionyl chloride in pyridine to give **14** (42% from **12**). At this stage of the synthesis the acetal functionality of **14** was cleaved with *N*-bromosuccinimide in dry benzene[20] to give crystalline **15** (66%) and regioisomer **20** (7%) due to cleavage at $C_4$. Confirmation of the structure of regioisomer

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(14) The preparation of **8** and **9** were developed in our laboratory by Dr. Robert W. Ashworth, Thesis, M.I.T. 1977.

(15) Fex, T.; Trofast, J.; Wickberg, B. *Acta Chem. Scand.* **1981**, *35*, 91–95.

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(17) (a) Schmidt, S. M.; Johnston, D. B. R.; Christensen, B. G. *J. Org. Chem.* **1980**, *45*, 1135–1142, 1142–1148. (b) Scartazzini, R.; Peter, H.; Bickel, H.; Heusler, K.; Woodward, R. B. *Helv. Chim. Acta* **1972**, *55*, 408–417. (c) Displacement on dimethyl bromomalonate with the alkoxide of **12** was not attempted since such displacement reactions are notoriously poor: Takemura, K. H.; Pulickal, M.; Hoff, F. O. *J. Org. Chem.* **1971**, *36*, 3646–3648.

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**15** is provided from the $^1$H NMR (250 MHz) spectrum which shows $H_4$ as a doublet of doublets at $\delta$ 5.67, $J_{H_5-H_4}$ = 6.3 Hz and $J_{H_4-H_5}$ = 9.4 Hz. The absorption of $H_5$ appears as a doublet of triplets at $\delta$ 4.34, $J_{H_5-H_{6\alpha}}$ and $J_{H_5-H_{6\beta}}$ = 9.4 and 5.4 Hz. Reduction of **15** (Zn, 9:1 HOAc/$H_2O$ in ethyl acetate) afforded **16** in 74% yield.[21]

Reaction of **16** with *N,N*-dimethylmethyleneammonium iodide (Eschenmoser's salt) in the presence of 1 equiv of triethylamine resulted in quantitative conversion to **17**. Mannich base **17** was quaternized with methyl iodide, and the salt was heated at 85–90 °C in dimethyl sulfoxide to effect fragmentation to **18** (64% from **16**). Of particular interest was the observation that Mannich base **17** was also formed in high yield from reaction of chloromalonate **15** with Eschenmoser's salt (2 equiv) in the presence of 1 equiv of triethylamine. In this case the reaction was considerably slower, requiring 3–4 days for complete reaction whereas formation of **17** from **16** was complete after 1 h. The reaction did not occur in the absence of triethylamine. It appears that the reaction occurs by $I^-$ attack at the chlorine atom of **15** to displace the anion of **16** which reacts with Eschenmoser's salt to afford the Mannich base (**17**). Triethylamine may drive the reaction forward by acting as a scavenger for ICl.[22]

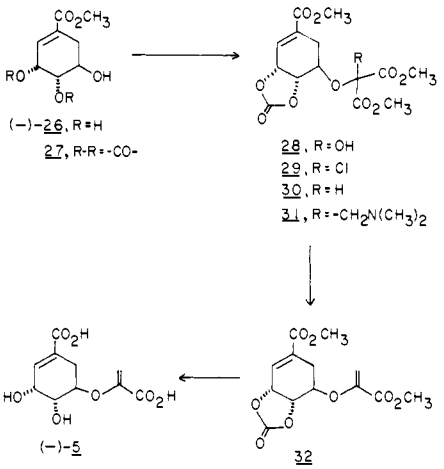
Reaction of **18** with methoxide ion in methanol effected cleavage of the benzoate ester with subsequent internal displacement of bromide ion to afford epoxide **19** in 46% yield after recrystallization. The crude reaction mixture contains a minor amount (15%) of **21** which is the only product from the reaction of **18** with DBN in $CDCl_3$.

Completion of the synthesis of **1** is outlined in Scheme IV. Epoxide **19** underwent regiospecific ring opening with phenyl selenide anion ($Ph_2Se_2$, $NaBH_4$, $CH_3OH$)[23] to give **23** (37%) and a minor amount (8%) of lactone **24**. After purification by chromatography on silica gel, **23** was treated with 30% hydrogen peroxide in $CH_2Cl_2$/THF at 0 °C followed by addition of 3 equiv of $NaHCO_3$ and stirring at room temperature for 1.5 h to effect elimination of the selenoxide. Crystalline, racemic dimethyl chorismate (**25**) was obtained in 77% yield after chromatographic purification. The IR and $^1$H NMR of **25** were in agreement with the spectroscopic data reported for **25** from the reaction of (−)-**1** with diazomethane.[24] The overall yield of **25** from **19** was 28%, and the yield remained constant when the sequence was repeated without chromatographic purification of selenide **23**.

Hydrolysis of **25** with 2.2 equiv of NaOH in THF/$H_2O$ for 3.5 h at 0 °C followed by treatment with Amberlite IR-120 resin and lyophilization gave a 3:2 mixture ($^1$H NMR) of racemic **1** and **22**. Acid **22** is the aromatization product from decomposition of **1** in aqueous base.[25] Successive recrystallization of the crude product from ethyl acetate/hexane, as described for (−)-**1**,[26] gave pure, racemic **1** as sharp melting microprisms. The maximum yield of analytically pure material was 11%. The IR, UV, $^1$H NMR, and mass spectra of synthetic **1** were identical with the corresponding spectra data of (−)-**1** prepared in our laboratory[26,27] from culture growth of *A. aerogenes* (62-1).[28]

The method of construction of the enolpyruvate functionality of **1** was applied also to a synthesis of **5** as outlined in Scheme V. The carbonate derivative (**27**) of (−)-methyl shikimate (**26**)[29]

Scheme V




was prepared by reaction with carbonyldiimidazole.[30] Carbonate **27** reacted with dimethyl oxomalonate in dry benzene to afford hemiketal **28**. Solvent was removed and replaced with THF for reaction at low temperature with thionyl chloride/pyridine to give **29**. Crude **29** was reduced (Zn, 90% HOAc) to **30** in 82% overall yield from **27**. Mannich base formation (Eschenmoser's salt, triethylamine) provided **31** which was quaternized with methyl iodide. The methiodide salt underwent fragmentation in dimethyl sulfoxide (70–80 °C, 3 h) to afford **32** in 73% yield from **30**. Hydrolysis of **30** with aqueous NaOH followed by acidification gave (−)-**5** (43%) which was >95% pure by $^1$H NMR. Compound **5** is isolated in salt form from natural sources.[6] Edwards[6d] has recorded the $^1$H NMR of **5**, and he kindly provided a copy for comparison. The method of synthesis and spectral data (see Experimental Section) of synthetic (−)-**5** establish the structural assignment.

## Experimental Section

Melting points were determined with a Thomas-Hoover Unimelt and are corrected. Infrared spectra were recorded with a Perkin-Elmer Model 238B or Nicolet Model 7199 Fourier transform spectrometer. Ultraviolet spectra were recorded with a Perkin-Elmer Model 552 spectrophotometer. $^1$H NMR spectra were measured at 60 MHz (Varian T-60 or Perkin-Elmer R24B), 250 MHz (Brüker WM-250), or 270 MHz (Brüker WM-270). Unless otherwise indicated, spectra were obtained at 250 or 270 MHz, and chemical shift values ($\delta$) are reported in parts per million downfield from tetramethylsilane. $^{13}$C NMR spectra were measured at 62.8 or 67.9 MHz (Brüker WM-250 or WM-270), and chemical shift values ($\delta$) are reported in parts per million downfield from tetramethylsilane. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Mass spectra were determined with a Varian MAT 44 instrument. 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.

**Methyl 7-Oxabicyclo[4.1.0]hept-3-ene-3-carboxylate (8).**[14] To a mixture of **7**[13] (58 g, 0.42 mol) and anhydrous sodium acetate (11.2 g) in 500 mL of $CHCl_3$ was added dropwise 84 mL (0.5 mol) of 40% peracetic acid, and the mixture was stirred at room temperature for 17 h. The mixture was washed with saturated $FeSO_4$ solution until there was no color transfer to the aqueous solution. It was then washed with saturated, aqueous NaCl solution and dried ($Na_2SO_4$). Filtration and evaporation left an oil which was distilled to give 50.5 g (80%) of **8** which crystallized on standing: mp 34–35 °C; IR ($CHCl_3$) 1712, 1658 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 60 MHz) $\delta$ 2.73 (4 H, m), 3.28 (2 H, m), 3.73 (3 H, s), 6.76 (1 H, m). Anal. Calcd for $C_8H_{10}O_3$: C, 62.39; H, 6.55. Found: C, 62.20; H, 6.67.

**Methyl 5-Hydroxy-1,3-Cyclohexadiene-1-carboxylate (9).**[14] A solution of **8** (15.4 g, 0.10 mol) and DBN (15.0 g, 0.12 mol) in 350 mL of ether was heated under reflux for 25 h. The mixture was washed with three 100-mL portions of saturated, aqueous NaCl solution and dried

(21) In our preliminary communication[10] we described Zn/HOAc reduction of chloromalonate **14** prior to cleavage of the benzylidine acetal. The sequence described herein is the superior procedure.

(22) The reaction of tertiary amines with halogens has been investigated: (a) Crane, C. W.; Forrest, J.; Stephenson, O.; Waters, W. A. *J. Chem. Soc.* **1946**, 827–830. (b) Challis, B. S.; Butler, A. R. "The Chemistry of the Amino Group"; Patai, S., Ed.; Interscience: New York 1968; pp 302–304.

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(27) We thank Dr. John H. Hoare and Peter P. Policastro for isolation of (−)-**1**.

(28) We thank Professor Frank Gibson for providing a sample of *A. aerogenes* (62-1).

(29) Diels, O.; Fritzsche, P. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 3018–3027.

(30) Kutney, J. P.; Ratcliffe, A. *Synth. Commun.* **1975**, *5*, 47–52.

($K_2CO_3$). The solvent was removed under reduced pressure to give 12.2 g (80%) of **9** as a pale yellow oil. Diene **9** could be distilled, bp 87–90 °C (0.1 mm), but due to extensive decomposition on distillation, it was used without purification: IR ($CHCl_3$) 3590, 1705, 1640, 1575 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 2.51 (1 H, br s), 2.75 (2 H, m), 3.75 (3 H, s), 4.36 (1 H, m), 6.18 (2 H, m), 7.03 (1 H, m).

**Methyl (1α,5β,6α)-5-Hydroxy-7-oxabicyclo[4.1.0]hept-2-ene-3-carboxylate (10).** Alcohol **9** (27.2 g, contaminated with ~10% of methyl benzoate, 0.16 mol) was dissolved in dry $CH_2Cl_2$ (200 mL) and cooled to 0 °C under $N_2$ with stirring. A solution of mCPBA (35 g of 85% technical grade, 1.1 equiv) in $CH_2Cl_2$ (200 mL) was added dropwise. The mixture was stirred overnight at room temperature and the solid removed by filtration. The filtrate was washed with 5% $Na_2SO_3$ solution, $NaHCO_3$ solution, and saturated NaCl solution and dried ($Na_2SO_4$). Solvent was removed under reduced pressure and methyl benzoate was removed under high vacuum with slight heating to leave crude **10** (17.0 g, 65%) as an oil of acceptable purity for further reactions. $^1H$ NMR indicated the product to be ~95% **10** and ~5% of the corresponding trans isomer. A sample could be distilled (Kugelrohr, 150 °C, 0.2 mm), but extensive resinification of the residue occurred: IR ($CH_2Cl_2$) 3580, 1715, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.02 (1 H, t, $J$ = 3.4 Hz, $H_2$), 4.15 (1 H, m, $H_5$), 3.76 (3 H, s, $OCH_3$), 3.67 (1 H, m, epoxy H), 3.53 (1 H, t, $J$ = 4.1 Hz, epoxy H), 2.92 (1 H, ddd, $\alpha H_4$), 2.69 (1 H, d, J = 7.8 Hz, OH), 2.13 (1 H, ddd, $\beta H_4$). Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.28; H, 6.02.

**Methyl 4-*epi*-Shikimate (6).** A solution of **10** (8.24 g, 48 mmol) in glacial HOAc (30 mL) was heated under reflux for 1.25 h and cooled. Solvent was removed under reduced pressure, and the residue was subjected to high vacuum with slight heating to remove final traces of HOAc. The residual syrup of crude **11** was dissolved in dry $CH_3OH$ (75 mL), and $NaOCH_3$ was added in portions until the solution was alkaline to litmus. The solution was stirred at room temperature for 1.5 h, and Amberlite IR-120 resin was added to acidify the solution. Charcoal was added. The mixture was stirred for 15 min and filtered through Celite. The filtrate was concentrated in vacuo, and final traces of solvent were removed under high vacuum. Dry ethyl acetate (50 mL) was added, and the mixture was heated with vigorous swirling as product crystallized. The mixture was chilled in a refrigerator and filtered. The precipitate was separated by filtration and washed with cold ethyl acetate to afford **6** (4.3 g, 47%): mp 152–154 °C (lit.[11] mp 154–155 °C); $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 167.0, 139.1, 128.0, 73.3, 68.8, 66.8, 51.8, 70.7.

**Methyl (1α,5α,6α)-5-Hydroxy-8-phenyl-7,9-dioxabicyclo[4.3.0]non-3-ene-3-carboxylate (12, 8α and 8β).** A mixture of **6** (1.0 g, 5.3 mmol), benzaldehyde (1.5 mL, 2.3 equiv), and a few crystals of *p*-toluenesulfonic acid in toluene (60 mL) was heated overnight at reflux under $N_2$ with a Dean–Stark trap to remove water. The mixture was cooled, washed (bicarbonate solution and saturated NaCl solution), dried ($Na_2SO_4$), and concentrated. The residual oil was warmed under high vacuum to remove excess benzaldehyde. Flash chromatography[31] on silica gel with 30% ethyl ether in $CH_2Cl_2$ afforded 1.06 g (72%) of **12** as a mixture of isomers (4:1) by $^1H$ NMR analysis: IR ($CH_2Cl_2$) 3580, 1715, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.49–7.35 (5 H, m), 6.98 and 6.95 (1 H, 2 m), 6.09 and 5.82 (1 H, 2 s, acetal H's), 4.46–4.37 (2 H, m), 4.19 and 4.10 (1 H, 2 m), 3.78 and 3.77 (3 H, 2 s), 3.28–3.14 (1 H, m), 2.85 (1 H, br d, OH), 2.46–2.34 (1 H, m); MS, $m/e$ 276 ($M^+$). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.23; H, 5.92.

**Methyl (1α,5α,6α)-5-[Bis(methoxycarbonyl)chloromethoxy]-8-phenyl-7,9-dioxabicyclo[4.3.0]non-3-ene-3-carboxylate (14, 8α and 8β).** A mixture of **12** (3.79 g, 13.7 mmol) and dimethyl oxomalonate[19] (2.20 g, 15.1 mmol) in dry toluene (50 mL) was stirred under $N_2$ at 40 °C for 12 h followed by 80 °C for 3 h. Solvent was removed under reduced pressure, and the residue was warmed under high vacuum (Kugelrohr, 80–85 °C) to remove excess oxomalonate and leave hemiketal **13** (4.8 g, 83%). A portion of **13** (450 mg, 1.1 mmol) was dissolved in dry THF (10 mL) with dry pyridine (103 μL, 1.2 equiv) and cooled under $N_2$ with stirring to −20 °C. Thionyl chloride (150 mg, 91 μL) was added dropwise, and stirring was continued at −20 °C for 0.5 h followed by 1 h at 0 °C. The mixture was filtered, and the filtrate was evaporated and subjected to high vacuum. The residue was chromatographed (silica gel, preparative plate, 40% ethyl acetate in hexane) to give 236 mg (50%) of **14**: IR ($CH_2Cl_2$) 1765, 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.47–7.35 (5 H, m), 7.07 and 7.00 (1 H, 2 m), 6.02 and 5.74 (1 H, 2 s), 4.83 and 4.72 (1 H, 2 m), 4.53 (2 H, m), 3.88, 3.86, 3.79, 3.77, and 3.69 (9 H, 5 s, $OCH_3$), 2.97 (1 H, md), 2.72–2.56 (1 H, m). Anal. Calcd for $C_{20}H_{21}ClO_9$: C, 54.49; H, 4.80; Cl, 8.04. Found: C, 55.65; H, 5.09; Cl, 6.78.

**Methyl (3β,4α,5β)-3-[Bis(methoxycarbonyl)chloromethoxy]-4-(benzoyloxy)-5-bromo-1-cyclohexene-1-carboxylate (15).** A solution of **14** (163 mg, 0.37 mmol) and *N*-bromosuccinimide (72 mg, 0.41 mmol) in 10 mL of dry benzene was stirred overnight at room temperature and was filtered. Solvent was removed under reduced pressure, and the residue was dissolved in the minimum amount of $CH_2Cl_2$. Ether and petroleum ether (1:1) were added, and the solution was cooled overnight to deposit colorless plates of **15** (65 mg), mp 141–142 °C. The filtrate was evaporated, and the residue was chromatographed (silica gel, preparative plate, 40% ethyl acetate in hexane) to afford 13 mg (7%) of an oil (**20** by $^1H$ NMR analysis) and an additional 62 mg of **15** (total yield 66%): IR ($CH_2Cl_2$) 1760, 1720, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.07 (2 H, dd, *o*-Ar-H), 7.59 (1 H, dt, *p*-Ar-H), 7.46 (2 H, t, *m*-Ar-H), 7.01 (1 H, m, $H_2$), 5.67 (1 H, dd, $J$ = 9.5, 6.3 Hz, $H_4$), 4.98 (1 H, m, $H_3$), 4.34 (1 H, dt, $J$ = 9.4, 5.4 Hz, $H_5$), 3.87 (3 H, s, $OCH_3$), 3.80 (3 H, s, $OCH_3$), 3.62 (3 H, s, $OCH_3$), 3.19 (1 H, dd, $J$ = 18.3, 5.4 Hz, $H_6$), 2.94 (1 H, mdd, $J$ = 18.3, 9.3 Hz, $H_6$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 165.3 (s), 164.9 (s), 164.4 (s), 163.6 (s), 134.8 (d), 133.3 (d), 131.2 (s), 129.9 (d), 129.5 (s), 128.4 (d), 94.3 (s), 75.5 (d), 73.7 (d), 54.1 (q), 52.3 (q), 43.7 (d), 33.7 (t). Anal. Calcd for $C_{20}H_{20}BrClO_9$: C, 46.22; H, 3.88; Br, 15.37; Cl, 6.82. Found: C, 46.52; H, 4.26; Br, 15.25; Cl, 6.89.

**Methyl (3β,4α,5β)-3-[Bis(methoxycarbonyl)methoxy]-4-(benzoyloxy)-5-bromo-1-cyclohexene-1-carboxylate (16).** A solution of **15** (300 mg, 0.50 mmol) in a mixture of 90% HOAc (6 mL) and ethyl acetate (5 mL) was stirred at 0 °C while powdered Zn (acid washed, 365 mg, 10 equiv) was added in portions over a period of 5 min. The mixture was stirred at 0 °C for 15 min and at room temperature for 30 min. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was triturated with $CH_2Cl_2$, and the supernatant was evaporated. The residual oil crystallized under high vacuum. Recrystallization (ether/hexane) gave 206 mg (74%) of **16** as needles: mp 124.5–125.5 °C; IR ($CH_2Cl_2$) 1760 (sh), 1740, 1720, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.07 (2 H, d, $J$ = 7.4 Hz, *o*-Ar-H), 7.60 (1 H, t, $J$ = 7.4 Hz, *p*-Ar-H), 7.48 (2 H, t, $J$ = 7.4 Hz, *m*-Ar-H), 7.01 (1 H, m, $H_2$), 5.62 (1 H, dd, $J$ = 10.0, 7.2 Hz, $H_4$), 4.74 (1 H, s, -C*H*($CO_2CH_3$)$_2$), 4.52 (1 H, m, $H_3$), 4.28 (1 H, dt, $J$ = 10.5, 6.0 Hz, $H_5$), 3.80 (3 H, s, $OCH_3$), 3.76 (3 H, s, $OCH_3$), 3.57 (3 H, s, $OCH_3$), 3.23 (1 H, dd, $J$ = 18.1, 6.1 Hz, $H_6$), 2.96 (1 H, m, $H_6$); MS, $m/e$ 484, 486 ($M^+$). Anal. Calcd for $C_{20}H_{21}BrO_9$: C, 49.50; H, 4.36; Br, 16.47. Found: C, 49.52; H, 4.43; Br, 16.72.

**Methyl (3β,4α,5β)-3-[[1-(Methoxycarbonyl)ethenyl]oxy]-4-(benzoyloxy)-5-bromo-1-cyclohexene-1-carboxylate (18). Method A (from 16).** To a stirring solution of **16** (150 mg, 0.31 mmol) in dry $CH_2Cl_2$ (10 mL) were added Eschenmoser's salt[32] (69 mg, 0.37 mmol) and triethylamine (43 μL). The mixture, which became homogeneous after 30 min, was stirred for 3 h. The solution was extracted with $H_2O$ and with saturated NaCl solution, dried ($Na_2SO_4$), and concentrated to give 170 mg (100%) of **17** that was a single spot on TLC: $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 8.03 (2 H, m), 7.6–7.2 (4 H, m), 5.53 (1 H, m), 4.85 (1 H, m), 4.38 (m, 1 H), 3.79 (6 H, s), 3.44 (3 H, s), 3.2–2.8 (2 H, m), 2.88 (2 H, s), 2.28 (6 H, s).

The Mannich base (**17**) and iodomethane (0.2 mL) were dissolved in $CH_2Cl_2$ (10 mL), and the solution was heated under reflux for 6 h. Evaporation and trituration with ether gave a pale yellow solid which was dried under vacuum and dissolved in a minimum amount of dry $Me_2SO$. The solution was heated under $N_2$ at 85–90 °C for 4 h, cooled, and filtered to remove insoluble material. Solvent was removed with warming under high vacuum, and the residue was triturated with $CH_2Cl_2$. The soluble material was chromatographed (silica gel, preparative plate, 40% ethyl acetate in hexane) to afford 87 mg (64%) of **18** as an oil: IR ($CH_2Cl_2$) 1721, 1619 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.03 (2 H, dd, $J$ = 8.5, 1.5 Hz, *o*-ArH), 7.59 (1 H, t, $J$ = 7 Hz, *p*-ArH), 7.46 (2 H, dt, $J$ = 7.7, 2 Hz, *m*-ArH), 6.94 (1 H, m, $H_2$), 5.73 (1 H, dd, $J$ = 10.7, 7.3 Hz, $H_4$), 5.50 (1 H, d, $J$ = 2.6 Hz, *trans*-OC=CH), 4.93 (1 H, m, $H_3$), 4.88 (1 H, d, $J$ = 2.6 Hz, *cis*-OC=CH), 4.34 (1 H, dt, $J$ = 10.3, 5.9 Hz, $H_5$), 3.80 (3 H, s, $OCH_3$), 3.69 (3 H, s, $OCH_3$), 3.27 (1 H, dd, $J$ = 18.2, 5.7 Hz, $H_6$), 2.99 (1 H, m, $H_6$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 165.2 (s), 165.1 (s), 163.1 (s), 150.0 (s), 134.0 (d), 133.3 (d), 131.2 (s), 129.8 (d), 129.5 (s), 128.4 (d), 100.2 (t), 76.2 (d), 74.2 (d), 52.3 (q), 44.2 (d), 34.7 (t); high-resolution mass spectrum, calcd for $C_{19}H_{19}BrO_7$, 438.0314, 440.0294; found, 4388.0322, 440.0278.

**Method B (from 15).** A mixture of **15** (1.17 g, 2.25 mmol), Eschenmoser's salt[32] (890 mg, 4.81 mmol), and triethylamine (230 mg, 1 equiv) in dry $CH_2Cl_2$ (20 mL) was stirred under $N_2$ in the dark for 72 h. Workup as described in method A afforded 1.14 g of Mannich base **17** (80% pure by $^1H$ NMR). Reaction of **17** as described in method A gave 424 mg (43%) of **18** that was identical with **18** prepared by method A.

**Methyl (1β,5β,6β)-5-[[1-(Methoxycarbonyl)ethenyl]oxy]-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylate (19).** To a solution of **18** (374 mg,

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0.85 mmol) in dry $CH_3OH$ (5 mL) at 0 °C under $N_2$ was added freshly prepared $NaOCH_3$ (46 mg, 1 equiv). The mixture was stirred at 0 °C for 1 h, at room temperature for 1 h, and at reflux for 0.75 h. The mixture was cooled and concentrated under reduced pressure. The residue was dissolved in $CH_2Cl_2$, filtered through Celite, and concentrated under reduced pressure. The residual oil was dissolved in a minimum amount of $CH_3OH$ and chilled to give 83 mg of **19** as white needles: mp 119–120 °C. The filtrate contained unreacted **18** so a methanolic solution of the residue was treated with 18 mg of $NaOCH_3$ for 2 h at room temperature and 1 h at reflux. Amberlite IR-120 resin was added to acidify the mixture. The solution was concentrated and chilled to deposit an additional 17 mg of crystalline **19** (46% total yield): IR ($CH_2Cl_2$) 1720, 1621 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.83 (1 H, m, $H_4$), 5.59 (1 H, d, $J$ = 3.3 Hz, *trans*-OC=CH), 4.94 (1 H, m, $H_5$), 4.93 (1 H, d, $J$ = 3.3 Hz, *cis*-OC=CH), 3.82 (3 H, s, $OCH_3$), 3.76 (3 H, s, $OCH_3$), 3.48 (1 H, m, $H_1$ or $H_6$), 3.40 (1 H, m, $H_1$ or $H_6$), 2.94 (1 H, dm, $J$ = 19.8 Hz, $H_2$), 2.76 (1 H, dm, $J$ = 19.8 Hz, $H_2$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 166.4 (s), 163.1 (s), 149.8 (s), 129.3 (d), 128.9 (s), 97.1 (t), 68.8 (d), 52.5 (q), 51.2 (q), 50.7 (d), 50.2 (d), 24.3 (t). Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.55; H, 5.59.

**Dimethyl Chlorismate (25).** Diphenyl diselenide (41 mg, 0.13 mmol) was dissolved in dry $CH_3OH$ (5 mL) and treated with portions of $NaBH_4$ until the stirred solution decolorized.[23] Epoxide **19** (67 mg, 0.26 mmol) in 4 mL of $CH_3OH$ was added, and the mixture was stirred at room temperature for 72 h. Small portions of $NaBH_4$ were added from time to time to keep the solution decolorized. Amberlite IR-120 resin was added tothe stirred mixture, and after 3 min the solution was filtered and concentrated. The $CH_2Cl_2$-soluble oil was applied to a preparative silica gel plate and eluted wiht 25% ether in $CH_2Cl_2$. The UV-active band at $R_f$ 0.77 afforded 8 mg (8%) of lactone **24**): mp 192 °C (d); IR ($CH_2Cl_2$) 1737, 1715 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.72–7.68 (2 H, m), 7.40–7.27 (3 H, m), 6.72 (1 H, m), 5.68 (1 H, d, $J$ = 1.8 Hz), 5.10 (1 H, d, $J$ = 1.8 Hz), 4.62 (1 H, m), 4.18 (1 H, dd, $J$ = 11.9, 8.1 Hz), 3.75 (3 H, s), 3.36 (1 H, dt, $J$ = 11.7, 6.2 Hz), 3.02 (1 H, m), 2.52 (1 H, m); MS, $m/e$ 380, 378 ($M^+$).

The UV-active band at $R_f$ 0.57 contained 4 mg (6%) of unreacted **19** and 40 mg (37%) of **23**: $^1H$ NMR ($CDCl_3$) $\delta$ 7.68–7.63 (2 H, m, Ar H), 7.37–7.29 (3 H, *m*, ArH), 6.71 (1 H, m, $H_2$), 5.58 (1 H, d, $J$ = 2.9 Hz, *trans*-OC=CH), 4.89 (1 H, d, $J$ = 2.9 Hz, *cis*-OC=CH), 4.67 (1 H, m, $H_3$), 3.81 (1 H, s, $OCH_3$), 3.81 (1 H, m, $H_4$), 3.71 (3 H, s, $OCH_3$), 3.30 (1 H, dt, $J$ = 11.7, 5.4 Hz, $H_5$), 2.95 (1 H, dd, $J$ = 18.0, 5.4 Hz, $H_6$), 2.47 (1 H, m, $H_6$).

Selenide **23** was dissolved in $CH_2Cl_2$ (2 mL) and stirred at 0 °C while $H_2O_2$ (10.6 $\mu$L, 31.2%, 1 equiv) in 3 mL of THF was added. After the mixture stirred at 0 °C for 0.5 h, 40 mg of $NaHCO_3$ was added; and stirring was continued at room temperature for 1.5 h. Filtration through Celite and removal of solvent under reduced pressure gave crude **25** (36 mg). Chromatography (silica gel, preparative plate, 3% $CH_3OH$ in $CHCl_3$) afforded a major UV-active band, $R_f$ 0.3, which upon elution with ethyl acetate gave pure **25**[24] (19 mg, 77% from **23**) as an oil that solidified on standing: mp 94–96 °C; IR ($CH_2Cl_2$) 3580, 1730, 1627 $cm^{-1}$; UV ($CH_3OH$) $\lambda_{max}$ 280 nm ($\epsilon$ 1950); $^1H$ NMR ($CDCl_3$) $\delta$ 6.91 (1 H, br s, $H_2$), 6.35 (1 H, br d, $J$ = 10.3 Hz, $H_5$ or $H_6$), 6.05 (1 H, dd, $J$ = 10.3, 2.0 Hz, $H_5$ or $H_6$), 5.56 (1 H, d, $J$ = 2.9 Hz, *trans*-OC=CH), 4.90 (1 H, d, $J$ = 13.2 Hz, $H_3$ or $H_4$). 4.86 (1 H, d, $J$ = 13.2 Hz, $H_3$ or $H_4$), 4.80 (1 H, d, $J$ = 2.9 Hz, *cis*-OC=CH), 3.83 (3 H, s, $OCH_3$), 3.79 (3 H, s, $OCH_3$), 3.15 (1 H, br s, OH); $^{13}C$ NMR ($CDCl_3$) $\delta$ 164.7 (s), 163.6 (s), 149.4 (s), 133.7 (d), 132.0 (d), 129.4 (s), 121.7 (d), 98.7 (t), 81.6 (d), 70.9 (d), 52.6 (q), 52.1 (q); high-resolution mass spectrum, calcd for $C_{12}C_{14}O_6$, 254.0782; found, 254.0790.

**Chorismic Acid (1).** A solution of **25** (21 mg, 0.08 mmol) in THF (0.3 mL) was cooled to 0 °C. Water (50 $\mu$L) and 1 N NaOH (180 $\mu$L, 2.2 equiv) were added, and the mixture was stirred at 0 °C for 3.5 h. Amberlite IR-120 resin (200 mg) was added, and the mixture was stirred at 0 °C for 2 min. The resin was removed by filtration, and the solvent was rapidly removed under high vacuum. $^1H$ NMR (270 MHz) analysis indicated complete conversion of **25** to a 3:2 mixture of **1** and **22**.[25] The material was triturated with ethyl acetate, insoluble inorganic material was removed by centrifugation, and hexane was added to the supernatant to a cloud point. Cooling to −10 °C deposited an off-white solid that was recrystallized from ethyl acetate/hexane to obtain **1** that was 86% pure (14% **22**). Three additional recrystallizations provided 1.5 mg of pure **1**. In additional runs the maximum yield of analytically pure **1** was 3 mg (11%) from 30 mg of **25** after three recrystallizations: mp 139.5–141 °C; FT IR (THF) 3410 (br), 1739 (sh), 1721, 1622 $cm^{-1}$. UV, $^1H$ NMR, and mass spectral data are documented elsewhere.[3,24]

**Methyl [1*R*-(1$\alpha$,5$\alpha$,6$\alpha$)]-5-Hydroxy-8-oxo-7,9-dioxabicyclo[4.3.0]-non-2-ene-3-carboxylate (27).** A solution of (−)-**26**[29] (1.12 g, 5.95 mmol) in dry THF (150 mL) was brought to reflux under $N_2$. Carbonyl diimidazole (3.86 g, 4 equiv) was added in portions over a period of 5 h. Reflux was continued for 1 h, and the mixture was allowed to cool. A solution of 6 N HCl (15 mL) was added, and the mixture was stirred at room temperature for 2 h. Most of the THF was removed under reduced pressure, and the residue was partitioned between ethyl acetate and $H_2O$. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried and concentrated to give an oil which was stirred under rflux for 2 h with 150 mL of ether. Insoluble material was separated, and the ether solution was evaporated under reduced pressure to give 1.21 g (95%) of **27** as an oil of high purity by $^1H$ NMR. On distillation (Kugelrohr, bp 200 °C, 0.005 mm) the oil crystallized to a white solid: mp 80–82.5 °C; $[\alpha]^{25}_D$ −61.4° (*c* 4.13, $CHCl_3$); IR ($CH_2Cl_2$) 3600, 3500, 1805, 1720, 1650 $cm^{-1}$; $^1H$ NMR (acetone-$d_6$) $\delta$ 6.85 (1 H, m, $H_2$), 5.48 (1 H, dd, $J$ = 7.5, 3.5 Hz, $H_5$), 4.84 (1 H, t, $J$ = 7.5 Hz, $H_6$), 4.09 (1 H, dt, $J$ = 7.5, 4.8 Hz, $H_1$), 3.78 (3 H, s, $OCH_3$), 2.77 (1 H, m, $H_4$), 2.38 (1 H, m, $H_4$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 165.8, 154.2, 133.3, 129.1, 78.2, 73.2, 66.6, 52.4, 28.3. Anal. Calcd for $C_7H_{10}O_6$: C, 50.47; H, 4.71. Found: C, 50.43; H, 4.91.

**Methyl [1(*R*)-(1$\alpha$,5$\alpha$,6$\alpha$)]-5-[Bis(methoxycarbonyl)methoxy]-8-oxo-7,9-dioxabicyclo[4.3.0]non-2-ene-3-carboxylate (30).** A mixture of **27** (7.15 g, 0.038 mol) and dimethyl oxomalonate[19] (4.88 g, 1 equiv) in dry benzene under $N_2$ was stirred overnight at room temperature and then for 2 h under reflux. Solvent was removed under reduced pressure to afford hemiketal **38** which was dissolved in a mixture of dry THF (200 mL) and dry pyridine (3.77 mL, 1.4 equiv). The solution was cooled to −20 °C, and freshly distilled thionyl chloride (3.33 mL, 1.4 equiv) was added dropwise with stirring under $N_2$. The mixture was stirred at −20 °C for 30 min and at 0 °C for 45 min. Solid material was removed by filtration, and solvent was removed under reduced pressure to give **29** as a yellow oil. Crude **29** was dissolved in 150 mL of 90% HOAc at 0 °C. Powdered Zn (22 g, 10 equiv) was added, and the mixture was stirred at 0 °C for 45 min and then at room temperature for 1.5 h. The mixture was filtered through Celite, and the solvent was removed under reduced pressure. The residue was dissolved in $CH_2Cl_2$, dried ($Na_2SO_4$), and evaporated. The residual oil was chromatographed on silica gel with $CH_2Cl_2$ and then ether to give **30** (8.41 g, 73% overall) as an oil that solidified to a waxy solid on standing: $[\alpha]^{25}_D$ −30.4° (*c* 3.63, $CHCl_3$); IR ($CH_2Cl_2$) 1810, 1740, 1720, 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.83 (1 H, m), 5.25 (1 H, m), 4.88 (1 H, t, $J$ = 7.2 Hz), 4.70 (1 H, s), 3.96 (1 H, m), 3.75 (3 H, s), 2.87 (1 H, m), 2.48 (1 H, m). Anal. Calcd for $C_{14}H_{16}O_4$: C, 48.84; H, 4.69. Found: C, 48.58; H, 4.79.

**Methyl [1(*R*)-(1$\alpha$,5$\alpha$,6$\alpha$)]-5-[[1-(Methoxycarbonyl)ethenyl]oxy]-8-oxo-7,9-dioxabicyclo[4.3.0]non-2-ene-3-carboxylate (32).** To a solution of **30** (8.42 g, 24.5 mmol) in dry $CH_2Cl_2$ (150 mL) was added Eschenmoser's salt[32] (54.3 g, 29 mmol) and triethylamine (2.5 g, 24.5 mmol). The mixture was stirred at room temperature for 3 h. Water was added, and the mixture was vigorously shaken. The aqueous layer was extracted (4×) with $CH_2Cl_2$, and the combined organic extracts were dried ($Na_2SO_4$). Solvent was removed under reduced pressure to give **31** (9.13 g, 93%) as an oil: $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 6.85 (1 H, m), 5.45–4.88 (2 H, m), 4.55 (1 H, m), 3.82 (9 H, br s), 3.25–2.48 (2 H, m), 2.92 (2 H, s), 2.28 (6 H, s).

Mannich base **31** (9.13 g) was dissolved in dry $CH_2Cl_2$ with a 10-fold molar excess of $CH_3I$ (141.1 mL), and the mixture was heated under reflux with stirring for 5 h. Solvent was removed under reduced pressure, and the residue was triturated with dry ether. Filtration and vacuum drying gave 11.7 g of the quaternary salt as a pale yellow powder. The salt was dissolved in the minimum amount of dry $Me_2SO$, and the solution was heated at 75–80 °C with stirring under $N_2$ for 4 h. Insoluble material was removed by filtration, and most of the solvent was removed by high-vacuum distillation. The residue was triturated with cold water. The gummy precipitate was dissolved in $CH_2Cl_2$, and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic phases were dried ($Na_2SO_4$) and concentrated. The residue was purified by flash chromatography[31] on silica gel (1:1 ethyl acetate/hexane) to afford 5.85 g (80% overall) of **32** as an oil: $[\alpha]^{25}_D$ −59.6° (*c* 5.10, $CHCl_3$); IR ($CH_2Cl_2$) 1805, 1720, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.93 (1 H, m), 5.62 (1 H, d, $J$ = 3.1 Hz), 5.38 (1 H, m), 4.98 (1 H, m), 4.90 (1 H, d, $J$ = 3.1 Hz), 4.57 (1 H, m), 3.82 (3 H, s), 3.80 (3 H, s), 2.88 (1 H, md, $J$ = 18.2 Hz), 2.64 (1 H, dd, $J$ = 18.2, 5.6 Hz). Anal. Calcd for $C_{13}H_{14}O_8$: C, 52.35; H, 4.73. Found: C, 52.11; H, 4.84.

**(−)-5-Enolpyruvylshikimic Acid ("Compound $Z_1$", 5).** To a solution of **32** (221 mg, 0.74 mmol) in dioxane (3 mL) at 0 °C was added 1 N NaOH (2.96 mL, 4 equiv). The mixture was stirred at room temperature for 2 h, and solvent was removed under reduced pressure. Water (2 mL) was added, and sufficint Amberlite IR-120 resin was added with stirring to bring the solution to pH 3.5. The mixture was filtered, and the filtrate was rapidly concentrated under high vacuum. The resulting glass was triturated with dry methanol. The mixture was filtered, and the filtrate was concentrated under reduced pressure. Dry ether was added, and the white flocculent precipitate was isolated by centrifugation. The material

was redissolved in methanol, precipitated by addition of ether, and isolated by centrifugation. Air drying gave 77 mg (43%) of (−)-**5** as a white powder that retained traces of solvent but was >95% pure by $^1$H NMR: mp 191–193 °C dec; $[\alpha]^{25}_D$ −220° (*c* 3.00, $CH_3OH$); IR (KBr) 3600–3000, 1685 cm$^{-1}$; $^1$H NMR (methanol-$d_4$) $\delta$ 6.57 (1 H, dd, $J$ = 4.8, 1.8 Hz, $H_2$), 5.21 (1 H, d, $J$ = 1.3 Hz, =$CH_2$), 4.53 (1 H, d, $J$ = 1.3 Hz, =$CH_2$), 4.37 (1 H, t, $J$ = 4.6 Hz, $H_3$), 4.27 (1 H, dt, $J$ = 9.4, 5.6 Hz, $H_5$), 3.80 (1 H, dd, $J$ = 9.5, 4.3 Hz, $H_4$), 3.21 (1 H, dd, $J$ = 18.1, 5.6 Hz, $H_{6eq}$), 2.12 (1 H, ddd, $J$ = 18.1, 9.5, 1.8 Hz, $H_{6ax}$).

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# Synthesis of Alkenes with *P*-($\alpha$-Lithioalkyl)phosphinothioic Amides

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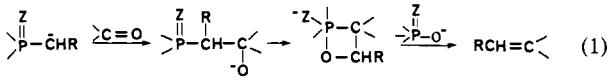
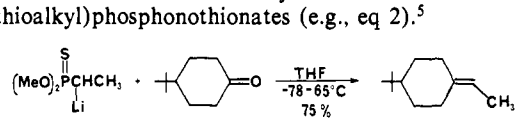
**Abstract:** *N,N,P*-Trimethyl-*P*-phenylphosphinothioic amide (**1**) was prepared from phenylphosphonothioic dichloride by sequential treatment with methylmagnesium halide, sulfuryl chloride, and dimethylamine. Treatment of **1** in tetrahydrofuran with butyllithium afforded *P*-(lithiomethyl)-*N,N*-dimethyl-*P*-phenylphosphinothioic amide (**2**). Aldehydes and ketones upon treatment with **2** provided stable $\beta$-hydroxy adducts, which upon treatment with methyl iodide and pyridine in acetone underwent smooth decomposition to yield alkenes. Alkylation of **2** provided higher homologues of **1** that were demonstrated to be useful in the production of tri- and tetrasubstituted alkenes. Pure (*E*)- and (*Z*)-alkenes were prepared by chromatographic separation of appropriate $\beta$-hydroxy adducts prior to treatment with methyl iodide and pyridine.

Relatively few reactions discovered in the last 30 years have had the impact on synthetic organic chemistry as has the Wittig reaction.[1,2] In many systems the reaction is problem free. In other cases difficulties can arise from threee sources—problems occur in separation of the triphenylphosphine oxide from the alkene, difficultly separable mixtures of (*E*)- and (*Z*)-alkenes are often formed, and low or neglible yields can result due to the moderate reactivity of phosphonium ylides. A number of phosphorus-stabilized carbanionic reagents also have been used in carbonyl alkylidenation reactions; the names of Horner, Wittig, Wadsworth, and Emmons are associated with these reactions.[2-4] The cycloelimination of alkenes from the oxyanion formed by addition of the carbanion to the carbonyl groups occurs readily in those cases where the alkene is conjugated to another $\pi$ system (C=C, Ar, C=O, C=N, etc.). The elimination is presumed to occur via the intermediacy of a cyclic phosphorane (eq 1). In



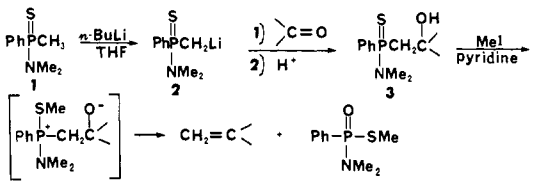
(1)

the P=O class of stabilized carbanions, the majority of the work has been done with phosphonates, most of which are readily available through Arbuzov reactions, but phosphine oxide carbanions have received some attention.[2] There are surprisingly few reports on the chemistry of P=S stabilized carbanions.[2] The most cogent study is that of Corey and Kwiatkowski who examined the production of alkenes from aldehydes and ketones and dimethyl (1-lithioalkyl)phosphonothionates (e.g., eq 2).[5]

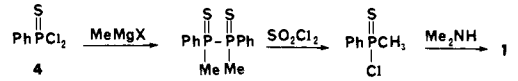


(2)

Scheme I



Scheme II



In this paper we describe a new phosphorus-based method for the alkylidenation of ketones and selected aldehydes that we believe will find considerable utility, especially in those cases that are inert or sluggish in their reactions with phosphonium ylides. Our method is outlined in Scheme I. The synthesis of the parent reagent, *N,N,P*-trimethyl-*P*-phenylphosphinothioic amide (**1**) (bp 110 °C (0.1 mm)),[5] is shown in Scheme II. The starting phenylphosphonothioic dichloride (**4**) is commercially available[6] and quite inexpensive.[7]

The choice of (dimethylamino)phenylphosphinothioyl carbanions as reagents was based on the premises that the carbanions would be considerably more nucleophilic than phosphonium ylides and that activation of the phosphorus centers toward nucleophilic additions of the oxyanions to form the necessary phosphoranes for cycloelimination of the alkenes could be achieved by facile alkylations of the initial adducts **3** at sulfur.[8,9]

(1) Maercker, A. *Org. React.* (*N.Y*) **1965**, *14*, 270.
(2) Cadogan, J. I. G., Ed. "Organophosphorus Reagents in Organic Synthesis"; Academic Press: New York, 1979.
(3) Wadsworth, W. S., Jr. *Org. React.* (*N.Y*) **1977**, *25*, 73.
(4) Sulfur- and silicon-based reagents have also proven to be of considerable utility in carbonyl alkylidenation reactions. For leading references for sulfur-based reagents, see: Johnson, C. R.; Kirchhoff, R. A. *J. Am. Chem. Soc.* **1979**, *101*, 3602. For a recent review of silicon-based olefinations, see: Colvin, E. "Silicon in Organic Synthesis"; Butterworths: London, 1981.
(5) Corey, E. J.; Kwiatowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654.
(6) Aldrich Chemical Company, Inc. Milwaukee, Wi.
(7) The preparation of *P*-methyl-*P*-phenylphosphinothioic chloride by the method shown in Scheme II has been described. For example, see: Maier, L. *Chem. Ber.* **1961**, *94*, 3034, 3051. Schlor, H.; Schrader, G. German Patent 1067021, 1961; *Chem. Abstr.* **1962**, *56*, 10191f.
(8) The P=S functionality is well-known to undergo alkylation at sulfur; for a recent example, see: Omelanczulk, J.; Perkokowska, W.; Mikolajczyk, M. *J. Chem. Soc., Chem. Commun.* **1980**, 24.
(9) Electrophilic activation of a P=S group toward addition of a $\beta$-oxygen function has been achieved by Corey and Kwiatkowski (ref 5) using silver ion.

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