for 1.8 h, 1.3 h, and 3.0 h, respectively, at −5 °C under an argon atmosphere. The reaction progress was monitored by TLC and/or ^{1}H NMR. Only keto oxetane **3**-PQ was photolabile under these conditions, affording significant amounts of dihydrodioxin **6**-PQ.

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for generous financial support. For spectral services we thank Dr. G. Lange (MS) and Dr. D. Scheutzow (NMR).

Registry No. **1**, 76897-39-7; **2**-BQ, 116053-49-7; (±)-**2**-PQ, 116053-56-6; **3**-BQ, 116053-53-3; **3**-PQ, 116053-55-5; (±)-*cis*-**4**-BQ, 116053-51-1; (±)-*trans*-**4**-BQ, 116053-52-2; (±)-*cis*-**5**-BQ, 116053-50-0; **6**-BQ, 116053-48-6; **6**-PQ, 116053-54-4; BQ, 106-51-4; PQ, 84-65-1; qinghaosu, 63968-64-9.

Supplementary Material Available: Tables of atomic coordinates and isotropic thermal parameters of **2**-PQ (Table I) and *trans*-**4**-BQ (Table II), bond angles (Table III), bond lengths (Table IV), and a crystallographic section (5 pages). Ordering information is given on any current masthead page.

Uncatalyzed and Chorismate Mutase Catalyzed Claisen Rearrangement of (*Z*)-9-Methylchorismic Acid

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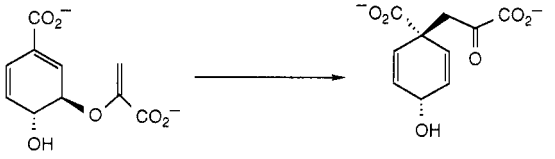
A synthesis of (−)- and (±)-(*Z*)-9-methylchorismic acid (**3**) is reported. The half-life for the uncatalyzed Claisen rearrangement of (±)-**3** in H_2O (pH 7.5, 30 °C) is 5.7 h. Chorismate analogue (−)-**3** was a modest substrate for chorismate mutase (chorismate mutase–prephenate dehydrogenase from *E. coli*): K_m = 4.0 mM, $k_{cat.}/k_{uncat.}$ = 4.2 × 10^4. It was established that the enzyme-catalyzed Claisen rearrangement of (−)-**3** proceeds through a chairlike transition state in similar fashion to the chorismate mutase catalyzed rearrangement of (−)-chorismic acid (**1**).

Chorismate (**1**) is the last common intermediate in the biosynthesis of aromatic amino acids and growth factors via the shikimate pathway in bacteria, fungi, and higher plants.[1] The first step in the biosynthesis of phenylalanine and tyrosine from **1** is the Claisen rearrangement to prephenate (**2**). The reaction is catalyzed by chorismate

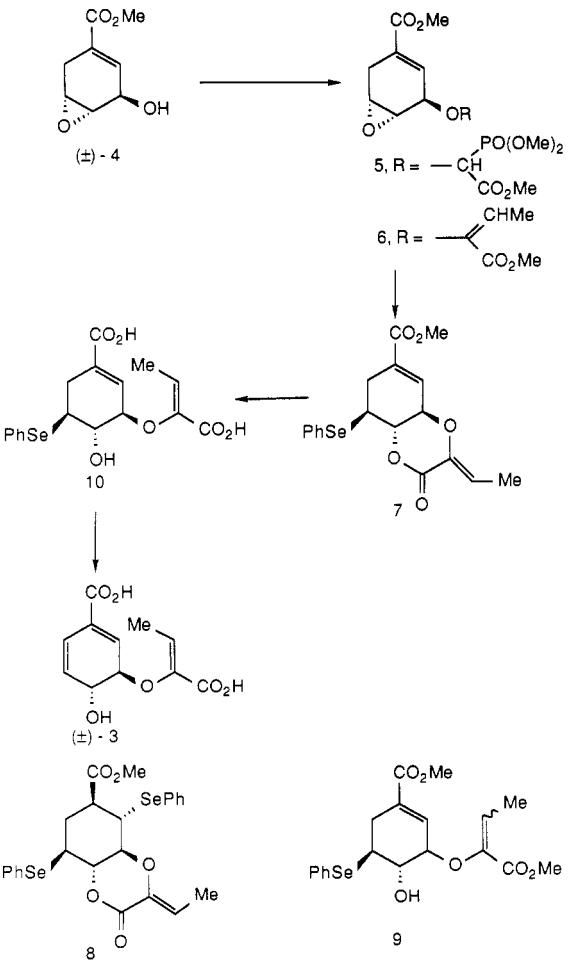


1 **2**

mutase. Recent investigations of labeled **1** with chorismate mutase–prephenate dehydrogenase from *Escherichia coli*[2] and with whole cells of *E. coli*[3] have established that the enzyme-catalyzed isomerization of **1** to **2** proceeds through a chairlike transition state. The uncatalyzed rearrangement of **1** to **2** also proceeds through a chairlike transition state.[4]

As part of our interest in structural features required in the substrate for catalysis of the Claisen rearrangement by chorismate mutase, we were interested in the (*Z*)-9- and (*E*)-9-methyl derivatives of **1**. Synthetic routes investigated provided (±)- and (−)-(*Z*)-9-methylchorismic acid (**3**), but the (*E*)-methyl isomer could not be obtained in sufficient purity for enzymatic studies. Described below are these synthetic investigations and studies of the thermal and chorismate mutase catalyzed Claisen rearrangement of (±)- and (−)-**3**.

Scheme I



The synthesis of (±)-**3** is outlined in Scheme I. The $Rh_2(OAc)_4$-catalyzed reaction of $MeO_2CC(N_2)PO(OMe)_2$ with (±)-**4**[5] gave a ~1:1 mixture of diastereomers **5**, which,

(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.

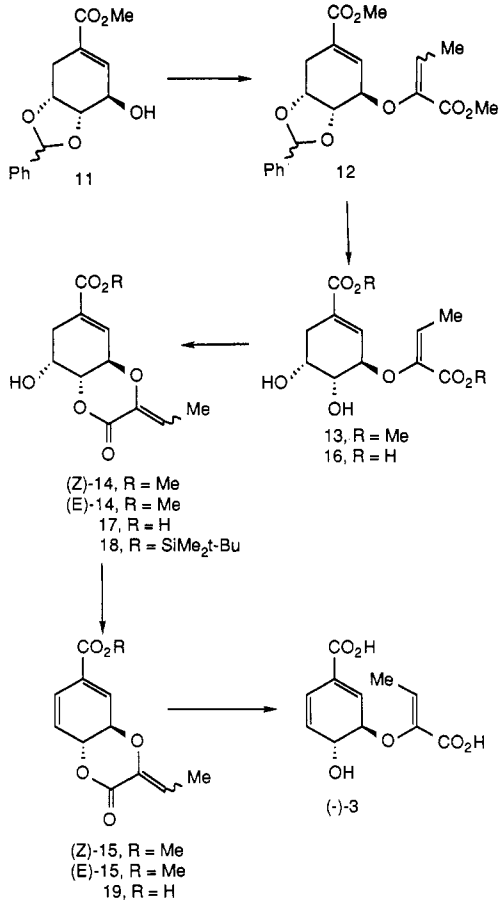
(2) Sogo, S. G.; Widlanski, T. S.; Hoare, J. H.; Grimshaw, C. E.; Berchtold, G. A.; Knowles, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 2701-2703.

(3) Asano, Y.; Lee, J. J.; Shieh, T. L.; Spreafico, F.; Kowal, C.; Floss, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 4314-4320.

(4) Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 5306-5308.

0022-3263/88/1953-4992$01.50/0

Scheme II



without purification, were converted to the lithium salt with $LiN(SiMe_3)_2$ in tetrahydrofuran (THF) at −78 °C and quenched with acetaldehyde to give **6** in 34% yield from (±)-**4** after purification by flash chromatography. Diester **6** was a 1:9 mixture of the *Z*/*E* isomers.[6] Reaction of **6** with PhSeLi in THF at room temperature effected opening of the epoxide group and subsequent lactone formation to provided **7** as the major product. Chromatography of the crude reaction mixture gave pure *Z*-isomer **7** (44% yield) and two minor products, **8** (14%) and **9** (<2%), the structures of which were assigned on the basis of spectroscopic data. (See Experimental Section.) Hydrolysis of **7** with NaOH in H_2O/THF and acidification gave *Z*-isomer **10**. Oxidation of **10** to the selenoxide and subsequent elmination gave (±)-**3**.

The synthesis of (−)-**3** (Scheme II) was accomplished from the diastereomeric benzylidene acetals of the methyl ester of (−)-4-*epi*-shikimic acid (**11**), which was prepared as described previously.[7] The procedure described above for conversion of (±)-**4** to **6** effected conversion of **11** to **12** (77%) as a mixture of four isomers in a ratio of 1(9-*Z*):2(9-*Z*):6(9-*E*):12(9-*E*). The benzylidene acetal protecting group of **12** was removed with 4:1 HOAc/H_2O, and recrystallization of the crude product (*Z*/*E*, 1:6) gave pure *E*-isomer **13** in 74% yield. Lactonization of crude **13** (*Z*/*E*, 1:6) with a catalytic amount of *p*-toluenesulfonic acid (TosOH) in refluxing benzene for 25 h gave (*Z*)-**14** and (*E*)-**14** in a ratio of 7:1.[8] The isomers were separated by chromatography, and each was dehydrated with Martin's reagent[9] without isomerization to provide pure (*Z*)-**15** and (*E*)-**15**. Unfortunately, base-catalyzed hydrolysis of either isomer gave aromatic products with only trace quantities of (*Z*)- or (*E*)-**3**. Consequently an alternate route from **13** was developed.

Base-catalyzed hydrolysis (NaOH in THF/H_2O) of crude **13** (*Z*/*E*, 1:6) followed by acidification gave diacid **16** (72%, *Z*/*E*, 1:4). Diacid **16** was lactonized to **17** (62%, *Z*/*E*, 1:3) with IR-120 resin in refluxing benzene/dioxane. Protection of the carboxyl group of **17** with *t*-$BuMe_2SiOTf$ (40% conversion, 56% **17** recovered) gave silyl ester **18**. Dehydration of **18** with Martin's reagent[9] followed by cleavage of the silyl ester with THF/HOAc/H_2O gave **19** (*Z*/*E*, 2.6:1). Hydrolysis of **19** (NaOH in THF/H_2O) followed by acidification and recrystallization of the crude product gave 9-methylchorismic acid (*Z*/*E*, 8:1). Further recrystallization gave the *Z* isomer, (−)-**3**, in 95% purity (5% *E* isomer) in 13% yield. Chromatography of the filtrate from recrystallization gave an additional 44% of the *Z* and *E* isomers, but attempts by chromatography to obtain the *E* isomer without contamination by the *Z* isomer were not successful.

The assignment of *Z* and *E* stereochemistry of all intermediates and products in the synthesis of (±)-**3** and (−)-**3** is based on the ^1H NMR chemical shift of the side-chain vinyl hydrogen and the side-chain *C*-methyl group. In each case where both isomers are obtained, the isomer with the methyl group absorption at higher field and the vinyl hydrogen at lower field is assigned the *Z* isomer due to the deshielding effect of the side-chain carboxylic acid or carboxylate ester group when it is *Z* to the vinyl hydrogen (or *Z* to the methyl group in the case of the *E* isomers). These assignments are consistent with those established for the C_9 vinyl hydrogen atoms of chorismic acid and intermediates in the synthesis of (*Z*)-[9-^2H]- and (*E*)-[9-^2H]chorismic acid.[10] For all of the substances of the present study, the *Z*-isomer methyl absorption appears between 1.76 and 1.89 ppm, and the vinyl hydrogen absorption appears between 6.13 and 6.64 ppm. In the *E* isomers, the methyl absorption appears between 1.98 and 2.08 ppm, and the vinyl hydrogen absorption appears between 5.72 and 6.04 ppm. The ^1H NMR data are tabulated in the supplementary material.

Additional support of the stereochemical assignments is provided by the $E \rightarrow Z$ isomerizations observed in cases where the reaction medium is basic or relatively acidic. The initial phosphonate modification of the Wittig reaction to produce **6** and **12** affords predominately the less stable *E* isomer in each case (*Z*/*E*, 1:8–9). Reactions in which isomerization is observed must result in enrichment of the more stable *Z* isomer in the product mixture, and the stereochemical assignments from the ^1H NMR data are consistently in this direction with the exception of formation of **13** in which the minor amount of *Z* isomer doubtlessly was lost during purification.

Andrews and co-workers have investigated the thermal decomposition of chorismate (**1**) in H_2O (pH 7.5) over the temperature range 20–65 °C.[11] Approximately 80% of **1** was isomerized to prephenate (**2**), which partially aromatized to phenylpyruvate in a consecutive reaction, and approximately 20% of **1** underwent direct aromatization with *p*-hydroxybenzoate (**20**) as the main product. Both

(5) Hoare, J. H.; Policastro, P. P.; Berchtold, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6264–6267.
(6) Formation of (*E*)-**6** as the major isomer was expected: Wadsworth, W. S., Jr. *Organic Reactions*; Wiley: New York, 1977; Vol. 25, Chapter 2.
(7) Lesuisse, D.; Berchtold, G. A. *J. Org. Chem.* **1985**, *50*, 888–890.
(8) The *Z*/*E* ratio was 1:3 with 20 wt % of TosOH in refluxing benzene for 1.5 h.
(9) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003–5010.
(10) Hoare, J. H.; Berchtold, G. A. *J. Am. Chem. Soc.* **1984**, *106*, 2700.
(11) Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* **1973**, *12*, 3492–3498.

Scheme III

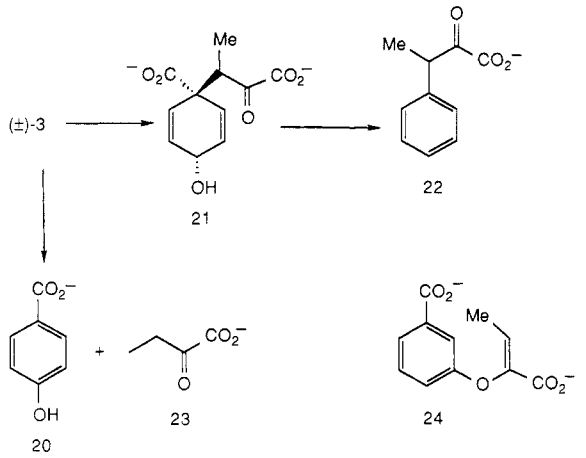


Table I. Data for the Uncatalyzed and Enzyme-Catalyzed Claisen Rearrangement of (-)-1 and (-)-3 at 30 °C

	(-)-1	(-)-3
$k_{uncat.}$, s^{-1}		
in H_2O (pH 7.5)	1.24×10^{-5} [a]	3.37×10^{-5} [b]
in D_2O (pD 7.4)	1.28×10^{-5}	3.06×10^{-5} [b]
K_m, mM	0.135	4.0
$k_{cat.}$, s^{-1}	19	1.4
$k_{cat.}/k_{uncat.}$	1.5×10^6	4.2×10^4

[a] Data from ref 11. [b] Determined with (±)-3.

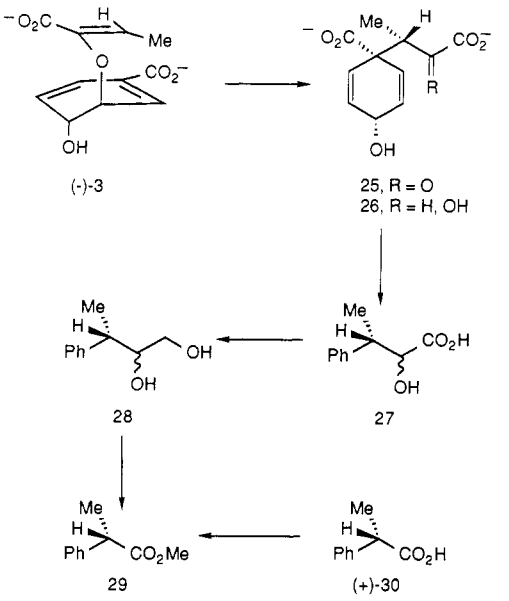
reactions of 1 were assumed to be first order. At 29.9 °C, the rate constant for 1 → 2 was 1.24×10^{-5} s^{-1} ($t_{1/2}$ = 15.6 h) and for 1 → 20 (and any other products from direct aromatization) was 3.62×10^{-6} s^{-1} ($t_{1/2}$ = 53.4 h).

The thermal reaction of (±)-3 in D_2O (pD 7.4) at 30 °C is presented in Scheme III. The reactions observed were similar to those observed for 1. The reaction was followed by integration of absorptions of (±)-3 and all products in the 250-MHz ^1H NMR spectrum (see Experimental Section). After complete reaction of (±)-3, the product mixture consisted of 21 (35%), 22 (42%), 20 (23%), and 23 (23%). Thus the major reaction pathway of (±)-3 (77% reaction) is the Claisen rearrangement to 21 (first-order rate constant = 3.06×10^{-5} s^{-1}), which undergoes decarboxylative dehydration in a consecutive reaction to afford 22. The minor pathway of decomposition of (±)-3 (23% reaction) is aromatization to 20 and 23 (first-order rate constant = 1.19×10^{-5} s^{-1}, $t_{1/2}$ = 16.2 h). No other product from direct aromatization of (±)-3 was observed. If (±)-3 does aromatize by dehydration to 24, it must constitute less than 3% of the reaction pathway.

Enzymatic investigations established that (-)-3 was a modest substrate for the mutase activity of chorismate mutase–prephenate dehydrogenase from *E. coli*[12] with a $k_{cat.}/k_{uncat.}$ = 4.2×10^4 compared to $k_{cat.}/k_{uncat.}$ = 1.5×10^6 for (-)-1. The enzyme processed (±)-3 at one-half the rate of (-)-3.[13] Uncatalyzed and enzyme-catalyzed rate data are summarized in Table I.

The geometry of the transition state for the enzyme-catalyzed rearrangement of (-)-3 was established as indicated in Scheme IV. The enzymatic reaction was carried out with sufficient enzyme to effect rapid conversion of

Scheme IV



Scheme V

(-)-3 to 25, and the mixture was quenched with $NaBH_4$ to reduce 25 to 26.[14] Acidification to pH 1 effected aromatization to 27, which was isolated in 61% yield by chromatography. Acid 27 was converted to the methyl ester with CH_2N_2, and the ester was reduced with diisobutylaluminum hydride (DIBAH) to provide 28. The ^1H NMR spectrum of diol 28 was identical with the corresponding spectrum of 28 prepared by the addition of Me_2CuLi to (+)-31 (Scheme V).[15] If the two diastereomers of 28 have different ^1H NMR chemical shifts, the ^1H NMR comparison establishes that 28 derived from (-)-3 is (2*S*,3*S*)-3-phenyl-1,2-butanediol. Oxidative cleavage of diol 28 from (-)-3 with $NaIO_4/RuCl_3$[16] and esterification with CH_2N_2 gave methyl hydratropate (29). ^1H NMR chiral shift studies with 29 derived from (-)-3 and with the methyl esters from reaction of (+)-30 and (±)-30 with CH_2N_2 established the *S* configuration for 29 derived from (-)-3, i.e., the same absolute configuration as (+)-30 (see Experimental Section). These results establish that the chorismate mutase catalyzed rearrangement of (-)-3 proceeds through a chairlike transition state in similar fashion to the enzyme-catalyzed rearrangement of (-)-1.[2]

Experimental Section[17]

Trimethyl diazophosphonoacetate was prepared in 31%

(12) Sampathkumar, P.; Morrison, J. F. *Biochim. Biophys. Acta* **1982**, *702*, 204–211. We thank Dr. Morrison for a generous supply of chorismate mutase–prephenate dehydrogenase.

(13) It was demonstrated previously that (+)-1 is not a substrate for the mutase activity of chorismate mutase–prephenate dehydrogenase from *E. coli*: Hoare, J. H.; Berchtold, G. A. *Biochem. Biophys. Res. Commun.* **1982**, *106*, 660–662.

(14) The procedure used was based on a similar synthesis of 3-phenyllactic acid from 1 developed by J. Knowles and co-workers. We thank Professor Knowles for providing experimental details.

(15) We thank Professor K. B. Sharpless for a sample of (+)-31.

(16) Carlsen, P. H., Jr.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

(17) Melting points were determined with a Thomas-Hoover Unimelt and are corrected. Unless otherwise indicated, ^1H NMR spectra were obtained at 250 MHz in $CDCl_3$ and ^{13}C NMR spectra were obtained at 67.9 MHz in $CDCl_3$ with chemical shift values (δ) in parts per million downfield from tetramethylsilane. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Flash chromatography refers to the procedure developed by Still and co-workers: Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

yield from trimethyl phosphonoacetate[18] by the literature procedure for the corresponding triethyl ester: IR (CH_2Cl_2) 2140, 1680, 1650 cm^{-1}; ^1H NMR δ 3.82 (s, 6 H), 3.87 (s, 3 H).

(±)-Methyl (1β,5β,6β)-5-[[1-(Methoxycarbonyl)-propenyl]oxy]-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylate (6). A mixture of (±)-4[5] (441 mg, 2.6 mmol), trimethyl diazophosphonacetate (593 mg, 2.9 mmol), and $Rh_2(OAc)_4$ (22 mg, 4 mol %) in benzene (100 mL) was heated at reflux under N_2 for 3 h. The solution was filtered through a plug of Celite and concentrated under reduced pressure to give **5** as a mixture of diastereomers. Crude **5** was dissolved in dry THF (100 mL). The solution was cooled to −78 °C, and a 1 M solution of $LiN(SiMe_3)_2$ in THF[19] (2.59 mL, 2.59 mmol) was added dropwise. The mixture was stirred for 15 min at −70 °C and quenched with excess acetaldehyde (1.6 mL). The cold bath was removed, and the mixture was stirred for 2 h. Saturated aqueous NH_4Cl (50 mL) was added, and the mixture was extracted with $CHCl_3$ (50 mL, 2 × 40 mL). The organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography on silica gel (1.5:3.5 EtOAc/petroleum ether) gave 238 mg (34%) of **6** (1:9 *Z*/*E*) as a colorless oil: ^1H NMR δ 6.80 (br s, 1 H), 6.46 (q, 0.1 H, *J* = 7.4 Hz, *Z* isomer), 5.86 (q, 0.9 H, *J* = 7.4 Hz, *E* isomer), 4.82 (br s, 0.1 H, *Z* isomer), 4.72 (br s, 0.9 H, *E* isomer), 3.82 and 3.76 (2 s, 6 H), 3.46 and 3.42 (2 m, 2 H), 2.94 and 2.72 (2 d, 2 H, *J* = 20 Hz), 2.02 (d, 2.7 H, *J* = 7.4 Hz, *E* isomer), 1.78 (d, 0.3 H, *J* = 7.4 Hz, *Z* isomer); ^{13}C NMR (*E* isomer) δ 166.5, 163.9, 144.1, 130.8, 128.1, 121.4, 70.8, 51.9, 51.7, 50.7, 50.5, 24.3, 12.7.

(±)-Methyl (Z)-(4aα,8β,8aβ)-2,3,4a,7,8,8a-Hexahydro-3-ethylidene-2-oxo-8-(phenylseleno)-1,4-benzodioxin-6-carboxylate (7). A solution of PhSeLi, prepared by addition of *n*-BuLi (0.215 mL, 2.66 M) to PhSeH (0.111 mL, 2 equiv) in dry THF (15 mL), was added to a solution of **6** (139 mg, 0.52 mmol), and the mixture was stirred at room temperature for 2 h. Saturated aqueous NH_4Cl (20 mL) was added, and the mixture was extracted with $CHCl_3$. The organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography on silica gel (EtOAc/petroleum ether, 1:9 → 1.5:3.5 → 1:1) gave three components in the following order: **7** (90 mg, 44%), **8** (39 mg, 14%), **9** (5 mg, 2%).

7: IR (CH_2Cl_2) 1720, 1440, 1375, 1250 cm^{-1}; ^1H NMR δ 7.71 (d, 2 H, *J* = 7.7 Hz), 7.40–7.26 (m, 3 H), 6.79 (br s, 1 H), 6.27 (q, 1 H, *J* = 7.4 Hz), 4.56 (m, 1 H), 4.12 (dd, 1 H, *J* = 12.0, 8.1 Hz), 3.75 (s, 3 H), 3.34 (dt, 1 H, *J* = 11.6, 6.1 Hz), 2.99 (dd, 1 H, *J* = 18.7, 6.0 Hz), 2.59–2.45 (m, 1 H), 1.76 (d, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 165.5, 160.4, 141.5, 137.4, 132.6, 129.4, 129.1, 125.4, 118.9, 78.2, 74.1, 52.4, 36.9, 32.9, 10.9; MS 397 (3), 396 (17), 395 (17), 394 (82), 393 (8), 392 (42), 391 (16), 390 (16), 153 (100).

8: partial ^1H NMR δ 7.23–7.75 (m, 10 H), 6.23 (q, 1 H, *J* = 7.5 Hz), 4.38 (dd, 1 H, *J* = 9.5, 9.4 Hz), 3.63 (s, 3 H), 1.60 (d, 3 H, *J* = 7.5 Hz).

9: ^1H NMR δ 7.75–7.52 and 7.29 (m, 5 H), 6.94 (br s, 1 H), 6.42 and 5.83 (q, 1 H, *J* = 7.5 Hz), 5.23 and 4.95 (br s, 1 H), 4.26 (m, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.50 (dd, 1 H, *J* = 8.0, 4.0 Hz), 3.08 and 2.55 (m, 2 H), 2.03 and 1.89 (d, 3 H, *J* = 7.5 Hz).

(±)-(Z)-(3β,4α,5β)-3-[(1-Carboxypropenyl)oxy]-4-hydroxy-5-(phenylseleno)-1-cyclohexene-1-carboxylic Acid (10). Aqueous NaOH (305 μL, 1 N, 3 equiv) was added to a solution of **7** (39.6 mg, 0.10 mmol) in THF (5 mL) at 0 °C. Water (~1 mL) was added until the solution was homogeneous. The mixture was stirred at room temperature for 12 h. Aqueous NaOH (50 μL, 1 N) was added, and stirring was continued for 1 h. The mixture was acidified with 1 N HCl and extracted with EtOAc. The organic extract was dried ($MgSO_4$) and concentrated to afford 27 mg (73%) of **10** as a white powder: IR (CH_2Cl_2) 3500, 1710 cm^{-1}; ^1H NMR δ 7.66 (d, 2 H, *J* = 7 Hz), 7.42–7.23 (m, 3 H), 6.85 (br s, 1 H), 6.64 (q, 1 H, *J* = 7.5 Hz), 4.51 (m, 1 H), 3.75 (m, 1 H), 3.26 (dt, 1 H, *J* = 11.3, 5.7 Hz), 2.92 (dm, 1 H, *J* = 19 Hz), 2.5–2.3 (m, 1 H), 1.85 (d, 3 H, *J* = 7.5 Hz); MS 380 (31), 314 (26) 312 (22), 158 (40), 157 (59), 156 (23), 155 (38), 154 (37), 139 (40), 122 (33), 105 (55); exact mass calcd for $C_{17}H_{16}O_5Se$ ($M^+ - H_2O$) 380.0163, found 380.0164.

(18) Regitz, M.; Anschütz, W.; Liedhegener, A. *Chem. Ber.* **19688** *101*, 3734–3743.

(19) Aldrich Chemical Co.

(±)-(Z)-9-Methylchorismic Acid (3). Hydrogen peroxide (30%, 13.5 μL, 0.13 mmol) was added to a solution of **10** (26.1 mg, 0.066 mmol) in acetone (4 mL) at 0 °C. After 1 h at 0 °C, the mixture was concentrated at reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 2:1, containing 1% HOAc) gave (±)-**3** (11 mg, 68%) as a white solid, which was recrystallized from EtOAc/pentane (1:2): ^1H NMR (CD_3COCD_3) δ 6.94 (br s, 1 H), 6.43 (q, 1 H, *J* = 7.2 Hz), 6.30 (dt, 1 H, *J* = 9.9, 1.8 Hz), 5.99 (dd, 1 H, *J* = 9.9, 2.9 Hz), 4.89 (dd, 1 H, *J* = 10.8, 3.1 Hz), 4.63 (dt, 1 H, *J* = 10.7, 2.5 Hz), 1.80 (d, 3 H, *J* = 7.2 Hz); UV (H_2O) λ_{max} 274 nm (ϵ 2900).

Methyl (3β,4α,5α)-3-[[1-(Methoxycarbonyl)propenyl]-oxy]-4,5-dihydroxy-1-cyclohexene-1-carboxylate (13). Benzylidene acetal diastereomers **11**[7] (7.75 g, 28.5 mmol) were converted to **12** (78%) by the same procedure for preparation of **6** from **4**. Product **12** was a mixture of four isomers in the ratio 12(*E*):6(*E*):2(*Z*):1(*Z*). The major isomers (*E*) could be separated by flash chromatography on silica gel (EtOAc/petroleum ether, 1:9 → 1.5:3.5).

Isomer A: ^1H NMR δ 7.47–7.26 (m, 5 H), 7.02 (m, 1 H), 6.09 (s, 1 H), 5.75 (q, 1 H, *J* = 7.6 Hz), 4.67 (m, 1 H), 4.52–4.42 (m, 2 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.05 (dd, 1 H, *J* = 16.2, 5.4 Hz), 2.54 (dm, 1 H, *J* = 16.2 Hz), 2.0 (d, 3 H, *J* = 7.7 Hz); exact mass calcd for $C_{20}H_{22}O_7$ 374.1366, found 374.1362.

Isomer B: ^1H NMR δ 7.47–7.25 (m, 5 H), 7.05 (br s, 1 H), 5.81 (s, 1 H), 5.72 (q, 1 H, *J* = 7.0 Hz), 4.61 (m, 1 H), 4.53 (m, 1 H), 4.45 (m, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.08 (dd, 1 H, *J* = 17, 5.7 Hz), 2.63 (dd, 1 H, *J* = 17, 3.7 Hz), 1.98 (d, 3 H, *J* = 7.0 Hz).

The C_9 vinyl hydrogen of the two minor isomers (*Z*) appeared as quartets at 6.41 and 6.62 ppm.

The mixture of isomers **12** (2.18 g, 5.8 mmol) in 80% AcOH (100 mL) was stirred for 12 h. Solvent was removed under high vacuum, and the residue was recrystallized (EtOAc/pentane, 1:1) to give 1.23 g (74%) of **13**: mp 81–82 °C; ^1H NMR δ 6.81 (br s, 1 H), 6.04 (q, 1 H, *J* = 7.5 Hz), 4.47 (br s, 1 H), 4.43 (br s, 1 H), 4.25 (b. s, 1 H), 3.85 (s, 3 H), 3.85 (br s, 1 H), 3.75 (s, 3 H), 3.0 (br s, 1 H), 2.60 (br m, 2 H), 2.01 (d, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 166.8, 165.2, 144.1, 133.8, 129.4, 122.7, 79.1, 72.2, 67.7, 52.2, 51.9, 30.9, 13.0. Anal. Calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.46; H, 6.34.

Methyl (4aα,8β,8aβ)-2,3,4a,7,8,8a-Hexahydro-3-ethylidene-2-oxo-8-hydroxy-1,4-benzodioxin-6-carboxylate (14). A sample of unrecrystallized **13** (1:6 *Z*/*E*) (44 mg, 0.16 mmol) and *p*-TosOH (5 mg) in C_6H_6 (20 mL) was heated under reflux for 25 h with removal of water with a Dean–Stark trap. The mixture was concentrated under reduced pressure. Chromatography on silica gel (EtOAc/petroleum ther, 1:1) gave 30 mg (71%) of a 7:1 *Z*/*E* mixture of **14**. When the reaction time was decreased to 1.5 h with 10 mg of *p*-TosOH, the *Z*/*E* ratio was 1:3. The pure isomers were obtained by MPLC on silica gel (EtOAc/hexane, 1.5:3.5).

(E)-14: ^1H NMR δ 6.88 (br s, 1 H), 5.96 (q, 1 H, *J* = 7.5 Hz), 4.82 (dm, 1 H, *J* = 9.4 Hz), 4.47 (br s, 1 H), 4.30 (dd, 1 H, *J* = 9.4, 1.9 Hz), 3.79 (s, 3 H), 2.86 (br s, 1 H), 2.74 (m, 2 H), 2.08 (d, 3 H, *J* = 7.5 Hz); ^{13}C NMR δ 166.2, 160.4, 140.1, 132.3, 129.7, 122.5, 79.2, 70.3, 64.9, 52.2, 32.1, 13.1; exact mass calcd for $C_{12}H_{14}O_6$ 254.0790, found 254.0790.

(Z)-14: mp 188 °C dec; IR (CH_2Cl_2) 3600, 1740, 1720, 1650 cm^{-1}; ^1H NMR δ 6.93 (br s, 1 H), 6.28 (q, 1 H, *J* = 7.4 Hz), 4.87 (br d, 1 H, *J* = 8.8 Hz), 4.47 (br s, 1 H), 4.32 (dd, 1 H, *J* = 8.8, 2.1 Hz), 3.80 (s, 3 H), 2.74 (m, 2 H), 2.65 (br s, 1 H), 1.79 (d, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 166.3, 161.1, 141.5, 132.3, 130.0, 119.5, 79.4, 70.6, 65.4, 52.4, 32.1, 11.0. Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.59; H, 5.60.

Methyl (E)- and (Z)-(4aα,8aβ)-2,3,4a,8a-Tetrahydro-3-ethylidene-2-oxo-1,4-benzodioxin-6-carboxylate [(E)-15 and (Z)-15]. A solution of Martin's reagent[9] (100 mg, 2.5 equiv) in CH_2Cl_2 was transferred to a solution of (*Z*)-**14** (14.9 mg, 58 μmol) in CH_2Cl_2 under an inert atmosphere. The mixture was stirred for 1 h at room temperature. Solvent was removed under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 1.5:3.5) gave 7.6 mg (60%) of (*Z*)-**15**: ^1H NMR δ 7.04 (br s, 1 H), 6.50 (br d, 1 H, *J* = 9.4 Hz), 6.28 (q, 1 H, *J* = 7.5 Hz), 6.13 (br d, 1 H, *J* = 9.4 Hz), 5.22 (br d, 1 H, *J* = 14.1 Hz), 4.91 (br d, 1 H, *J* = 14.1 Hz), 3.83 (s, 3 H), 1.81 (d, 3 H, *J* = 7.5 Hz).

The same procedure with (*E*)-**14** gave (*E*)-**15**: ^1H NMR δ 6.97

(br s, 1 H), 6.48 (br d, 1 H, J = 9.7 Hz), 6.12 (br d, 1 H, J = 9.7 Hz), 5.96 (q, 1 H, J = 7.5 Hz), 5.17 (br d, 1 H, J = 13.6 Hz), 4.84 (br d, 1 H, J = 13.6 Hz), 3.82 (s, 3 H), 2.07 (d, 3 H, J = 7.5 Hz).

(3β,4α,5α)-3-[(1-Carboxypropenyl)oxy]-4,5-dihydroxy-1-cyclohexene-1-carboxylic Acid (16). A 1 M NaOH solution (10.4 mL, 2.4 equiv) was added to a solution of **13** (1:6 Z/E) (1.23 g, 4.3 mmol) in 2:1 THF/H_2O (60 mL) at 0 °C, and the mixture was stirred overnight at room temperature. The mixture was acidified (1 N HCl) and extracted with EtOAc (1 × 100 mL, 2 × 80 mL). The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography on silica gel ($CHCl_3$/EtOH/AcOH, 90:10:3, followed by n-BuOH/H_2O/AcOH, 200:25:6) gave 798 mg (72%) of **16** (Z/E, 1:4) as a white powder: IR (KBr) 3400, 1690, 1640 cm^{-1}; ^1H NMR (CD_3OD) δ 6.82 (br s, 1 H), 6.43 (q, 0.2 H, J = 7.2 Hz, Z isomer), 5.80 (q, 0.8 H, J = 7.5 Hz, E isomer), 4.54 (br s, 1 H), 4.08 (br m, 1 H), 3.85 (m, 1 H), 2.54 (m, 2 H), 1.99 (d, 2.4 H, J = 7.6 Hz, E isomer), 1.78 (d, 0.6 H, J = 7.2 Hz, Z isomer); ^{13}C NMR (CD_3OD) (E isomer) δ 169.8, 167.5, 145.8, 134.8, 131.4, 120.0, 78.8, 72.6, 68.9, 31.9, 13.1, (Z isomer) δ 169.8, 167.4, 146.2, 135.5, 131.6, 126.0, 80.0, 73.1, 68.8, 31.3, 11.9.

(4aα,8β,8aβ)-2,3,4a,7,8,8a-Hexahydro-3-ethylidene-2-oxo-8-hydroxy-1,4-benzodioxin-6-carboxylic Acid (17). IR-120 Resin (3 cm^3) was added to a solution of **16** (1:4 Z/E) (321 mg, 1.32 mmol) in 1:1 C_6H_6/dioxane (50 mL), and the mixture was refluxed overnight. The solution was filtered, and solvent was removed under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 2:1, 1% AcOH) gave 184 mg (62%) of **17** (Z/E, 1:3) as a white foam: ^1H NMR (CD_3OD) δ 6.83 (br d, 0.25 H, J = 1.2 Hz, Z isomer), 6.76 (br d, 0.75 H, J = 1.5 Hz, E isomer), 6.17 (q, 0.25 H, J = 7.4 Hz, Z isomer), 5.90 (q, 0.75 H, J = 7.8 Hz, E isomer), 4.85 (dd, 0.25 H, J = 8.8, 2.3 Hz, Z isomer), 4.76 (dm, 0.75 H, J = 7.3 Hz, E isomer), 4.46–4.33 (m, 2 H), 2.62 (m, 2 H), 2.01 (d, 2.25 H, J = 7.8 Hz, E isomer), 1.76 (d, 0.75 H, J = 7.4 Hz, Z isomer); ^{13}C NMR (CD_3OD) (E isomer) δ 169.0, 162.1, 141.8, 132.9, 128.1, 118.9, 80.5, 71.9, 66.0, 29.5, 10.7, (Z isomer) δ 169.0, 162.8, 143.0, 133.2, 130.6, 122.4, 80.4, 71.6, 66.1, 33.8, 13.2.

(4aα,8aβ)-2,3,4a,8a-Tetrahydro-3-ethylidene-2-oxo-1,4-benzodioxin-6-carboxylic Acid (19). Lactone **17** (185 mg, 0.77 mmol) was suspended in CH_2Cl_2 (15 mL) and 2,6-lutidine (225 μL), and *tert*-butyldimethylsilyl triflate (202 μL, 1.2 equiv) was added dropwise. The mixture was stirred at room temperature for 2 h and then added to a column of silica gel. The column was washed with CH_2Cl_2 (50 mL), and the CH_2Cl_2 fractions were concentrated to give 109 mg (40%) of silyl ester **18**. Further elution of the column with EtOAc/petroleum ether (2:1) containing 1% AcOH anc concentration of the fractions containing **17** (TLC) gave 104 mg (56%) of recovered **17**.

A solution of Martin's reagent[9] (294 mg, 1.4 equiv) in CH_2Cl_2 was transferred to a solution of **18** (109 mg, 0.31 mmol) in CH_2Cl_2 (15 mL) under an inert atmosphere. The mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was dissolved in THF/AcOH/H_2O (6:1:1) (16 mL) and stirred at room temperature for 20 h. Concentration of the mixture and flash chromatography of the residue on silica gel (EtOAc/petroleum ether, 1:1, followed by EtOAc/petroleum ether, 2:1, containing 1% AcOH) gave 47 mg (68%) of **19** (Z/E, 2.6:1): ^1H NMR (CD_3COCD_3) δ 7.01 (br s, 0.72 H, Z isomer), 6.93 (br s, 0.28 H, E isomer), 6.49 (br d, 1 H, J = 9.5 Hz), 6.16 (br d, 1 H, J = 9.5 Hz), 6.13 (q, 0.72 H, J = 7.5 Hz, Z isomer), 5.91 (q, 0.28 H, J = 7.5 Hz, E isomer), 5.40 (d, 0.72 H, J = 15 Hz, Z isomer), 5.33 (d, 0.28 H, J = 15 Hz, E isomer), 5.10 (d, 0.72 H, J = 15 Hz, Z isomer), 5.03 (d, 0.28 H, J = 15 Hz, E isomer), 2.0 (d, 0.8 H, J = 7.5 Hz, E isomer), 1.78 (d, 2.2 H, J = 7.5 Hz, Z isomer); exact mass calcd for $C_{11}H_{10}O_5$ 222.0528, found 222.0526.

(−)-(Z)-9-Methylchorismic Acid [(−)-3]. An aqueous solution of NaOH (3.5 mL, 0.1 M, 0.35 mmol) was added dropwise to a solution of **19** (36 mg, 0.16 mmol) in THF (10 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The mixture was acidified with HCl (10 mL, 0.1 M) and extracted with ether (3 × 40 mL). The extracts were dried ($MgSO_4$) and concentrated. The residue (41 mg) crystallized from EtOAc/pentane as a mixture of Z/E isomers (8:1) of (−)-**3** (11 mg). Recrystallization from the same solvent gave 5 mg (13%) of 10:1 Z/E (−)-**3**: $[\alpha]^{25}_D$ −51° (c 0.18, acetone); the ^1H NMR spectrum of (−)-(Z)-**3** was identical with that of (±)-(Z)-**3**. Flash chromatography of the residue from the initial crystallization gave an additional 17 mg of the Z/E mixture, but further purification could not be accomplished.

Thermal Reaction of (±)-3. A sample of (±)-**3** (4.5 mg) was dissolved in D_2O (pD 7.4, phosphate buffer): ^1H NMR δ 6.42 (d, J = 3.8 Hz, H_2), 6.29 (dm, J = 9.4 Hz, H_6), 6.04 (q, J = 7.5 Hz, H_9), 5.89 (dd, J = 9.4, 3.8 Hz, H_5), 4.53 (dd, J = 7.5, 3.8 Hz, H_4), 4.38 (m, H_3), 1.53 (d, J = 7.5 Hz, CH_3). The rate of product formation at 30.0 °C was monitored by integration of the appropriate signals in the ^1H NMR spectrum: **21**, δ 0.85 (d, J = 7.5 Hz, CH_3); **22**, δ 1.28 (d, J = 7.5 Hz, CH_3); **20**, δ 7.65 (d, J = 8.5 Hz, H_3, H_5); **23**, δ 2.6 (q, J = 7.5 Hz, CH_2, no exchange of CH_2 hydrogens was observed during the reaction).

Enzyme Studies. Kinetic studies of the mutase-catalyzed rearrangement of (−)-1, (±)-**3**, and (−)-**3** with chorismate mutase–prephenate dehydrogenase from *E. coli*[12] were carried out as described by Heyde and Morrison.[20]

Methyl Hydratropate (29) from Chorismate Mutase–Prephenate Dehydrogenase Catalyzed Rearrangement of (−)-3. A solution of (−)-**3** (8 mg) and chorismate mutase–prephenate dehydrogenase (13 units)[12] in Tris·HCl buffer (8.5 mL) was kept at 30 °C for 4 h. The mixture was cooled in an ice bath, and $NaBH_4$ (5 mg) was added. After 15 min additional $NaBH_4$ (5 mg) was added, and the mixture was stirred for 20 min. The mixture was acidified to pH 1 with 2 N HCl and kept at 30 °C for 1 h. The mixture was extracted with ether (5 × 10 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography on silica gel (EtOAc/petroleum ether, 1:1, followed by EtOAc/petroleum ether, 2:1, containing 1% AcOH) gave 3.6 mg (61%) of **27**, which was converted to the methyl ester by treatment with CH_2N_2 in ether. The ester was dissolved in CH_2Cl_2 (1 mL), and DIBAH (0.1 mL, 20% in hexane) was added. THF (1 mL) was added, and the mixture was stirred overnight. The solution was mixed with 0.1 N HCl (5 mL), and the mixture was extracted with CH_2Cl_2 (5 × 6 mL). The organic extracts were dried ($MgSO_4$) and concentrated to afford crude **28**. The ^1H NMR spectrum of **28** was identical with the spectrum of authentic **28** prepared as described below. Diol **28** was dissolved in 0.35 mL of CCl_4/CH_3CN/H_2O (1:1:1.5), and $NaIO_4$ (32.5 mg) and $RuCl_3 \cdot 3H_2O$ (~1 mg) were added. The mixture was stirred at room temperature for 1 h. The mixture was extracted with CH_2Cl_2 (5 × 5 mL). The combined extracts were dried ($MgSO_4$) and concentrated to afford 1.8 mg of hydratropic acid, which was esterified with CH_2N_2 in ether to provide **29**. The ^1H NMR spectrum of **29** was identical with the spectrum of **29** prepared from authentic **30**.[21]

Preparation of 28 from (+)-31. Methyllithium (7.7 mL, 1.3 M in ether, 10 mmol) was added to a suspension of CuI (1.14 g, 5.8 mmol) in ether at −20 °C, and the mixture was stirred for 20 min. A solution of (+)-**31**[15] (376 mg, 2.5 mmol) in ether (25 mL) was added, and the mixture was stirred overnight at room temperature. The mixture was partitioned between ether and water (60 mL). The ether layer was separated, washed with saturated NH_4Cl solution, dried ($MgSO_4$), and concentrated. Flash chromatography on silica gel (EtOAc/petroleum ether, 1.5:3.5 followed by 1:1) afforded 134 mg (32%) of **28** as a colorless oil: ^1H NMR δ 7.26 (m, 5 H), 3.64 (m, 2 H), 3.47 (br s, 1 H, exchanged with D_2O), 3.38 (m, 1 H), 3.04 (br s, 1 H, exchanged with D_2O), 2.78 (quintet, 1 H, J = 7 Hz), 1.21 (d, 3 H, J = 7 Hz).

Determination of the Absolute Configuration of 29 from Chorismate Mutase–Prephenate Dehydrogenase Catalyzed Rearrangement of (−)-3. Commercial (±)-**30**[19] and (S)-(+)-**30**[21] were converted to (±)-**29** and (S)-(+)-**29**, respectively, by reaction with CH_2N_2 in ether. The chiral ^1H NMR shift reagent method[22,23] was used to establish that the absolute configuration of **29** derived from the chorismate mutase–prephenate dehydrogenase catalyzed rearrangement of (−)-**3** was identical with that of authentic (S)-(+)-**30**.

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(22) Lau, K. S. Y.; Fries, R. W.; Stille, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 4983–4986.
(23) The chiral shift reagent used in the present study was tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III)[19] instead of $Eu(tfac)_3$ used in ref 22.

Acknowledgment. We are grateful to the National Institutes of Health, Grant GM 31958, for financial support.

Registry No. (–)-1, 617-12-9; (±)-3, 116130-11-1; 3 (isomer 1), 116257-37-5; 3 (isomer 2), 116183-36-9; (±)-4, 76947-23-4; 5 (isomer 1), 116183-37-0; 5 (isomer 2), 116183-38-1; (*E*)-6, 116130-12-2; (±)-6, 116183-39-2; 7, 116130-13-3; 8, 116130-14-4; 9, 116130-15-5; 10, 116130-16-6; 11 (isomer 1), 94903-41-0; 11 (isomer 2), 116183-40-5; 12 (isomer 1), 116130-17-7; 12 (isomer 2), 116183-41-6; 12 (2somer 3), 116130-18-8; 12 (isomer 4), 116130-19-9; (*E*)-13, 116130-20-2; (*Z*)-13, 116183-42-7; (*Z*)-14, 116130-21-3; (*E*)-14, 116183-43-8; (*Z*)-15, 116130-22-4; (*E*)-15, 116183-44-9; (*Z*)-16, 116130-23-5; (*E*)-16, 116183-45-0; (*Z*)-17, 116130-24-6; (*E*)-17, 116183-46-1; (*Z*)-18, 116130-25-7; (*E*)-18, 116183-47-2; (*Z*)-19, 116130-26-8; (*E*)-19, 116183-48-3; 20, 99-96-7; 21, 116130-27-9; 22, 116130-28-0; 23, 600-18-0; 27 (isomer 1), 116130-29-1; 27 (isomer 2), 116130-30-4; 27 (methyl ester, isomer 1), 91828-70-5; 27 (methyl ester, isomer 2), 116130-31-5; 28 (isomer 1), 116183-49-4; 28 (isomer 2), 116183-50-7; 29, 28645-07-0; (±)-29, 2328-26-9; (+)-30, 7782-24-3; (±)-30, 2328-24-7; (+)-31, 98819-68-2; trimethyl diazophosphonoacetate, 60190-78-5.

Supplementary Material Available: Table of the ^1H NMR chemical shift of the C_9 methyl group and the C_9 vinyl hydrogen of *Z* and *E* isomers (1 page). Ordering information is given on any current masthead page.

Formation of Polycyclic Dimers from Vinyl Nitroxides and Their Dissociation and Isomerization[1]

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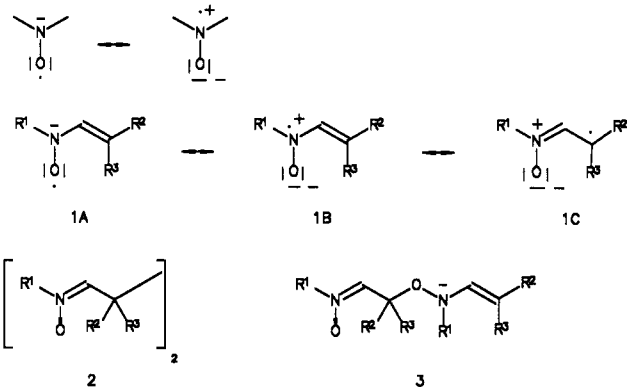
The ambiphilic vinyl nitroxides (VN) **6** dimerize, affording either tricyclic dimers (TRI-DI) **8** or bicyclic dimers (BI-DI) **7**. Formation of **8** is rationalized by C–C bond formation followed by an intramolecular (3 + 2 + 2) cycloaddition involving one nitrone and two carbonyl groups, whereas **7** must arise from O–C bond formation followed by an intramolecular (3 + 2) cycloaddition of nitrone and alkene moiety. Since the BI-DIs **7** are the thermodynamically more stable dimers, the course of the reaction depends on the question of whether it is possible to overcome the activation barrier for its formation. The crucial reaction step, the 1,3 dipolar cycloaddition involving the nitrone and alkene moiety, is favored by *N*-phenyl substitution and retarded by *N*-*tert*-butyl substitution of the nitrone group. Thus, BI-DIs **7** arise from *N*-phenyl-substituted VNs, whereas VNs with R^1 = *tert*-butyl yield TRI-DIs **8** at room temperature. Most of the TRI-DIs **8** dissociate at room temperature or slightly elevated temperatures. Dissociation is favored either by steric congestion of **8** or by enhanced stabilization of the acyl group R^3CO of the VNs **6**. Tetracyclic dimers (TET-DI) **12** arise from TRI-DIs **8** in refluxing methanol or in the presence of acids at room temperature. Isomerization in aprotic solvents in the absence of acids requires higher temperatures. Under these conditions formation of TET-DIs **12** is frequently accompanied by formation of BI-DIs **7** which must be formed via the VNs **6**.

The extraordinary thermodynamic stabilization of the nitroxide group by delocalization of the unpaired electron between nitrogen and oxygen atom is well documented.[2] Since the delocalization energy is in the order of 30 kcal/mol, dimerization by O–O bond formation is expected to be extremely unfavorable.[3] Thus, di-*tert*-alkyl nitroxides are persistent radicals that can be isolated in most cases. In contrast, vinyl nitroxides (VN) **1** are likely to be very reactive radicals. Since delocalization of the unpaired electron to the β-carbon atom of the vinyl group is possible (see mesomeric formula C), dimerization of these radicals with formation of C–C- or O–C-bonded dimers **2** or **3** is

Scheme I



anticipated to be energetically favorable (Scheme I).

Indeed, VNs formed by oxidation of the corresponding nitrones or hydroxylamines cannot generally be detected under standard conditions by ESR spectroscopy if they are only monosubstituted at the β-position (R^3 = H).[1a] Usually they are trapped rapidly by their precursor nitrones which are excellent spin traps.[4] If substituent R^2 is capable of conjugation (phenyl or an electron-acceptor group such as acyl or alkoxycarbonyl), dimers **2** or the corresponding dehydro dimers are formed in moderate to

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