30.25, 30.34, 30.46, 30.50, 35.02, 38.93, 38.93, 43.29, 44.46, 87.05, 115.62, 138.79, 159.61, 163.56, 223.2, 223.2.

Concentrated HNO_3 Oxidation. A 25-mg sample of 1 was dissolved in about 2 mL of ice-cold concentrated nitric acid. The solution was stirred for 2 h at room temperature and then heated at 100 °C for 24 h. Contents of the cooled solution were diluted with water (25 mL) and freeze-dried to yield 15 mg of crystalline solid. Thermospray mass spectrum revealed the presence of three dicarboxylic acids, namely, pimelic, suberic, and azelaic acids [(M + 1) 161, 175, and 189 and intensity 60%, 100%, and 38%, respectively]. This was confirmed by TLC [Analtech, silica gel plates, solvent system 1-butanol-xylene-phenol-formic acid-water, 10:70:30:8:2 (v/v), showed *Rf* values 0.3, 0.4, and 0.45, respectively][6] and paper chromatographic comparisons (Whatman No. 1 paper, solvent system 1-propanol-2 N ammonia, 70:30, R_f 0.32, 0.38, and 0.44, respectively),[7] with authentic samples.

Hydrolysis with Barium Hydroxide. A solution of 50 mg (0.1 mM) of 1 in 15 mL of 0.5 N barium hydroxide was refluxed for 20 h. The aqueous hydrolysate was filtered and acidified to pH 5.0 with sulfuric acid, the precipitated barium sulfate was removed, and the filtrate was lyophilized to give 36.7 mg of crude solid [FABMS 415 (M + H)].

This crude solid was acetylated by stirring with 10 mL of a mixture of acetic anhydride and pyridine (1:1.5), overnight, at room temperature and under anhydrous conditions. The reaction was quenched by pouring the reaction mixture into ice. The aqueous solution was extracted with ethyl acetate, and the organic layer was washed with dilute HCl and brine and dried (Na_2SO_4). Solvent was removed to give a gummy solid. This product was purified by silica gel chromatography using chloroform-methanol (95:5) as the eluting solvent. The pure acetate derivative **6** (17.6 mg, yield 31%; oil, pure by ^{13}C NMR and TLC on silica gel $CHCl_3$-MeOH, 9:1) was obtained: FABMS 583 (M + H); IR (KBr) 3300, 2930, 1735, 1660, 1380, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.3 (br, 1 H), 5.63 (br, 1 H), 5.57 (br s, 1 H), 5.03 (br s, 1 H), 5.0 (m, 1 H), 4.85 (dt, J = 2, 7 Hz, 1 H), 3.75 (m, 1 H), 3.65 (m, 1 H), 3.45 (t, J = 7 Hz, 2 H), 3.23 (dd, J = 7, 15 Hz, 2 H), 2.13 (s, 3 H), 2.08 (s, 3 H), 2.01 (s, 3 H), 1.95 (s, 3 H), 1.2-1.7 (br, 30 H); ^{13}C NMR ($CDCl_3$) (ppm) 21.03, 21.33, 23.14, 23.34, 26.82, 27.25, 27.32, 29.00, 29.12, 29.27, 29.29, 29.32, 29.36, 29.55, 31.93, 32.14, 34.05, 39.88, 39.88, 42.32, 43.33, 52.10, 56.22, 70.66, 74.35, 164.75, 168.15, 169.25, 170.96, 171.24.

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Registry No. 1·HCl, 119948-40-2; **3**, 119948-41-3; **4**, 119948-42-4; **5**, 119948-43-5; **6**, 119948-44-6.

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(7) Howe, J. R. *J. Chromatogr.* **1960**, *3*, 389.

Sulfoxide Analogues of Dihydro- and Tetrahydroprephenate as Inhibitors of Prephenate Dehydratase

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The sulfoxide derivatives **4-7** were prepared as analogues of tetrahydro- and dihydroprephenate, respectively, and a synthesis was attempted for **8**, the prephenate mimic itself. As expected, the saturated analogues **4** and **5** were modest, reversible inhibitors (IC_{50}/K_m = 16 and 27, respectively) of prephenate dehydratase, the enzyme responsible for the Grob-type fragmentation of prephenic acid to phenylpyruvic acid. The unsaturated analogues **6** and **7** were envisaged as potential suicide substrates of the enzyme, if they could undergo an enzyme-induced Pummerer-type fragmentation. However, these compounds also proved to be modest, reversible inhibitors (IC_{50}/K_m = 29 and 21, respectively), and the synthesis of **8** failed because of apparent instability of this compound.

The shikimic acid pathway is a key biosynthetic sequence in plants and microorganisms, leading to the production of the aromatic amino acids as well as cofactor precursors and isoprenoid quinones.[1] This sequence has been a fertile area for investigation since it is replete with enzymatic transformations of unusual or unique mechanisms. In addition, the absence of this pathway in mammals and the success of the inhibitor glyphosate have made it an attractive target for herbicide development.[2]

Among the final steps in the biosynthesis of phenylalanine are the formal Claisen rearrangement of chorismic acid (**1**) to prephenic acid (**2**) and the Grob-type fragmentation of the latter to phenylpyruvic acid (**3**). In *Escherichia coli*, both of these steps are catalyzed by the bifunctional enzyme chorismate mutase/prephenate dehydratase. Chemical modification,[3] mutation,[4] and kinetic studies[5] all suggest that the active sites for the two activities are separate.

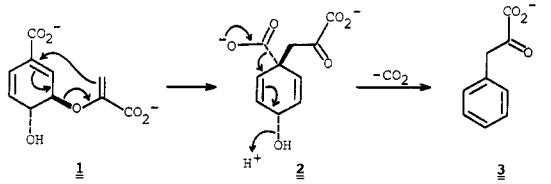

Table I. Structural Comparison of Carbinols and Sulfoxides[7]

	Bond Lengths (Å)		
C—C	1.51-1.52	C—S	1.78-1.80
C—OH	1.44-1.46	S=O	1.45-1.49
	Bond Angles (deg)		
C—C—C	111-112	C—S—C	96-100
C—C—OH	107-111	C—S=O	105-108
	pK_a		
$C—OH_2^+$	-2 to -5	$>S^+—OH$	-1 to -3

The structure of prephenate and the presumed mechanism of the dehydratase reaction presented an opportunity to test an idea for inhibition of enzymes that promote the

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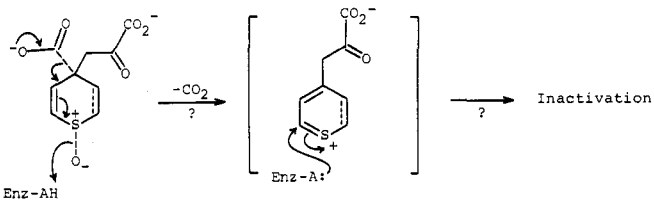
(3) Gething, M. J. H.; Davidson, B. E. *Eur. J. Biochem.* **1977**, *78*, 103-110; **1977**, *78*, 111-117.
(4) Baldwin, G. S.; Davidson, B. E. *Arch. Biochem. Biophys.* **1981**, *211*, 66-75.
(5) Duggleby, R. G.; Sneddon, M. K.; Morrison, J. F. *Biochemistry* **1978**, *17*, 1548-1554.

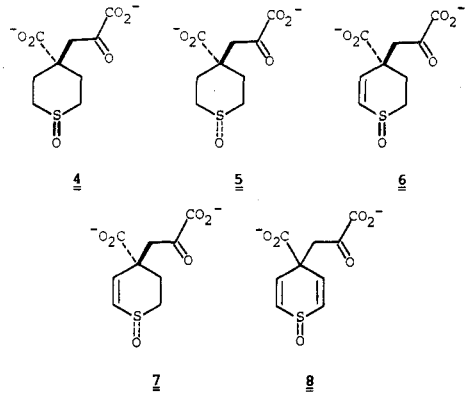
0022-3263/89/1954-2404$01.50/0

Scheme I



loss of a hydroxyl group, namely, to replace the carbinol moiety of the substrate with a sulfinyl moiety. As illustrated in Table I, the sulfoxide tetrahedron is distorted in comparison to that of the carbinol moiety; however, the overall shape of the target molecules and the basicities of the oxygen atoms are quite similar. In addition, heterolytic cleavage of the sulfur–oxygen bond can be induced by electrophilic activation, leading to the Pummerer reaction[6] and formation of a reactive sulfonium species.

We describe here the synthesis of the prephenate analogues **4–7** and their evaluation as inhibitors of the chor-



4 **5** **6**

7 **8**

ismate mutase/prephenate dehydratase enzyme complex from *E. coli*. It was anticipated that the saturated analogues would be competitive inhibitors, whereas the unsaturated derivatives might undergo an enzyme-induced Pummerer-type decarboxylation and thereby act as irreversible inhibitors of the enzyme by alkylation of an active-site nucleophile (Scheme I). Since the related enzyme, prephenate dehydrogenase, is known to bind dihydro- and tetrahydrodeoxoprephenate,[8] we anticipated that these compounds should be accommodated in the dehydratase active site. A synthesis of the doubly unsaturated analogue **8**, which would be the closest mimic of prephenate, was also attempted.

The synthesis of compounds **4–7** is depicted in Scheme II, starting from α-ketoglutaric acid. Conversion to the dimethyl ketal dimethyl ester **9** is readily effected with methanol, HCl, and trimethyl orthoformate. Generation of the ester enolate with lithium diisopropylamide (LDA) and alkylation with the tetrahydropyranyl (THP) ether of iodoethanol affords the monoalkylated product **10**. Repetition of this procedure then gives the dialkylated material **11**. Removal of the THP acetals under mildly acidic conditions, in anticipation of converting the hydroxyl groups into suitable leaving groups, results only in formation of the γ-lactone. However, treatment of **11** with triphenylphosphine dibromide provides the dibromide **12** directly, as previously demonstrated by Sonnet.[9] Ring closure with potassium sulfide in analogy with the work of Prelog and Cerkovnikoff[10] then affords the cyclic sulfide **13**.

The resistance of the α-carboxy ketal toward mild acid hydrolysis leads to difficulties in its removal after introduction of the sulfoxide function; therefore an alternative protection scheme was necessary. In their synthesis of prephenic acid, Danishefsky and Hirama employed a pseudoester (analogous to **14**) to block this moiety;[11] such a protection scheme allows the keto diacid to be unmasked on treatment with aqueous base. Following this precedent, saponification of the diester **13**, acidification and cyclization on Dowex 50W-X8 cation exchange resin (H^+ form), and reesterification of the free carboxyl group with diazomethane provide the bicyclic pseudoester **14**. This material is readily oxidized to an isomeric mixture of the sulfoxides **15** on treatment with $NaIO_4$ at 5 °C.[12] Hydrolysis with 2 equiv of NaOH gives the cis and trans isomers **4** and **5**, which are readily separated by preparative reverse-phase HPLC.

For preparation of the unsaturated analogues, sulfoxides **15** are treated with trimethylsilyl triflate and ethyldiisopropylamine[13] to afford vinyl sulfide **16**, also a mixture of diastereomers. When this material is oxidized with $NaIO_4$, a mixture of four sulfoxide diastereomers, **17**, is obtained. In our initial experiments, this material was hydrolyzed, and separation of the cis and trans sulfoxide isomers **6** and **7** was attempted by reverse-phase HPLC. However, these compounds proved to be unstable to isolation after purification in this manner; hence separation of the four diastereomers of **17** is accomplished prior to hydrolysis. Saponification of the separated isomers then provides pure samples of the cis and trans diacids **6** and **7**. Treatment of vinyl sulfoxide **17** with trimethylsilyl triflate and ethyldiisopropylamine yields the doubly unsaturated sulfide **18**, which is readily oxidized to the sulfoxides **19** with *m*-CPBA at 0 °C. However, treatment of this compound with base, even under very mild conditions (0.1 N NaOH at 0 °C), leads immediately to formation of a black, intractable material, which could not be characterized. Whether this material is the thiopyrylium species (as depicted in Scheme I)[14] or a decomposition product thereof could not be determined.

Stereochemical assignment of the sulfoxide isomers was made on the basis of their NMR behavior. Within each pair of isomers, one presented sharp, resolved ^1H NMR resonance patterns for the methylene protons of the ring system, whereas the other displayed broad, unresolved singlets. The pyruvyl side chain is more demanding sterically than a carboxylate[15] and therefore prefers the equatorial position; the sulfoxide oxygen in contrast shows a slight preference for the axial configuration.[16] For the

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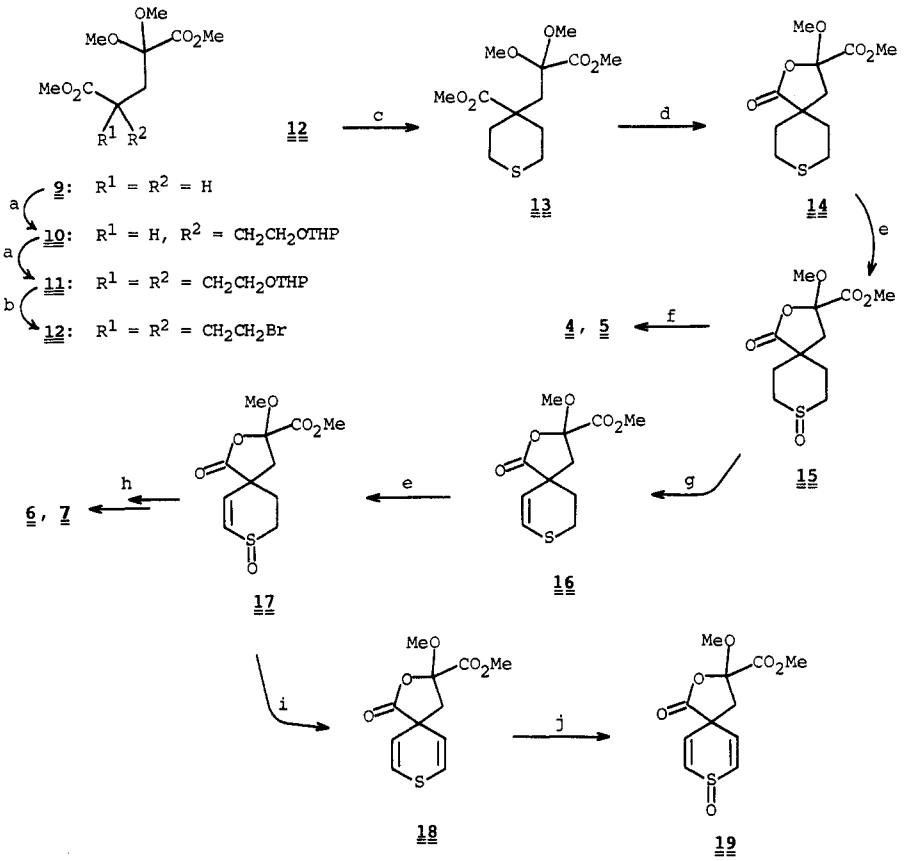
Scheme II[a]



[a] (a) LDA, ICH_2CH_2OTHP, THF/HMPA, −10 °C (63–76%); (b) Ph_3P, Br_2, CH_2Cl_2 (48%); (c) K_2S, THF/H_2O, Δ (48%); (d) KOH, H^+, CH_2N_2 (53%); (e) $NaIO_4$, MeOH/H_2O, 5 °C (92–95%); (f) KOH, THF/H_2O; (g) $EtiPr_2N$, $Me_3SiO_3SCF_3$, CH_2Cl_2, 21 °C (70%); (h) NaOH, MeOH/H_2O, 0 °C; (i) $EtiPr_2N$, $Me_3SiO_3SCF_3$, CH_2Cl_2, 0 °C (35%); (j) *m*CPBA, CH_2Cl_2 (84%).

Table II. Inhibition of Prephenate Dehydratase by Sulfoxide Analogues

entry	inhibitor	IC_{50}/K_m[a]
1	4	16 ± 3
2	5	27 ± 8
3	6	29 ± 14
4	7	21 ± 6

[a] Determined at pH 8.2; K_m(prephenate) = 1.3 mM (entries 1 and 2), 0.8 mM (entries 3 and 4).

isomers in which these groups are cis (**4** and **6**), these preferences are satisfied in a single chair conformation for which a well-resolved coupling pattern is expected. For the isomers in which these groups are trans (**5** and **7**), an equilibrium mixture of conformers and average coupling patterns are seen.

Purification of chorismate mutase/prephenate dehydratase from *E. coli* K12 (strain JP492) was carried out according to the most recent procedure of Davidson.[17] Catalytic activity was determined by removing aliquots and monitoring the absorbance at 320 nm after quenching the reaction with hydroxide. Two preparations of enzyme were utilized for inhibition studies; at pH 8.2 Tris buffer, 37 °C, the substrate K_m value was found to be 0.8 or 1.3 mM, depending on the preparation. These values and their variability correspond to the range from 0.5 to 1.0 mM previously reported.[17] Because of this variation, the affinity of the inhibitors is expressed as the dimensionless

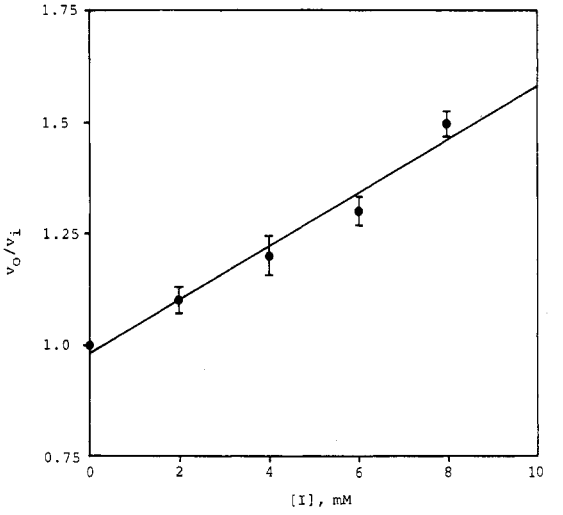


Figure 1. Inhibition of prephenate dehydratase by sulfoxide **7**. Determined at pH 8.2, 37 °C, as described in the Experimental Section.

ratio of IC_{50}/K_m. All four of the sulfoxide inhibitors proved to be reversible inhibitors of the enzyme, with IC_{50}/K_m values ca. 20 (Table II). A representative plot of v_0/v_i versus $[I]$ is shown in Figure 1 for compound **7**. Preincubation of the enzyme with any of the sulfoxides at concentrations up to 10 mM and for time periods up to 1.5 h did not result in any irreversible inactivation of the enzyme. Moreover, monitoring the UV spectra of the unsaturated analogues **6** and **7** during extended incubation with the enzyme showed no change, indicating that the

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inhibitors were not being converted to a different product.

All of the sulfoxides showed modest competitive inhibition, with affinities approximately an order of magnitude weaker than that of the substrate, as judged by the K_m value of the latter. There is no significant difference in the affinity of any of the inhibitors, which suggests that these compounds may not be binding as substrate analogues. In the dihydro series, in particular compound **7**, the sulfoxide moiety does not appear to be labile enough to undergo the hoped-for Pummerer reaction. Indeed, at 37 °C in the absence of enzyme, compound **7** does not undergo decarboxylation at an appreciable rate until pH 0, conditions under which prephenate would be rapidly aromatized; even then direct decarboxylation and no Pummerer-type reaction is seen.

Experimental Section[18]

Synthesis of Inhibitors. α-Oxo-1-carboxy-4-tetrahydrothiopyranpropanoic Acid, *S*-Oxide, Disodium Salt (4 and 5). To a solution of 312 mg (1.13 mmol) of **15** (see below) in 2 mL of 3:1 water/THF at 5 °C was added 90 mg (2.26 mmol) of powdered KOH. This solution was allowed to warm slowly to 21 °C and to stir for a total of 18 h before lyophilization. The isomeric products were separated by reverse-phase HPLC on a Whatman C-18 preparative column eluted with 100 mM triethylammonium bicarbonate (TBK) in 1% MeOH, pH 7.4. The separate isomers were further purified by anion exchange chromatography on DEAE-Sephadex using a step-gradient of 50 mM triethylammonium bicarbonate (TBK), pH 7.3 (1 column vol), 250 mM TBK (1 column vol), and 500 mM TBK (3 column vol). After lyophilization, each isomer was converted to the corresponding disodium salt by exchange on sodium Dowex 50-W-X8 resin to afford 39 mg of the cis sulfoxide **4** and 35 mg of the trans sulfoxide **5** as white solids.

Isomer 4: IR (KBr) 3400 (br), 2940, 1770, 1640 (br), 1400, 1200, 1150, 1020; ^{1}H NMR (D_2O) δ 3.11 (m, 2), 2.81 (m, 2), 2.50 (br s, 2), 2.01 (m, 2), 1.99 (m, 2); ^{13}C(^{1}H) NMR (D_2O/H_2O) δ 203.0, 181.1, 169.5, 48.4, 43.7, 42.0, 23.7; HRMS (FAB) calcd for $C_9H_{10}O_6SNa_2$ m/z 293.0072, found 293.0070.

Isomer 5: IR 3400 (br), 2940, 1770, 1630 (br), 1395, 1245, 1205, 1010 cm^{-1}; ^{1}H NMR (D_2O) δ 2.96 (br t, 2, J = 11 Hz), 2.92 (s, 2), 2.79 (br t, 2, J = 10 Hz), 2.22 (br t, 2, J = 10 Hz), 1.61 (br t, 2, J = 11 Hz); ^{13}C(^{1}H) NMR (D_2O/H_2O) δ 203.0, 181.6, 169.3, 44.5, 43.7, 43.4, 26.0; HRMS (FAB) calcd for $C_9H_{10}O_6SNa_2$ m/z 293.0072, found 293.0073.

α-Oxo-1-carboxy-5,6-dihydrothiopyranpropanoic Acid, *S*-Oxide, Disodium Salt (6 and 7). The diastereomers of 175 mg of **17** (see below) were separated by reverse-phase HPLC on a Whatman C-18 preparative column (60:40 H_2O/MeOH). The first two peaks and the last two peaks eluted from the column were combined to afford 30 mg and 62 mg of the cis and trans sulfoxides, respectively.

Isomer 6. To a solution of 30 mg of the cis sulfoxide isomers in 1.54 mL of water and 550 μL of MeOH at 0 °C was added 220 μL of 1 M NaOH. This solution was stirred at 0 °C for 1 h, diluted with 2 mL of water, and lyophilized to afford **7** as an orange, hygroscopic solid: IR (KBr) 3400 (br), 1715, 1635, 1595, 1395, 1115 cm^{-1}; UV λ_{max} 215 (broad, ε = 3700), 250 (shoulder); ^{1}H NMR (D_2O) δ 6.54 (d, 1, J = 10 Hz), 6.35 (d, 1, J = 10 Hz), 3.12 (ddd, 1, J = 2, 11, 14 Hz), 3.04 (d, 1, J = 19 Hz), 2.96 (d, 1, J = 19 Hz), 2.89 (ddd, 1, J = 2, 9, 14 Hz), 2.25 (ddd, 1, J = 2, 11, 15 Hz), 1.81 (ddd, 1, J = 2, 9, 15 Hz); ^{13}C(^{1}H) NMR (D_2O) δ 202.4, 179.9, 169.3, 141.9, 125.5, 46.4, 46.1, 42.0, 23.9; HRMS calcd for $C_9H_8O_6SNa_2$ + H m/z 290.9913, found 290.9914.

Isomer 7. In a similar manner, 62 mg of the trans sulfoxide isomers were hydrolyzed and lyophilized: IR 3400 (br), 1720, 1620 (br), 1395, 1340, 1115, 1085 cm^{-1}; UV λ_{max} 215 (broad, ε = 3600); ^{1}H NMR (D_2O) δ 6.53 (d, 1, J = 10 Hz), 6.47 (d, 1, J = 10 Hz), 3.20 (d, 1, J = 19 Hz), 2.99 (d, 1, J = 19 Hz), 2.93 (m, 2), 2.01 (m, 2); ^{13}C(^{1}H) NMR (D_2O) δ 201.8, 178.2, 168.7, 142.6, 123.7, 46.7, 46.1, 41.1, 22.1; HRMS calcd for $C_9H_8O_6SNa_2$ + H m/z 290.9913, found 290.9923.

Dimethyl 2,2-Dimethoxyglutarate (9). To 5.57 g (38.1 mmol) of α-ketoglutaric acid (Aldrich) were added 50 mL of methanol, 14.6 mL (133 mmol) of trimethyl orthoformate (Kodak), and 1 mL of concentrated H_2SO_4. The solution was heated at reflux for 20 h. After cooling, solid $NaHCO_3$ was added to saturation, the solution was filtered, and the methanol was removed under reduced pressure. The remaining oil was dissolved in 60 mL of CH_2Cl_2 and washed with 5 mL each of saturated $NaHCO_3$ and brine. The CH_2Cl_2 layer was dried and the solvent was removed under reduced pressure to afford 6.31 g (75% yield) of **9** as a colorless liquid: IR 2970, 2855, 1750 (br), 1443, 1205 (br), 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3), 3.67 (s, 3), 3.27 (s, 6), 2.31 (t, 2, J = 8.7 Hz), 2.21 (t, 2, J = 8.7 Hz); ^{13}C(^{1}H) NMR ($CDCl_3$) δ 172.7, 168.9, 101.4, 52.4, 51.6, 49.7, 28.4, 27.9; ^{13}C(coupled) NMR δ 52.4 (q), 51.6 (q), 49.7 (q), 28.4 (tt), 27.9 (tt). Anal. Calcd for $C_9H_{16}O_6$: C, 49.10; H, 7.32. Found: C, 48.90; H, 7.31.

2-(2-Iodoethoxy)tetrahydropyran. To a solution of 6.30 g (36.6 mmol) of 2-iodoethanol (Aldrich) and 4.62 g (54.9 mmol) of dihydropyran in 80 mL of CH_2Cl_2 was added 916 mg (3.66 mmol) of pyridinium *p*-toluenesulfonic acid,[20] and the mixture was stirred for 4 h at 21 °C. The solution was washed with 10 mL of half-saturated brine and dried, and the solvent was removed under reduced pressure. Chromatography (3:1 hexane/ether) then afforded 8.35 g (89% yield) of a colorless liquid, which was stored over copper at 0 °C: IR 2960, 2890, 1460, 1445, 1395, 1355, 1265, 1205, 1125 cm^{-1}; ^{1}H NMR δ 4.68 (br s, 1), 3.95 (dt, 1, J = 11, 6.4 Hz), 3.89 (t, 1, J = 9.3 Hz), 3.72 (dt, 1, J = 11, 6.4 Hz), 3.53 (m, 1), 3.29 (m, 2), 1.84 (m, 1), 1.72 (t, 1, J = 13 Hz), 1.65–1.53 (br m, 4); ^{13}C(^{1}H) NMR δ 98.6, 68.2, 62.2, 30.4, 25.3, 19.2, 3.5; ^{13}C-(coupled) NMR δ 98.6 (d), 68.2 (t), 62.2 (t), 30.4 (t), 25.3 (t), 19.2 (t), 3.5 (t); HRMS calcd for $C_7H_{13}O_2I$ (M − 1) 254.9870, found 254.9876.

Dimethyl 2,2-Dimethoxy-4-(2-(2-tetrahydropyranyloxy)-ethyl)glutarate (10). To a solution of 5.99 mL (42.7 mmol) of diisopropylamine in 80 mL of THF under nitrogen at −78 °C was added 24.9 mL (38.8 mmol) of 1.56 M *n*-BuLi in hexane via syringe. After 10 min, 8.55 g (38.8 mmol) of diester **9** in 5 mL of THF was added via syringe. After an additional 30 min, a solution of 19.9 g (77.7 mmol) of the above iodide in 13.5 mL (77.7 mmol) of HMPA was added via syringe. The solution was allowed to warm slowly to −10 °C and stirred for a total of 12 h. Ten milliliters of 5% $NaHCO_3$ solution was then added and the solution was extracted with three 50-mL portions of EtOAc. The combined organic extracts were washed with 15 mL each of saturated $NaHCO_3$ and brine, dried, and evaporated. Chromatography (1:1 EtOAc/hexane) then afforded 8.46 g (63% yield) of the monoalkylated product **10** as a colorless oil: IR 2960, 2880, 2850, 1750 (br), 1440, 1380, 1350, 1330–1020 cm^{-1}; ^{1}H NMR δ 4.55 (t, 0.5, J = 3.3 Hz), 4.53 (t, 0.5, J = 3.5 Hz), 3.83 (dt, 1, J = 2.6, 8.6 Hz), 3.79 (s, 3), 3.72 (m, 1), 3.66 (s, 3), 3.48 (m, 1), 3.34 (dt, 1, J = 15.9, 5.6 Hz), 3.26 (s, 3), 3.24 (s, 3), 2.61 (m, 1), 2.42 (m, 1), 1.97 (dd, 1, J = 14.6, 3.1 Hz), 1.90 (m, 1), 1.77 (m, 2), 1.67 (m, 1), 1.58–1.50 (br m, 4); ^{13}C(^{1}H) NMR δ 175.7, 169.2, 101.5, 98.9, 98.6, 64.8, 62.3, 61.9, 52.6, 51.7, 50.0, 37.8, 37.6, 35.8, 33.5, 30.6, 25.5, 19.5, 19.3; ^{13}C(coupled) NMR δ 98.9 (d), 98.6 (d), 64.8 (t), 62.3 (t), 61.9 (t), 52.6 (q), 51.7 (q), 50.0 (q), 37.8 (d), 37.6 (d), 35.8 (t), 33.5 (t), 30.6 (t), 25.5 (t), 19.5 (dd), 19.3 (dd). Anal. Calcd for $C_{16}H_{28}O_8$: C, 55.16; H, 8.10. Found: C, 55.13; H, 8.13.

Dimethyl 2,2-Dimethoxy-4,4-bis(2-(2-tetrahydropyranyl-oxy)ethyl)glutarate (11). To a solution of 5.75 mL (41.1 mmol) of diisopropylamine in 80 mL of THF under nitrogen and at −78

(18) Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran was distilled from sodium/benzophenone immediately prior to use. The references for ^{1}H NMR chemical shifts were tetramethylsilane or the residual HOD signal. The references for ^{13}C NMR chemical shifts were $CDCl_3$ or external THF. Carbon multiplicity was determined by DEPT or coupled DEPT and data are tabulated in order: chemical shift (multiplicity). Unless otherwise noted: $MgSO_4$ was employed as the solution drying agent, and chromatography was performed on silica gel according to the method of Still, Kahn, and Mitra, eluting with the indicated solvent.[19] IR spectra were obtained on thin films, and NMR spectra in $CDCl_3$ solution, unless otherwise indicated.

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *40*, 2923–2925.

(20) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.

°C was added 23.9 mL (37.3 mmol) of 1.56 M *n*-BuLi in hexane via syringe. After 5 min, a solution of 13.00 g (37.3 mmol) of **10** in 5 mL of THF was added via syringe. After an additional 30 min, a solution of 19.11 g (74.6 mmol) of the above iodide in 13.0 mL (74.6 mmol) of HMPA was added via syringe. The solution was allowed to warm slowly to −10 °C and stirred for a total of 14 h. Fifteen milliliters of 5% $NaHCO_3$ was added and the solution was extracted with three 50-mL portions of EtOAc. The combined organic extracts were washed with 15 mL each of saturated $NaHCO_3$ and brine, dried, and evaporated. Chromatography (3:1 CH_2Cl_2/EtOAc) then afforded 13.50 g (76% yield) of the dialkylated product **11** as a colorless oil: IR 2960, 2885, 1750 (br), 1460, 1445, 1390, 1360, 1330, 1270, 1205, 1190–1110 cm^{-1}; ^1H NMR δ 4.54 (br s, 2), 3.83 (m, 1), 3.78 (s, 3), 3.74 (m, 1), 3.65 (s, 3), 3.49 (m, 2), 3.41 (t, 1, J = 11.7 Hz), 3.35 (t, 1, J = 9.9 Hz), 3.27 (s, 6), 2.29 (d, 2, J = 2.5 Hz), 2.05 (m, 2), 1.98 (m, 2), 1.80 (m, 2), 1.67 (tt, 2, J = 12.9, 2.8 Hz), 1.58–1.49 (br m, 10); $^{13}C(^1H)$ NMR δ 175.9, 169.3, 100.8, 98.8, 63.6, 62.0, 52.5, 51.6, 50.1, 44.5, 39.8, 39.7, 34.3, 34.1, 34.0, 30.6, 25.5, 19.4; ^{13}C(coupled) NMR δ 98.8 (d), 63.6 (t), 62.0 (t), 52.5 (q), 51.6 (q), 50.1 (q), 39.8 (t), 39.7 (t), 34.3 (t), 34.1 (t), 34.0 (t), 30.6 (t), 25.5 (t), 19.4 (t). Anal. Calcd for $C_{23}H_{40}O_{10}$: C, 57.97; H, 8.46. Found: C, 57.86; H, 8.65.

Dimethyl 2,2-Bis(2-bromoethyl)-4,4-dimethoxyglutarate (12). To a solution of 7.92 g (30.19 mmol) of triphenylphosphine in 150 mL of CH_2Cl_2 under nitrogen and in a cool water bath was added 1.55 mL (30.19 mmol) of bromine dropwise over 10 min. A solution of 6.85 g (14.38 mmol) of **11** in 10 mL of CH_2Cl_2 was added in one portion, and the mixture was stirred for 1 h at 21 °C. Two milliliters of methanol was added and the solution was stirred for an additional 10 min. The solvent was removed on a rotary evaporator and the brown residue was chromatographed on neutral alumina (3:1 hexane/EtOAc). The residue was crystallized from hexane to afford 2.97 g (48% yield) of the dibromide **12** as a white solid, mp 68–71 °C. This material was recrystallized from EtOAc/hexane for analysis: mp 73–75 °C; IR (KBr) 2970, 2775, 1765, 1735, 1460, 1445, 1330, 1275, 1245, 1215, 1195 cm^{-1}; ^1H NMR δ 3.82 (s, 3), 3.70 (s, 3), 3.34–3.30 (m, 2), 3.29 (s, 6), 3.28–3.24 (m, 2), 2.26–2.21 (m, 4), 2.23 (s, 2); $^{13}C(^1H)$ NMR δ 174.2, 169.0, 100.5, 52.8, 52.2, 50.3, 48.3, 38.7, 37.9, 26.9; ^{13}C(coupled) NMR δ 52.8 (q), 52.2 (q), 50.3 (q), 38.7 (t), 37.9 (t), 26.9 (t). Anal. Calcd for $C_{13}H_{22}O_6Br_2$: C, 35.97; H, 5.11; Br, 36.81. Found: C, 35.98; H, 5.21; Br, 36.67.

Methyl α,α-Dimethoxy-1-(methoxycarbonyl)-4-tetrahydrothiopyranpropanoate (13). To 110 mL of degassed methanol under nitrogen at 0 °C was added in portions 914 mg (23.4 mmol) of potassium metal. After reaction was complete, hydrogen sulfide was bubbled through the solution for 15 min. The solution was then placed under reduced pressure (aspirator) for 10 min. The resulting solution of K_2S was cooled to 0 °C under nitrogen and 4.83 g (11.1 mmol) of **12** in 10 mL of THF was added. The solution was heated and kept at reflux for 2 h and cooled, and 10 mL of water was added. The solvent was removed on a rotary evaporator and the solution was extracted with four 30-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL each of saturated $NaHCO_3$ and brine, dried, and evaporated, and the residue was chromatographed (1:1 EtOAc/hexane) to afford 1.62 g (48% yield) of the cyclic sulfide **13** as a colorless oil: IR 2960, 2850, 1750 (br), 1445 (br), 1365, 1285, 1205, 1185, 1140, 1105, 1085, 1050 cm^{-1}; ^1H NMR δ 3.79 (s, 3), 3.71 (s, 3), 3.23 (s, 6), 2.69 (td, 2, J = 14, 2 Hz), 2.47 (dm, 2, J = 14 Hz), 2.41 (dm, 2, J = 14 Hz), 2.19 (s, 2), 1.62 (td, 2, J = 14, 3 Hz); $^{13}C(^1H)$ NMR δ 174.9, 169.2, 100.2, 52.4, 51.7, 49.9, 43.8, 43.6, 35.4, 24.9; ^{13}C(coupled) δ 52.4 (q), 51.7 (q), 49.9 (q), 43.6 (t), 35.4 (t), 24.9 (t). Anal. Calcd for $C_{13}H_{22}O_6S$: C, 50.96; H, 7.24; S, 10.46. Found: C, 50.66; H, 7.17; S, 10.17.

Methyl 1-Oxo-3-methoxy-2-oxa-7-thiaspiro[4.5]decane-3-carboxylate (14). To a solution of 2.43 g (7.92 mmol) of **13** in 28 mL of 3:1 water/THF was added 1.90 g (47.5 mmol) of KOH, and the solution was heated to 90 °C for 2.5 h. After cooling, the solution was passed through an 80-mL Dowex 50W-X8 ion exchange column in the H^+ form with three column volumes of water and lyophilized. The solid residue was dissolved in 40 mL of CH_2Cl_2, cooled in an ice bath, and treated with diazomethane. The solvent was removed on a rotary evaporator and the residue was chromatographed (5% EtOAc/benzene) to afford 1.10 g (53% yield) of the pseudoester **14** as a clear oil. A sample was further purified for analysis for chromatography: IR 2980, 2930, 2860, 1790, 1760, 1440, 1290, 1255, 1230, 1215, 1155, 1120, 1060, 1025, 985 cm^{-1}; ^1H NMR δ 3.86 (s, 3), 3.43 (s, 3), 2.82 (m, 1), 2.76 (m, 1), 2.65 (ddd, 1, J = 2.9, 10.1, 13.2 Hz), 2.54 (ddd, 1, J = 2.8, 10.3, 13.5 Hz), 2.42 (d, 1, J = 14.0 Hz), 2.25 (d, 1, J = 14.0 Hz), 2.19–2.12 (m, 2), 2.03 (ddd, 1, J = 3.0, 6.3, 13.5 Hz), 1.82 (ddd, 1, J = 2.7, 6.4, 13.7 Hz); $^{13}C(^1H)$ NMR δ 178.1, 167.7, 103.0, 53.3, 53.2, 43.7, 43.1, 35.0, 34.5, 23.7; ^{13}C(DEPT) δ 53.3 (q), 53.2 (q), 43.7 (t), 35.0 (t), 34.5 (t), 23.7 (t). Anal. Calcd for $C_{11}H_{16}O_5S$: C, 50.76; H, 6.20; S, 12.32. Found: C, 50.45; H, 6.13; S, 12.19.

Methyl 1-Oxo-3-methoxy-2-oxa-7-thiaspiro[4.5]decane-3-carboxylate 7-Oxide (15). To a solution of 1.07 g (4.09 mmol) of **14** in 8 mL of methanol in an ice bath was added 919 mg (4.30 mmol) of $NaIO_4$ in 12 mL of water, and the heterogeneous solution was stirred at 5 °C for 21 h. The iodate precipitate was removed by filtration, and the supernatant was extracted with five 15-mL portions of CH_2Cl_2. The combined organic layer was washed with 10 mL of brine, dried, and evaporated to afford 1.04 g (92% yield) of the sulfoxide **15** a clear oil. This material was recrystallized from EtOAc/diethyl ether for analysis: IR 2960, 2940, 2860, 2240, 1780, 1760, 1440, 1305, 1225, 1210, 1185, 1150, 1120, 1065, 1030, 995, 975 cm^{-1}; ^1H NMR δ 3.89 (s, 1.7), 3.88 (s, 1.3), 3.45 (s, 1.7), 3.44 (s, 1.3), 3.36 (m, 0.6), 3.15–3.08 (m, 1.3), 2.89–2.83 (m, 1.0), 2.79–2.66 (m, 1.2), 2.62–2.54 (m, 0.9), 2.52–2.46 (d[2.50], J = 14.0 Hz; m, 0.9), 2.42–2.34 (d[2.40], J = 14.2 Hz; d[2.37], J = 14.0 Hz; d[2.35], J = 14.2, 1.6 Hz), 2.16 (m, 0.6), 1.95–1.88 (m, 1.2), 1.67 (m, 0.6); $^{13}C(^1H)$ NMR δ 177.0, 176.8, 167.02, 166.99, 102.9, 102.6, 53.2, 53.10, 53.08, 53.06, 46.5, 42.2, 42.0, 41.6, 40.1, 23.9, 23.8; ^{13}C(DEPT) δ 53.2 (q), 53.10 (q), 53.08 (q), 53.06 (q), 46.5 (t), 42.2 (t), 42.0 (t), 41.6 (t), 23.9 (t), 23.8 (t). Anal. Calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; S, 11.60. Found: C, 47.64; H, 5.93; S, 11.43.

Methyl 1-Oxo-3-methoxy-2-oxa-7-thiaspiro[4.5]dec-5-ene-3-carboxylate (16). To a solution of 1.012 g (3.68 mmol) of **15** and 1.41 mL (8.10 mmol) of diisopropylethylamine in 15 mL of CH_2Cl_2 under nitrogen and at 0 °C was added 1.42 mL (7.36 mmol) of trimethylsilyl trifluoromethanesulfonate, and the solution was allowed to warm to 21 °C slowly and stir under nitrogen for 23 h. The mixture was then diluted with 20 mL of CH_2Cl_2 and washed with 5 mL each of saturated $NaHCO_3$(aq) and brine, dried, and evaporated. The residue was chromatographed (3:1 hexane/EtOAc) to afford 664 mg (70% yield) of the dehydro derivative **16** as a clear oil: IR 3010, 2960, 2860, 1790, 1760, 1605, 1440, 1300, 1260, 1240, 1215, 1145, 1115, 1080, 1060, 1030, 1005 cm^{-1}; ^1H NMR δ 6.39 (d, 0.4, J = 10.1 Hz), 6.33 (d, 0.6, J = 10.1 Hz), 5.75 (d, 0.6, J = 10.1 Hz), 5.49 (d, 0.4, J = 10.1 Hz), 3.88 (s, 1.2), 3.87 (s, 1.8), 3.50 (ddd, 0.6, J = 2.8, 10.2, 13.1 Hz), 3.46 (s, 0.6), 3.45 (s, 0.4), 3.22 (ddd, 0.4, J = 2.7, 9.0, 13.1 Hz), 2.81 (ddd, 0.4, J = 2.6, 8.6, 13.1 Hz), 2.76 (ddd, 0.6, J = 2.6, 7.2, 13.1 Hz), 2.50 (d, 1, J = 13.9 Hz), 2.39 (d, 0.4, J = 14.1 Hz), 2.39 (m, 0.4), 2.36 (d, 0.6, J = 13.9 Hz), 2.27 (ddd, 0.6, J = 2.6, 7.2, 13.8 Hz), 2.17 (ddd, 0.4, J = 2.7, 9.0, 13.8 Hz), 1.94 (ddd, 0.6, J = 2.8, 10.2, 13.8 Hz); $^{13}C(^1H)$ NMR δ 177.4, 176.7, 167.5, 167.4, 125.0, 123.8, 119.8, 119.6, 103.0, 102.8, 53.27, 53.20, 53.15, 46.7, 46.4. 42.9, 42.3, 31.2, 31.1, 22.0, 21.9; ^{13}C(DEPT) δ 125.0 (d), 123.8 (d), 119.8 (d), 119.6 (d), 53.27 (q), 53.20 (q), 53.15 (q), 46.7 (t), 46.4 (t), 31.2 (t), 31.1 (t), 22.0 (t), 21.9 (t). Anal. Calcd for $C_{11}H_{14}O_5S$: C, 51.15; H, 5.46; S, 12.41. Found: C, 50.97; H, 5.46; S, 12.22.

Methyl 1-Oxo-3-methoxy-2-oxa-7-thiaspiro[4.5]dec-5-ene-3-carboxylate 7-Oxide (17). To a solution of 193 mg (0.748 mmol) of **16** in 1.4 mL of methanol at 5 °C was added, with stirring, a cold solution of 167 mg (0.784 mmol) of $NaIO_4$ in 2.1 mL of water, and the heterogeneous mixture was stirred at 5 °C for 18 h. The iodate precipitate was removed by filtration and the filtrate was extracted with five 10-mL portions of CH_2Cl_2. The combined organic layer was washed with 5 mL of brine, dried, and evaporated to afford 195 mg (95% yield) of sulfoxide **17** as an 8:3:2:1 mixture of diastereomers: IR 3010, 2955, 2850, 2240, 1785, 1755, 1615, 1440, 1410, 1300, 1265, 1235, 1205, 1140, 1110, 1060, 1035, 1025, 1000, 980, 970 cm^{-1}; ^1H NMR δ isomer A 6.73 (dd, 1, J = 1, 10 Hz), 6.38 (dd, 1, J = 1, 10 Hz), 3.86 (s, 3), 3.59 (ddd, 1, J = 2, 13, 15 Hz), 3.45 (s, 3), 2.89 (m, 1), 2.58 (d, 1, J = 14 Hz), 2.48 (d, 1, J = 14 Hz), 2.48 (m, 1), 2.16 (m, 1); isomer B 6.78 (dd, 1, J = 1, 10 Hz), 6.03 (d, 1, J = 10 Hz), 3.85 (s, 3), 3.45 (s, 3), 3.35 (ddd, 1, J = 2, 12, 14 Hz), 3.11 (m, 1), 2.88 (m, 1), 2.59 (d, 1, J = 14 Hz), 2.49 (d, 1, J = 14 Hz), 2.37 (m, 1); isomer C 6.62 (dd, 1, J = 1, 10 Hz), 6.27 (d, 1, J = 10 Hz), 3.85 (s, 3), 3.48

(ddd, 1, J = 2, 11, 13 Hz), 3.45 (s, 3), 2.58 (d, 1, J = 14 Hz), 2.32 (d, 1, J = 14 Hz), 2.55 (m, 1), 2.5 (m, 1), 1.85 (ddd, 1, J = 2, 11, 15 Hz); isomer D 6.69 (d, 1, J = 10 Hz), 6.01 (d, 1, J = 10 Hz), 3.83 (s, 3), 3.44 (s, 3), 3.30 (m, 1), 3.01 (m, 1), 2.65 (m, 1), 2.5 (d, 1, J = 14 Hz), 2.36 (d, 1, J = 14 Hz), 2.11 (m, 1); $^{13}C(^1H)$ NMR δ 174.7, 174.4, 174.2, 174.0, 166.70, 166.69, 166.63, 135.3, 135.1, 134.5, 134.2, 133.6, 133.4, 132.9, 131.0, 103.4, 103.1, 103.0, 53.62, 53.58, 53.52, 53.42, 53.38, 45.8, 45.1, 45.0, 44.5, 44.0, 43.9, 43.8, 43.6, 42.9, 41.3, 41.4, 25.8, 25.2, 23.3, 22.4; ^{13}C(DEPT δ 135.3 (d), 135.1 (d), 134.5 (d), 134.2 (d), 133.6 (d), 133.4 (d), 132.9 (d), 131.0 (d), 53.62 (q), 53.58 (q), 53.52 (q), 53.42 (q), 53.38 (q), 45.8 (t), 45.1 (t), 45.0 (t), 43.8 (t), 43.6 (t), 42.9 (t), 41.8 (t), 41.4 (t), 25.8 (t), 25.2 (t), 23.3 (t), 22.4 (t); HRMS calcd for $C_{11}H_{14}O_6S$ m/z 274.049, found 274.051.

Methyl 1-Oxo-3-methoxy-2-oxa-7-thiaspiro[4.5]deca-5,8-diene-3-carboxylate (18). To a solution of 29 mg (0.11 mmol) of sulfoxide **17** and 41 μL (0.23 mmol) of ethyldiisopropylamine in 0.5 mL of CH_2Cl_2 at 0 °C and under nitrogen was added 41 μL (0.21 mmol) of trimethylsilyl trifluoromethanesulfonate dropwise, and the solution was stirred under nitrogen at 0 °C for 2 h. The mixture was diluted with 10 mL of dichloromethane and washed with 2 mL each of saturated $NaHCO_3$ and brine, dried, and evaporated. The residue was chromatographed (3:1 hexane/EtOAc) to afford 9.6 mg (34% yield) of the didehydro derivative **18** as a clear oil: ^1H NMR δ 6.42 (dd, 1, J = 10, 2.6 Hz), 6.35 (dd, 1, J = 10, 2.6 Hz), 5.76 (dd, 1, J = 10, 1.8 Hz), 5.47 (dd, 1, J = 10, 1.8 Hz), 3.86 (s, 3), 3.47 (s, 3), 2.55 (d, 1, J = 14 Hz), 2.37 (d, 1, J = 14 Hz); ^{13}C NMR δ 174.7, 167.3, 121.6, 120.1, 119.6, 118.7, 103.3, 53.4, 53.2, 49.6, 45.3.

Methyl 1-Oxo-3-methoxy-2-oxa-7-thiaspiro[4.5]deca-5,8-diene-3-carboxylate (19). To a solution of 3.6 mg (.014 mmol) of diene **18** in 250 μL of CH_2Cl_2 under nitrogen at −78 °C was added a solution of 2.9 mg (.017 mmol) of *m*-chloroperbenzoic acid in 200 μL of CH_2Cl_2 dropwise, and the solution was stirred at −78 °C for 25 min and then allowed to warm to 21 °C. After dilution with 4 mL of CH_2Cl_2, the mixture was washed with 0.5 mL each of saturated $NaHCO_3$ and brine, dried, and evaporated to afford 3.9 mg of sulfoxide **19** as a 2:1 mixture of sulfoxide isomers contaminated with 16% of the sulfone arising from overoxidation: ^1H NMR δ isomer A 6.95 (dd, 1, J = 2.6, 10 Hz), 6.85 (dd, 1, J = 2.6, 10 Hz), 6.45 (dd, 1, J = 1.3, 10 Hz), 6.08 (dd, 1, J = 1.3, 10 Hz), 3.92 (s, 3), 3.50 (s, 3), 2.83 (d, 1, J = 14 Hz), 2.78 (d, 1, J = 14 Hz); isomer B δ 6.80 (dd, 1, J = 3.2, 11 Hz), 6.73 (dd, 1, J = 3.2, 11 Hz), 6.61 (dd, 1, J = 2.6, 11 Hz), 6.27 (m, 1), 3.92 (s, 3), 3.53 (s, 3), 2.74 (d, 1, J = 14 Hz), 2.70 (d, 1, J = 14 Hz); sulfone δ 6.91 (dd, 1, J = 2.6, 9 Hz), 6.85 (m, 1), 6.49 (dd, 1, J = 1.3, 10 Hz), 6.27 (m, 1), 3.90 (s, 3), 3.52 (s, 3), 2.54 (d, 1, J = 14 Hz), 2.40 (d, 1, J = 14 Hz). This material was not further characterized in view of the fact that no defined compound could be isolated from its hydrolysis product(s).

Enzyme Assays. Prephenate Purity. Purity of the prephenate employed (Sigma) was determined by conversion to phenylpyruvate according to the method of Zalkin.[21]

Enzyme Purification and Assay. The procedures of Davidson[18] were employed for the purification and assay of chorismate mutase/prephenate dehydratase. The enzyme was isolated from *E. coli*, strain JP492, which was a gift from Professor John F. Morrison (Canberra).

Preincubation Studies. Stock enzyme solution (in 20 mM Tris pH 8.2, 1 mM EDTA, 1 mM dithioerythritol, 0.02% sodium azide) was diluted with an equal amount of 20 mM inhibitor solution (in 20 mM Tris pH 8.2, 20 mM mercaptoethanol, 1 mM EDTA, 0.01% bovine serum albumin) and incubated at 37 °C. Aliquots were removed at 15-min intervals over the course of 1.5 h and assayed for activity. A control in which enzyme was diluted with buffer solution containing no inhibitor was also incubated alongside the inhibitor solution.

Competitive Inhibition Studies. Stock substrate solution (1 mM prephenate in 20 mM Tris pH 8.2, 1 mM EDTA, 0.01% bovine serum albumin, 40 mM mercaptoethanol) was diluted with an equal amount of inhibitor solutions of varying concentrations (in 20 mM Tris pH 8.2, 1 mM EDTA, 0.01% bovine serum albumin) and equilibrated at 37 °C for 5 min. Enzyme was added and the solution was incubated an additional 5 min before being quenched with hydroxide. Two inhibitor incubations were run along with a blank to which no enzyme was added.

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Registry No. **4**, 119948-17-3; **5**, 119948-18-4; **6**, 119948-19-5; **7**, 119948-20-8; **8**, 119948-21-9; **9**, 4469-60-7; **10**, 119948-04-8; **11**, 119948-05-9; **12**, 119948-06-0; **13**, 119948-07-1; **14**, 119948-08-2; *trans*-**15**, 119948-09-3; *cis*-**15**, 119948-13-9; *cis*-**16**, 119948-10-6; *trans*-**16**, 119948-16-2; **17** (isomer 1), 119948-03-7; **17** (isomer 2), 120020-84-0; **17** (isomer 3), 120020-85-1; **17** (isomer 4), 120020-86-2; **18**, 119948-11-7; *cis*-**19**, 119948-12-8; *trans*-**19**, 119948-14-0; **19** sulfone, 119948-15-1; K_2S, 1312-73-8; prephenate dehydratase, 9044-88-6; α-ketoglutamic acid, 328-50-7; 2-(2-iodoethoxy)tetrahydropyran, 96388-83-9; dihydropyran, 110-87-2; 2-iodoethanol, 624-76-0.

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Total Synthesis of Leukotriene B_4 [(+)-LTB_4] and Homo-LTB_4 from D-Mannitol

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A convergent total synthesis of leukotriene B_4 and its homo analogue has been carried out via enantiomerically pure α-hydroxy aldehydes, chiral key intermediates obtained from D-mannitol and connected at a four carbon atom interval by Wittig reactions.

In the last few years, there has been considerable interest in hydroxylated eicosatetraenoic acids derived from arachidonic acid by lipoxygenase metabolic pathways. Leukotriene B_4 biosynthetized via the 5-lipoxygenase pathway[1] is one of the most potent chemotactic agents produced by human polymorphonuclear leukocytes. Implicated as mediator in inflammation and allergic reactions,[2] LTB_4 is also supposed to play an important role in immunobiological reactions.[3]

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