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STEREOCONTROLLED SYNTHESIS OF HIGHLY FUNCTIONALIZED CYCLOHEXENES. A SHORT SYNTHESIS OF A CHORISMIC ACID PRECURSOR†

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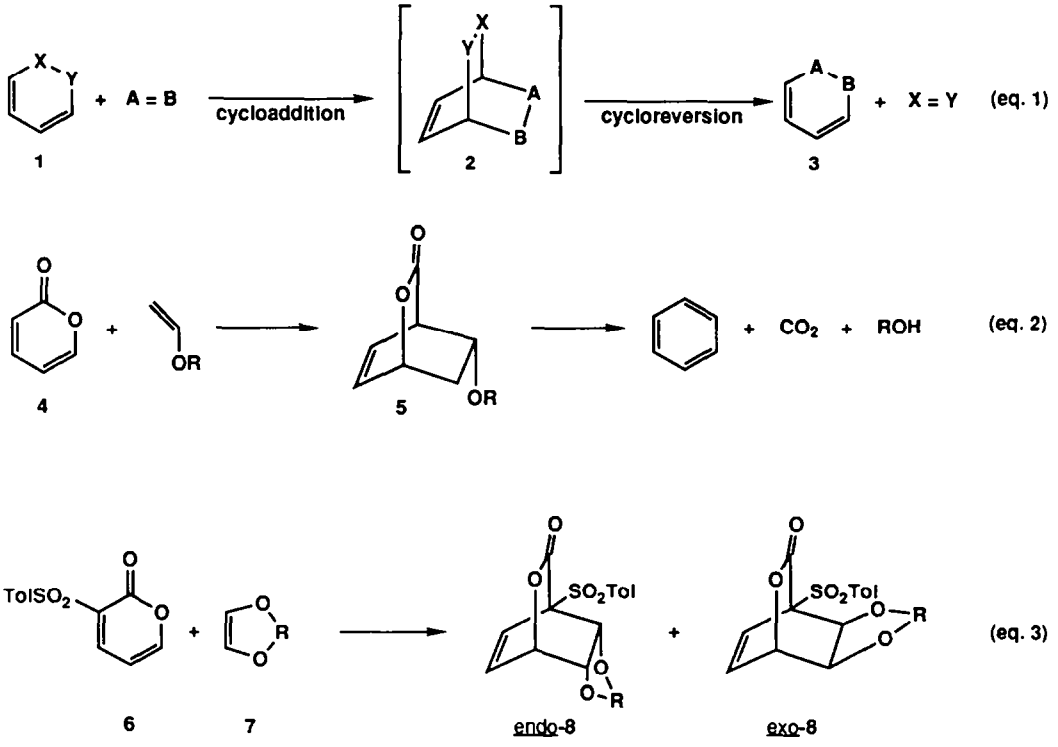
Abstract– A convenient and mild thermal procedure has been developed for stereoselective 2+4-cycloadditions of electron-rich 1,2-dioxygenated olefins **7** to electron-deficient 3-sulfonyl-2-pyrone **6** allowing isolation of the structurally and stereochemically rich initial bicyclic adducts **8**. These bicyclic adducts are shown to be useful building units as exemplified by a very short and high-yield preparation of a chorismic acid precursor.

2+4-Cycloadditions of heteroaromatics **1** with dienophiles A=B produce bicyclic intermediates **2** that often undergo cycloreversion to form dienes **3** and fragments X=Y (eq. 1).[1] For example, 2-pyrones (e.g. **4**) react at high temperature with electron-rich dienophiles such as vinyl ethers to form cycloadducts **5** that spontaneously cyclorevert with loss of CO_2; the cyclohexadienes so produced typically aromatize in situ via extrusion of ROH (eq. 2).[2] Such inverse-electron-demand Diels-Alder cycloadditions between structurally diverse 2-pyrones and various electron-rich dienophiles have been developed in recent years into an effective protocol for preparing several classes of biologically important aromatic compounds.[3] With only a few exceptions,[4] attempts to isolate the non-aromatic bicylic intermediates such as **5** have failed due to the relatively facile loss of CO_2 under the vigorous reaction conditions (typically $\geq$ 150°C) required for the initial 2+4-cycloadditions. This situation is unfortunate; rigid, bridged, bicyclic lactones such as **5** are structurally rich building units having fixed and useful stereochemical relationships among the various functional groups. We have found that when an electron-withdrawing sulfinyl[5] or sulfonyl[6] substituent (but not an alkoxycarbonyl group)[2] is attached to the 3-position of a 2-pyrone, then cycloadditions with electron-rich vinyl ethers and vinyl thioethers are facilitated so that reaction conditions are sufficiently mild as to allow isolation of the desired initial bicycloadducts in excellent yields. To broaden the synthetic utility of this kind of inverse-electron-demand Diels-Alder cycloaddition for highly stereocontrolled construction of functionalized cyclohexenes, we report here results on 2+4-cycloaddition of electron-deficient pyrone sulfone **6**[7] with more highly functionalized electron-rich 1,2-dioxygenated olefins **7** (eq. 3).

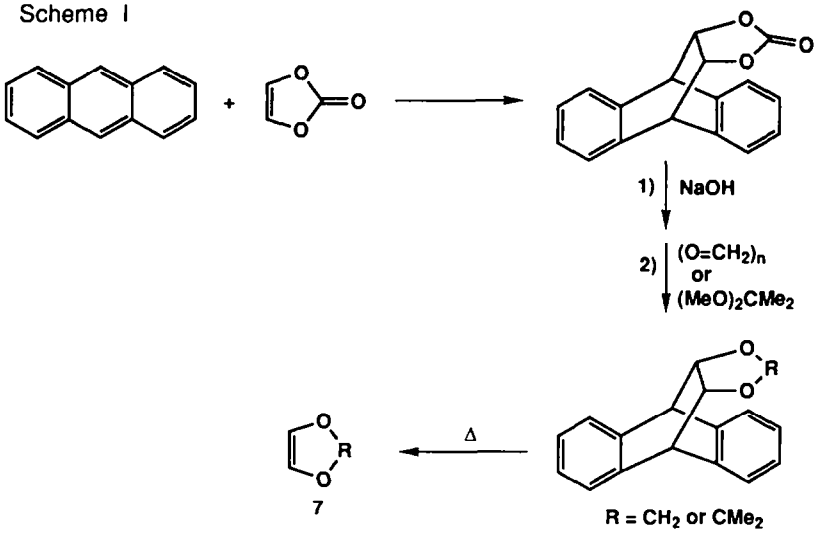
†Dedicated to Professor David Ollis on the occasion of his 65th birthday.



Results and Discussion

Several 1,2-dioxygenated olefins **7** were prepared to explore two questions: relative reactivity and stereochemical outcome of cycloaddition. Preparation of 1,2-dioxygenated olefins **7** via Scheme I using a modified literature procedure,[8a] while at first tedious and often capricious, ultimately became easy and reliable when the final step was performed first with mild heating (10-15 minutes) and then with vigorous heating of the anthracene cycloadduct and with efficient trapping of the volatile dioxoles produced (see experimental section for details). Typical overall yields in Scheme I were 25-35%, and several grams of dioxoles **7** were prepared routinely at one time and were stored at -20°C for several weeks without decomposition. Scheme I, like the major subject of this publication, illustrates additional utility of 2+4-cycloaddition (and cycloreversion) chemistry.

Scheme I



The relative reactivity of 1,2-dioxygenated olefins **7** toward pyrone **6** was expected for steric as well as electronic reasons to be less than that of mono-oxygenated olefins.[6] Indeed whereas vinyl ethers cycloadded to pyrone **6** smoothly at room temperture,[6] dioxoles **7** and pyrone **6** were unreactive at 25°C for several days. Based on this lack of reactivity at ambient temperature and on literature precedent,[3] it was not clear at all that any thermal conditions could be found that would allow cycloaddition of dioxoles **7** with pyrone **6** without spontaneous cycloreversion of the initial bicyclic lactone adducts (i.e. loss of CO_2). It was gratifiying, therefore, to find that after 1.5-3 days at 60-80°C bicyclic adducts could in fact be isolated in good yields (Table I). When cycloaddition was performed at 105°C, however, adduct decomposition was evident. Unsubstituted dioxole **7** (R = CH_2) was more reactive than 2,2-dimethyldioxole (**7**, R = CMe_2). For example, whereas only 36 hours at 80°C were necessary for complete reaction of the unencumbered parent dioxole with pyrone sulfone **6**, 69 hours were needed for complete reaction with dimethydioxole **7**. Vinylene carbonate did not add to pyrone sulfone **6** even under forcing conditions. Attempts to use some Lewis acids (e.g. zinc dibromide, [5b], [9a], zinc triflate[9b]) to promote cycloaddition between dioxoles **7** and pyrone sulfone **6** were not promising; decomposition especially of dimethyldioxole **7** upon exposure to the zinc Lewis acids was apparent. Although $Eu(hfc)_3$[10] did not cause decomposition of dimethyldioxole **7**, use of this Lewis acid offered no advantage. Likewise, Yamamoto's aluminum-based "MAD" Lewis acid was not effective in promoting cycloaddition.[11]

Concerning stereochemistry, as expected from examination of molecular models, both unsubstituted dioxole **7** and its dimethyl analog gave endo-addducts **8** in which the dioxole oxygen atoms are trans to the lactone bridge with very good stereochemical selectivity (Table I). endo-Adducts **8** were distinguished from exo-adducts **8** by their characteristic 400 MHz ^{1}H NMR spectra; the olefinic protons in endo-**8** regularly appeared as two multiplets with one centered at 6.6 δ and one centered at 6.8 δ, whereas exo-**8** showed the same protons as a noticeably closer pair of multiplets centered at 6.67 δ and at 6.74 δ. Ultimately the assignment of structure to endo-**8** was confirmed by correlation with chorismic acid (see below). Comparable stereochemical results were obtained when the cycloaddition was performed at room temperature but under a pressure of 11-13 Kbar.[12] More encumbered 2,2-diisopropyldioxole (**7**, R = i-Pr$_2$) was considerably less reactive than dimethyldioxole **7**, and even after 5 days at 25°C and 12.5 Kbar this diisopropyldioxole gave only 20% endo-**8**, R = i-Pr$_2$, with recovery of a substantial amount of reactant pyrone **6**. Of note also is that the pyrone sulfoxide[5] corresponding to sulfone **6** was considerably less reactive than sulfone **6** and did not show much reaction with dimethyldioxole **7** at room temperature even under 11-13 Kbar of pressure.

Table I. Cycloaddition of pyrone **6** and enediol **7**

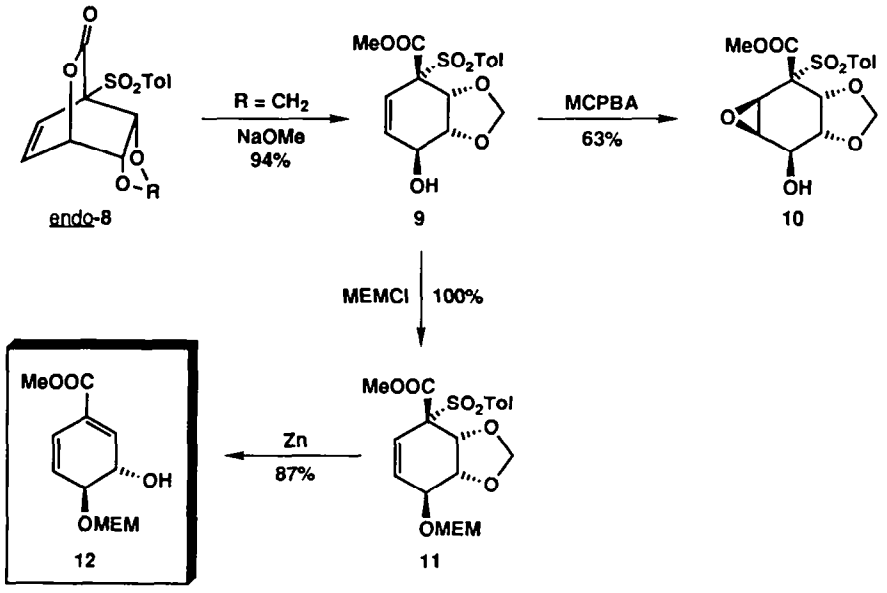
enediol **7** R	conditions	% of yield of isolated cycloadducts endo-**8**	exo-**8**
CH_2	36 hr, 80°C	78%	15%
	11-12.5 Kbar, 25°C	86%	14%
CMe_2	64 hr, 60°C	63%	14%[a]
	69 hr, 80°	77%	23%
$C(i\text{-}Pr)_2$	12.5 Kbar, 25°C	20%	0%

[a] 19% of reactant pyrone **6** was recovered

Bridged, bicyclic lactones **8** are rigid, highly oxygenated cyclohexenes capable of undergoing various stereocontrolled transformations such as olefin oxygenation (e.g. epoxidation, dihydroxylation), allylic carboxylate displacement,[13] and lactone opening. We illustrate some of these possibilities with the following results.

Room temperature methanolysis[14] of the lactone bridge of dioxole cycloadduct endo-**8** proceeded smoothly to form cyclohexene **9** (Scheme II) in which every carbon atom of the six-membered carbocycle is functionalized! m-Chloroperbenzoic acid epoxidation of allylic cyclohexenol **9** gave cyclohexane **10** that is stereospecifically pentaoxygenated and that is rich in possibilities for further manipulations. Protection of the free hydroxyl group in cyclohexenol **9** as a MEM ether[15] and then zinc-promoted reductive cleavage of the sulfonyl group caused spontaneous unzipping of the dioxolane functionality to produce cyclohexadiene **12**, identical in all respects to a sample prepared previously via an independent route by us[5b] and by the Cornell group.[16] This cyclohexadiene monoprotected trans-diol has been converted previously directly into (+)-chorismic acid, a key intermediate in the shikimate biosynthetic pathway that bacteria and lower plants use to transform carbohydrates into aromatic compounds.[17]

Scheme II



In summary, efficient preparation of 1,2-dioxygenated olefins **7** on multigram scale and inverse-electron-demand cycloadditions of these electron-rich dioxoles **7** to electron-deficient pyrone sulfone **6** have led via a convenient and mild thermal procedure to stereoselective formation of useful, rigid, polyoxygenated, bicyclic lactones **8**. The relative ease of these cycloadditions might reasonably be due to the powerful inductively electron-withdrawing nature of the sulfonyl group[18] irrespective of its

orientation relative to the pyrone ring, especially in contrast to the corresponding pyrone carboxylate esters[2] in which the full resonance electron-withdrawing effect of the carboxyl group requires coplanarity of this group with the pyrone nucleus. Finally, chorismic acid intermediate **12** was prepared from pyrone sulfone **6** in only 4 steps and in 60-65% overall yield; this sequence represents the shortest synthetic approach to chorismic acid on record. We are continuing to study applications of this methodology for direct and stereocontrolled preparation of other highly functionalized cyclohexenes.

Acknowledgment

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Experimental

General. Tetrahydrofuran was distilled from sodium-benzophenone ketyl, and methylene chloride was distilled from calcium hydride immediately prior to use. Chloroform and diisopropylamine were distilled from calcium hydride. Methanol was distilled from magnesium/iodine. All reactions that were performed under an inert atmosphere were equipped with flame-dried glassware. FT-IR spectra were determined as solutions in chloroform using a Perkin-Elmer Model 1600 FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were determined as solutions in deuterated chloroform (unless noted otherwise) on a Varian XL-400 spectrometer operating at 400 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Coupling constants are given in hertz (Hz). High resolution mass spectra were obtained on a two sector high resolution VG-70S mass spectometer run at 70 eV. Elemental analyses were performed by Atlantic Microlab, Atlantic, GA. A Leco Corp. Model #PG-200-HPC 13 Kbar apparatus was used for the high-pressure experiments.

Preparation of Dioxoles 7.

A. Anthracene and Vinylene Carbonate Cycloadduct.

A 500 mL round-bottomed flask was charged with 54.6 g (0.31 mol) of anthracene, 26.4 g (0.31 mol) of vinylene carbonate, and 100 mL of 1,2-dichlorobenzene. This mixture was refluxed for 1.5 days. After cooling the reaction

mixture to room temperature 200 mL of hexane was added and this mixture stirred for 30 minutes. This was then filtered and the solid was washed with hexane until no color persisted in the organic solvent to give 76.0 g (0.29 mol, 93%) of light brown crystalline cycloadduct, m.p. 252-255°C, literature[8b] m.p. 253-254°C; ^{1}H NMR δ 7.23-7.42 (m, 8H), 4.91 (s, 2H), 4.72 (s, 2H).

B. Hydrolysis of Carbonate Cycloadduct.

A 2 liter round-bottomed flask was charged with 69.0 g (0.26 mol) of the carbonate cycloadduct, 1 liter of methanol, 150 mL of water, and 19.5 g (0.49 mol) of sodium hydroxide. The reaction mixture was refluxed overnight, cooled to room temperature, acidified with 2N hydrochloric acid, and then filtered. The diol was recrystallized from methanol/water to give 57.2 g (0.24 mol, 92%) of the solid diol, m.p. 202-204°C, literature[8b] m.p. 203°C; ^{1}H NMR δ 7.15-7.40 (m, 8H), 4.42 (s, 2H), 4.07 (s, 2H), 2.13 (bs, 2H).

C. Acetalization of Diol.

A 500 mL round-bottomed flask was charged with 14.2 g (0.060 mol) of the diol, 75 mg of *p*-toluenesulfonic acid, 4.4 g of paraformaldehyde, and 150 mL of benzene. The reaction mixture was then refluxed, with the water being removed by a Dean Stark trap, for 2.5 days. After the reaction mixture had cooled it was diluted with methylene chloride, washed with aqueous sodium bicarbonate, washed with water, dried over magnesium sulfate, and the solvent removed. This residue was then recrystallized from hexane to give 12.0 g (47.9 mmol, 80%) of the white dioxolane product, m.p. 241-242°C, literature[8a] m.p. 239-241°C; ^{1}H NMR δ 7.12-7.37 (m, 8H), 4.73 (s, 1H), 4.58 (t, J=1.6 Hz, 2H), 4.47 (t, J=1.6 Hz, 2H), 4.10 (s, 1H).

D. Ketalization of Diol.

A 250 mL round-bottomed flask was charged with 12.3 g (51.6 mmol) of the diol, 75 mL of 2,2-dimethoxypropane, and 0.5 g of *p*-toluenesulfonic acid. This was stirred for 24 hours at room temperature. The reaction mixture was diluted with 500 mL of methylene chloride, washed with 5% aqueous sodium bicarbonate (2 x 75 mL), washed with water, dried over magnesium sulfate, and the solvent removed. The residue was recrystallized from hexane to afford 13.6 g (48.9 mmol, 95%) of acetonide product as white needles, m. p. 137-139°C, literature[8a] m.p. 131-137.5°C; ^{1}H NMR δ 7.13-7.34 (m, 8H), 4.52-4.53 (m, 2H), 4.47 (t, J=1.9 Hz, 2H), 1.22 (s, 3H), 0.67 (s, 3H).

E. Cracking of the Anthracene Cycloadducts.

To a flame-dried 100 mL 24/40 (standard-taper) round-bottomed flask,

containing the anthracene cycloadduct and a few crystals of 2,6-di-*tert*-butyl-4-methyltoluene (BHT), a Vigreux distillation head containing a short water condenser was adjoined. The condenser was equipped with a bent vacuum adapter connected to a 10 mL 14/20 (standard-taper) pear-shaped flask (*trap #1*). A piece of tygon tubing was attached to the outlet on the vacuum adapter and run to a U-tube (*trap #2*). A nitrogen line was attached to the top of the Vigreux distillation head and a slow stream of nitrogen passed through the apparatus which was then flame-dried. After cooling, both traps were placed in a -78°C bath (Dry Ice/acetone). Under the slow stream of nitrogen the solid was gently heated with a bunsen burner (ca. 10-15 minutes) until rapid boiling occurred at which time vigorous heating was employed until no more dioxole was distilled (ca. 45 min.-1 hour). Caution must be taken so that sublimed material does not enter the water condenser. To achieve this the flame may need to be removed periodically.

F. Preparation of 1,3-Dioxole 7, R = CH_2.

In a 100 mL round-bottomed flask 16.00g (63.9 mmol) of the anthracene cycloadduct (R=CH_2), containing a few crystals of BHT, was cracked in the manner described above. The clear yellow liquids from *trap #1* and *trap #2* were stored over BHT and sodium carbonate at -20°C overnight. The fractions were combined and passed through a short path distillation apparatus to give 2.14g (29.7 mmol, 46%) of the colorless dioxole. The dioxole was stored at -20°C over sodium carbonate for a period of weeks without polymerization. ^{1}H NMR δ 6.38 (s, 2H), 5.57 (s, 2H); HRMS, *m/z* calcd for $C_3H_4O_2$ 72.0211, found 72.0212.

G. Preparation of 2,2-Dimethyl-1,3-Dioxole 7, R = CMe_2.

In a 100 mL round-bottomed flask 22.18g (79.7 mmol) of the anthracene cycloadduct (R=CMe_2), containing a few crystals of BHT, was cracked in the manner described above. The clear yellow liquid from *trap #1* was stored over BHT and sodium carbonate at -20°C then passed through a short path distillation apparatus to give 4.05g (40.5 mmol, 51%) as a colorless liquid. The colorless dioxole from *trap #2* (1.20g, 12.0 mmol, 15%) was used without further purification. The dioxole was stored at -20°C over sodium carbonate for a period of weeks without polymerization (total yield: 52.5 mmol, 66%). ^{1}H NMR δ 6.18 (s, 2H), 1.52 (s, 6H).

Cycloaddition of Pyrone Sulfone 6 with Parent Dioxole 7.

A. Thermal Conditions.

A 1.5 mL hydrolysis tube (Kontes, cat. #896860-2860) was charged with 73.8 mg (0.30 mmol) of 3-*p*-toluenesulfonyl-2-pyrone (**6**),[7] 15.4 mg of barium carbonate, 171.2

mg (2.4 mmol, 8.1 eq.) of 1,3-dioxole and 0.7 mL dry methylene chloride. The tube was sealed under nitrogen and warmed to 80°C for 36.5 hours. The reaction mixture was cooled, diluted with methylene chloride, filtered and the solvent removed under vacuum. This was then purified by preparative tlc (50% ethyl acetate/hexane) to give 74.5 mg (0.23 mmol, 78%) of pure endo-**8** Diels-Alder adduct and 14.3 mg (0.04 mmol, 15%) of pure exo-**8** Diels-Alder adduct both as white solids. Endo-**8**: Rf = 0.44 (50% ethyl acetate/hexane), mp 167-169°C. ^{1}H NMR δ 8.07 (d, J=8 Hz, 2H), 7.31 (d, J=8 Hz, 2H), 6.83 (dd, J=8, 1.5 Hz, 1H), 6.63 (dd, J=8, 3 Hz, 1H), 5.27 (m, 1H), 5.18 (s, 1H), 4.95 (s, 1H), 4.77 (d, J=5 Hz, 1H), 4.71 (dd, J= 6, 2 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR δ 163.35, 146.04, 133.19, 131.25, 130.95, 129.50, 127.64, 99.41, 77.0 (shoulder of center $CDCl_3$ resonance), 74.06, 73.0, 72.61, 21.78; FT-IR 3028, 2928, 1776, 1598, 1374, 1333, 1220, 1215, 1210, 1159 cm^{-1}. *Anal.* Calcd for $C_{15}H_{14}O_6S$: C, 55.89; H, 4.38; S, 9.95. Found: C, 55.80; H, 4.41; S, 9.88. Exo-**8**: Rf = 0.31 (50% ethyl acetate/hexane), mp 249-251°C upon gradual warming, the solid became brown at ca. 190°C. ^{1}H NMR δ 8.10 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.0 Hz, 2H), 6.74 (dd, J=8, 2 Hz, 1H), 6.68 (dd, J=8.0, 5.2 Hz, 1H), 5.25-5.27 (m, 1H), 5.18 (s, 1H), 4.95 (s, 1H), 4.93 (d, J=7.6 Hz, 1H), 4.46 (dd, J= 8, 2 Hz, 1H), 2.46 (s, 3H); FT-IR 3020, 1779, 1598, 1520, 1328, 1224, 1220, 1216, 1212, 1160, 1129, 1094 cm^{-1}. HRMS, *m/z* calcd for $C_{15}H_{14}O_6S$ 322.0511, found 322.0513.

B. High Pressure Conditions.

A 12 cm piece of 3/8" heat shrinkable teflon tubing (Ace Glass, cat. #12685-40) was sealed on one end with a glass plug by using a heat gun. To this 111.0 mg (0.44 mmol) of pyrone sulfone **6**, 167 mg (2.3 mmol, 15.3 eq.) of 1,3-dioxole, 9.5 mg of barium carbonate, and 3 mL of dry methylene chloride was added. The open end of tubing was then sealed in a similar fashion with a second glass plug. This 'sealed tube' was then pressurized at 11.0-12.5 Kbar at room temperature for 4 days. The reaction mixture was diluted with 100 mL of methylene chloride, washed with water, and the aqueous portion back extracted with methylene chloride. The organic portions were mixed, dried over magnesium sulfate, the solvent concentrated on a rotary evaporator, and the residue was purified by preparative tlc (50% ethyl acetate/hexane) to give 123 mg (0.38 mmol, 86%) of the endo-**8** Diels-Alder adduct and 20 mg (0.06 mmol, 14%) of the exo-**8** Diels-Alder adduct both as white solids.

Cycloaddition of Pyrone Sulfone 6 with Dimethyldioxole 7 under Thermal Conditions.

A 5 mL hydrolysis tube (Kontes cat. #896860-4010) was charged with 39.6 mg (0.16 mmol) of pyrone sulfone **6**, 6.5 mg of barium carbonate, 515.7 mg (5.2 mmol, 33 eq.) of 2,2-dimethy-1,3-dioxole and 3.2 mL of dry methylene chloride. The tube was

sealed under nitrogen and warmed to 60°C for 64 hours. The reaction was cooled, diluted with methylene chloride, filtered, and the solvent removed under vacuum. This yellow oil was purified by column chromatography (silica gel, elution gradient, 100% hexane-50% ethyl acetate/hexane) to give endo-**8** adduct (Rf=0.54, 50% ethyl acetate/hexane), exo-**8** adduct (Rf=0.46, 50% ethyl acetate/hexane), and recovered starting material. After removal of the solvent, each of the three fractions was passed through a plug of silica gel twice to remove polymeric material to give 35.1 mg of the endo-**8** adduct (0.10 mmol, 63%), 8.0 mg of the exo-**8** adduct (0.02 mmol,14%), and 7.6 mg of recovered sulfone pyrone **6** (0.03 mmol, 19%). Endo-**8**: m. p; 171-172°C, ^{1}H NMR δ 8.05 (d, J=8 Hz, 2H), 7.31 (d, J=8 Hz, 2H), 6.78 (dd, 1H, J=8,2 Hz, 1H), 6.11 (m, 1H), 5.20 (m, 1H), 4.89 (dd, J=6, 2 Hz, 1H), 4.74 (dd, J=8,2 Hz, 1H), 2.45 (s, 3H), 1.55 (s, 3H), 1.39 (s, 3H). *Anal.* Calcd for $C_{17}H_{18}O_6S$: C, 58.27; H, 5.18; S, 9.15. Found: C, 58.19; H, 5.11; Exo-**8**: m.p. 166-167°C; ^{1}H NMR δ 8.08 (d, J=8 Hz, 2H), 7.33 (d, J=8 Hz, 2H), 6.69 (dd, 1H, J=8,2 Hz, 1H), 6.63 (m, 1H), 5.14 (m, 1H), 4.93 (dd, J=6, 2 Hz, 1H), 4.48 (dd, J=8,2 Hz, 1H), 2.44 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H). *Anal.* Calcd for $C_{17}H_{18}O_6S$: C, 58.27; H, 5.18; S, 9.15. Found: C, 58.26; H, 5.28; S, 9.45.

Methanolysis of Lactone endo-8, R=CH_2.

To a 10 mL flame-dried round-bottomed flask 17.2 mg (0.053 mmol) of the lactone, endo-**8**, R = CH_2, 1.5 mL of dry methylene chloride, and 1.0 mL of dry methanol were stirred under nitrogen. This was then cooled to 0°C and 10 ml of a freshly prepared sodium methoxide solution (25.7 mg of sodium in 5.0 ml of dry methanol) was added and stirred at 0°C for 50 minutes. The reaction was then allowed to stir at room temperature overnight. The reaction was diluted with methylene chloride, quenched with a drop of saturated aqueous ammonium chloride, dried over magnesium sulfate, and then filtered. Concentration of the solvent followed by column chromatography purification(gradient elution 50% ethyl acetate/hexane-100% ethyl acetate) afforded 17.8 mg (0.050 mmol, 94%) of the hydroxy ester **9** as a white solid, Rf = 0.33 (diethyl ether), mp 159.5-162°C. ^{1}H NMR δ 7.72 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 6.26 (dd, J=10.0, 2.8 Hz, 1H), 5.96 (dd, J=10.4, 1.6 Hz, 1H), 5.32 (s, 1H), 4.97 (s, 1H), 4.89 (d, J=8.0 Hz, 1H), 4.76 (bs, 1H), 4.23 (dd, J=8.0, 4.8 Hz, 1H), 3.78 (s, 3H), 2.53 (bs, 1H), 2.45 (s, 3H); ^{13}C NMR δ 167.27, 145.50, 136.99, 134.63, 130.94, 129.08, 122.58, 95.26, 80.39, 75.64, 74.77, 67.84, 53.83, 21.74; FT-IR 3608, 3028, 2955, 1735, 1597, 1436, 1328, 1254, 1146, 1095 cm^{-1}. *Anal.* Calcd for $C_{16}H_{18}O_7S$: C, 54.23; H, 5.12; S, 9.05. Found: C, 54.32; H, 5.14; S, 9.02.

Epoxidation of Allylic Alcohol 9.

To a 10 mL flame-dried round-bottomed flask 11.7 mg (0.033 mmol) of the alkene **9** and 1.0 mL of dry methylene chloride were added under nitrogen. This was then cooled to 0°C and 10.5 mg (0.05 mmol, 1.5 eq.) of 80-85% *m*-chloroperbenzoic acid was added and the reaction mixture slowly warmed to room temperature (25°C) and then stirred overnight. The reaction mixture was then diluted with methylene chloride, washed with saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. Concentration of the solvent and purification by preparative tlc (75% ethyl acetate/hexane) afforded 7.7 mg (0.021 mmol, 63%) of the white solid epoxide **10** and 2.4 mg (0.007 mmol, 21%) of recovered starting alkene **9**. Rf=0.59 (75% ethyl acetate/hexane); ^{1}H NMR δ 7.73 (d, J=8.4 Hz, 2H), 7.34 (d, J=8.4 Hz, 2H), 5.35 (s, 1H), 4.94 (d, J=6.4 Hz, 1H), 4.75 (s, 1H), 4.59 (d, J=8.8 Hz, 1H), 4.10 (m, 1H), 3.94 (d, J=4.0 Hz, 1H), 3.77 (s, 3H), 3.58 (d, J=4.0 Hz, 1H), 2.70 (bs, 1H), 2.45 (s, 3H); FT-IR 3600, 3006, 2938, 1739, 1435, 1224, 1220 cm^{-1}; HRMS, *m/z* calcd for $C_{16}H_{18}O_8S$ (M^+-1) 369.0644, found 369.0644.

Preparation of MEM-ether 11.

In a flame-dried 25-ml round-bottomed flask, 64.5 mg (0.18 mmol) of the hydroxy ester **9** was dissolved in 7.5 mL of dry chloroform under nitrogen. This reaction mixture was cooled to 0°C and 0.95 mL (5.5 mmol, 30 eq.) of diisopropylethylamine was added. After stirring for 15 minutes, 0.62 mL (5.5 mmol, 30 eq.) of 2-methoxyethoxymethyl chloride (MEMCl) was added and the resulting solution was stirred an additional 15 minutes at 0°C. After warming to room temperature the mixture was refluxed for 13 hours (while heating, the reaction mixture turned orange then brown). The reaction flask was allowed to cool to room temperature and then diluted with 150 mL of chloroform, washed with sat. sodium bicarbonate (1 x 10 ml), washed with water (2 x 20 ml), dried over magnesium sulfate, and the solvent removed under vacuum. The residue was passed through a plug of silica gel and then purified by using a chromatotron (2 mm rotor, 75%-100% ethyl acetate/hexane gradient) to afford the MEM ether **11** in quantitative yield as a colorless oil, Rf = 0.56 (75% ethyl acetate/hexane). ^{1}H NMR δ 7.75 (dd, J=8.4, 1.6 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H), 6.29 (dd, J=10.1, 3.7 Hz, 1H), 6.14 (dt, J=10.1, 0.8 Hz, 1H), 5.24 (s, 1H), 4.90 (d, J=7.6 Hz, 1H), 4.88 (s, 1H), 4.76 (d, J=2.8 Hz, 2H), 4.55 (dt, J=3.6, 1.2 Hz, 1H), 4.31 (dd, J=7.6, 4.0 Hz, 1H), 3.69 (s, 3H), 3.67 - 3.72 (m, 2H), 3.55 - 3.57 (m, 2H), 3.39 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (DMSO) δ 166.29, 145.28, 134.75, 134.42, 130.36, 129.27, 123.58, 94.06, 93.29, 77.48, 74.87, 74.27, 71.06, 70.18, 66.56, 58.04, 53.31, 21.15; FT-IR 3030, 2928, 2893, 1734, 1597, 1329, 1252, 1147, 1096, 1044 cm^{-1}; HRMS, *m/z*

calcd for $C_{20}H_{26}O_9S$ 442.1298, found 442.1299.

Reductive Cleavage to Chorismic Acid Precursor 12.

To 35.8mg (0.081 mmol) of the a-sulfonyl ester **11** in 15 mL of dry tetrahydrofuran under nitrogen was added 892 mg of activated zinc metal.[19] To this was added 3.5 mL of sat. ammonium chloride and the resulting mixture was stirred at room temperature for 16 hours. To the reaction mixture an additional 200 mg of activated zinc metal was added and stirred for 19.5 hours. The reaction mixture was then diluted with 100 mL of diethyl ether and 20 mL of water. The two-phase system was separated and the aqueous layer extracted with diethyl ether (2 x 100 ml). The organic portions were mixed, washed with 25 mL of water, 50 mL of brine, dried over magnesium sulfate, filtered, and the solvent removed under vacuum. Column chromatography (silica gel, 20% ethyl acetate/hexane-50% ethyl acetate/hexane) afforded 18.1 mg (87%) of the cyclohexadiene **12** as an oil, Rf = 0.40 (50% ethyl acetate/hexane). ^{1}H NMR δ 6.92 (m, 1H), 6.32 (d, J=10 Hz, 1H), 5.86 (d, J=10 Hz, 1H), 4.81 & 4.92 (AB, J=7.5 Hz, 2H), 4.75 (d, J=12 Hz, 1H), 4.47 (ddt, J=13, 2.6, 1 Hz, 1H), 3.77 (s, 3H), 3.54 - 3.92 (m, 4H), 3.40 (s, 3H); ^{13}C NMR δ 165.13, 139.94, 129.88, 127.28, 122.46, 96.03, 84.30, 84.30, 73.41, 71.55, 67.62, 59.00, 51.99; FT-IR 3430, 3026, 3013, 2953, 2896, 1719, 1439, 1257, 1105, 1050 cm^{-1}; HRMS, *m/z* calcd for $C_{12}H_{18}O_6$ 258.1093, found 258.1103.

References

1. a) For a thorough review of retro-Diels-Alder strategy with leading references, see Ichihara, A., Synthesis, **1987**, 207;
   b) for a thorough review of Diels-Alder chemistry with heterocyclic azadienes, see Boger, D.L.; Chem. Revs., **1986**, 86, 781.
   c) for a recent related example, see Whitney, S.E.; Winters, M.; Rickborn, B.; J. Org. Chem., **1989**, 55, 929.
2. a) Behringer, H.; Heckmaier, P.; Chem. Ber., **1969**, 102, 2835.
   b) Märkl, G.; Fuchs, R.; Tetrahedron Lett., **1972**, 4695;
   c) Corey, E.J.; Watt, D.S.; J.Am.Chem.Soc., **1973**, 95, 2303;
   d) Ireland, R.E.; McGarvey, G. J.; Anderson, R.C.; Badoud, R.; Fitzsimmons, B.; Thaisrivongs, S., Ibid, **1980**, 102, 6178 and Ireland, R. E.; McGarvey, G. J.; Anderson, R.C.; Badoud, R.; Fitzsimmons, B.; Thaisrivongs, S.; Wilcox, C. S.; Ibid, **1983**, 105, 1988;
   e) Gingrich, H.L.; Roush, D.M.; Van Saun, W.A.; J. Org. Chem., **1983**, 48, 4869;
   f) Moody, C.J.; Shah, P.; Knowles, P.; J. Chem. Soc. Perkin Trans. I, **1988**, 3249.
   g) Moody, C.J.; Shah, P.; Ibid. **1989**, 2463.

3. a) Boger, D.L.; Mullican, M.D.; J. Org. Chem., **1984**, 49, 4033;
b) Boger, D. L.; Brotherton, C.E.; Ibid. **1984**, 49, 4050;
4. a) Jung, M.E.; Usui, Y.; Vu, C.T.; Tetrahedron Lett., **1987**, 28, 5977;
b) Trost, B.M.; Schneider, S.; Angew. Chem. Int. Ed. Engl., **1989**, 28, 213;
c) cf. Gupta, R.B.; Franck, R.W.; J. Am. Chem. Soc., **1987**, 109, 5393, and Choudhury, A.; Franck, R. W.; Tetrahedron Lett., **1989**, 30, 4921.
5. a) Posner, G.H.; Harrison, W.; J.Chem. Soc., Chem. Comm., **1985**, 1786;
b) Posner, G.H.; Haces, A.H.; Harrison, W.; Kinter, C.M.; J. Org. Chem., **1987**, 52, 4836.
6. a) Posner, G.H.; Wettlaufer, D.G.; Tetrahedron Lett., **1986**, 27, 667;
b) Posner, G.H.; Wettlaufer, D.G.; J. Am. Chem.Soc., **1986**, 108, 7373;
c) Posner, G.H., Accts.Chem. Res., **1987**, 20, 72.
7. Posner, G.H.; Harrison, W.; Wettlaufer, D.G., J. Org. Chem., **1985**, 50, 5041.
8. a) Field, N.D., J.Am. Chem. Soc., **1961**, 83, 3504; b) Johnson, W.K.; Patton, T.L.; Chem. Abstr., **1960**, 54, 19628i; c) for alternative preparations of 1,3-dioxoles, see Frauenrath, H.; Synthesis, **1989**, 721; d) for some cycloadditions of dioxoles, see Scharf, H.-D.; Mattay, J.; Tetrahedron Lett., **1976**, 3509.
9. a) Arai, Y.; Takadoi, M., Koizumi, T.; Chem. Pharm. Bull., **1988**, 36, 4162.
b) Sato, K.; Kozikowski, A.P.; Tetrahedron Lett., **1989**, 30, 4073.
10. Bruenner, H.; Synthesis, **1988**, 645.
11. a) Maruoka, K.; Araki, A.; Yamamoto, H.; J. Am. Chem. Soc., **1988**, 110, 2650;
b) cf Posner, G.H.; Kinter, C.M.,; J. Org. Chem., submitted for publication.
12. For leading references to use of high pressure to promote Diels-Alder cycloadditions, see a) Dauben, W.G.; Baker, W.R.; Tetrahedron Lett., **1982**, 23, 2611;
b) Dauben, W.G., Bunce, R.A.; Ibid, **1982**, 23, 4875;
c) see also Tietze, L.F.; Hubsch, T.; Voss., E.; Buback, M.; Tost, W.; J. Am. Chem.Soc., **1988**, 110, 4065.
d) see also "Organic High Pressure Chemistry," W.J. le Noble, Ed., Elsevier, 1988.
13. a) Organocopper Chemistry: Posner, G.H.; "An Introduction to Synthesis Using Organocopper Reagents," Wiley-Interscience, 1980, pp. 91-99; and Underiner, T.L.; Paisley, S.D.; Schmitter, J.; Lesheski, L.; Goering, H.L., J. Org. Chem., **1989**, 54, 2369; and Klunder, J.M.; Posner, G.H.; in "Comprehensive Organic Synthesis," B.M. Trost and I. Fleming, Eds., Pergamon Press, Vol. 3, Ch. 3, in press;
b) Palladium Chemistry: Boldrini, G. P.; Mengoli, M., Tagliavini, E., Trombini, C.; Umani-Ronchi, A.; Tetrahedron Lett., **1986**, 27, 4223.
14. cf Sheffy, F.K.; Godschalx, J.P.; Stille, J.K.; J. Am. Chem. Soc., **1984**, 106, 4833.
15. a) Greene, T. W.; "Protective Groups in Organic Synthesis" John Wiley, New York, 1981;
b) Corey, E.J.; Gras, J.-L.; Ulrich, P.; Tetrahedron Lett., **1976**, 809.
16. a) Ikota, N.; Ganem, B. J. Chem. Soc. Chem. Commun., **1978**, 869;
b) Ganem, B.; Ikota, N.; Muralidharan, V.B.; Wade, W.S.; Young, S.D.; Yukimoto, Y. J. Am. Chem. Soc. **1982**, 104, 6787;

c) Lesuisse, D.; Berchtold, G.A. J. Org. Chem. **1985**, 50, 888 and references therein;
d) Pawlak, J.L.; Berchtold, G.A. Ibid. **1987**, 52, 1765.
17. a) Weiss, U.; Edwards, J.M. The Biosynthesis of Aromatic Compounds; Wiley: New York, 1974;
b) Haslam, E. The Shikimate Pathway; Wiley: New York, 1974;
c) Knowles, J.R.; Aldrichimica Acta, **1989**, 22, 59 and references therein.
18. a) March, J.; "Advanced Organic Chemistry," Wiley-Interscience, New York, 1985, 3rd ed., p. 17;
b) see also Ceppi, E.; Eckhardt, W.; Grob, C.A.; Tetrahedron Lett., 3627 (1973).
19. Holton, R.A.; Crouse, D.J.; Williams, A.D.; Kennedy, R.M.; J. Org. Chem., **1987**, 52, 2317.