under argon for 2 days. Filtration of the catalyst and solvent removal (Rotavap) gave 1.08 g (95%) of naphthacene (**20**) as orange crystals: mp 339–341 °C (lit.[23] mp 341 °C); ^{1}H NMR δ 7.40 (dd, 4 H), 8.00 (dd, 4 H), 8.67 (s, 4 H).

2,3-Dibromo-5,5a,6,11,11a,12-hexahydronaphthacene 5,12-Endoxide (17). From 1.04 g (10 mmol) of **4** and 3.02 g (10 mmol) of **15**[1] in 60 mL of toluene, in a reaction and workup as for **16**, there was obtained 3.61 g (89%) of **17** as colorless crystals: mp 179–181 °C, after recrystallization from methylene chloride–hexane; ^{1}H NMR δ 1.99 (dd, 2 H), 2.70 (dd, 2 H), 2.98 (dd, 2 H), 5.07 (s, 2 H), 7.13 (br s, 4 H), 7.49 (s, 2 H); ^{13}C NMR δ 32.75, 42.47, 83.96, 122.32, 124.38, 126.35, 126.90, 138.35, 146.65; mass spectrum, *m/e* (relative intensity) 278 (62), 276 (100), 274 (55), 248 (1), 195 (5), 169 (10), 167 (8), 128 (18), 115 (13).

8,9-Dibromo-5,12-dihydronaphthacene (19). From 2.84 g (7 mmol) of **17**, 70 mL of acetic anhydride, and 15 mL of concentrated hydrochloric acid, in a procedure and workup as for **18**, there was obtained 2.44 g (90%) of **19** as light yellow crystals, mp 224–226 °C, after recrystallization from toluene: ^{1}H NMR δ 4.06 (s, 4 H), 7.22 (dd, 2 H), 7.34 (dd, 2 H), 7.63 (s, 2 H), 8.07 (s, 2 H); ^{13}C NMR δ 36.78, 124.11, 126.49, 127.27, 131.54, 132.07, 136.44, 137.46, 137.77; mass spectrum, *m/e* (relative intensity) 390 (M^+ + 4, 65), 388 (M^+ + 2, 100), 386 (M^+, 55), 309 (39), 307 (42), 228 (87), 226 (74), 114 (38), 113 (34).

2,3-Dibromonaphthacene (21). From 1.16 g (3 mmol) of **19** in 50 mL of xylene containing 150 mg of 10% Pd/C there was obtained, in a procedure and workup as for **20**, 1.10 g (96%) of **21** as orange crystals, mp 336–338 °C. The compound was too insoluble to obtain an NMR spectrum. Mass spectrum, *m/e* (relative intensity) 388 (M^+ + 4, 4), 386 (M^+ + 2, 6), 384 (M^+, 4), 308 (4), 306 (4), 228 (9), 226 (13), 113 (10), 33 (100). Anal. Calcd for $C_{18}H_{10}Br_2$: C, 55.60; H, 2.61. Found: C, 55.26; H, 2.78.

Cycloadducts 22 and 23. A solution of **12** (1.40 g, 5 mmol) and **10** (0.97 g, 5 mmol) in 160 mL of xylene was heated at reflux for 5 days. The solid that deposited in the cooled solution was unreacted **12** (0.21 g). The filtrate was concentrated (Rotavap) and the residue chromatographed on silica gel with methylene chloride–hexane (1:3) as eluent to give 1.49 g (63%) of a mixture of **22** and **23**, mp 294–296 °C. For **22**: ^{1}H NMR δ 2.35 (s, 2 H), 3.82 (s, 4 H), 4.46 (s, 2 H), 5.06 (s, 2 H), 7.13 (dd, 2 H), 7.18 (s, 2 H), 7.20–7.31 (m, 6 H), 7.39 (dd, 2 H), 7.49 (s, 2 H), 7.72 (dd, 2 H). For **23**: ^{1}H NMR δ 2.32 (s, 2 H), 3.86 and 3.97 (AB q, 4 H, J = 16.1 Hz), 4.45 (s, 2 H), 5.07 (s, 2 H), 6.99 (dd, 2 H), 7.15–7.30 (m, 8 H), 7.39 (dd, 2 H), 7.50 (s, 2 H), 7.72 (dd, 2 H). For the mixture: mass spectrum, *m/e* (relative intensity) 474 (M^+, 9), 456 (4), 388 (6), 374 (4), 305 (9), 293 (46), 280 (16), 278 (19), 207 (21), 194 (26), 181 (67), 168 (56), 139 (13), 44 (100).

5,7,16,18-Tetrahydro-5,16[1′,2′]-benzenoheptacene (24). To a mixture of **22** and **23** (1.422 g, 3 mmol) in 60 mL of acetic anhydride there was added slowly (through the condenser) 12 mL of concentrated hydrochloric acid. After 12 h at reflux, the cooled mixture was poured into ice–water and extracted with methylene chloride. The organic extract was washed with 10% sodium carbonate and water, dried, and reduced in volume (Rotavap). Chromatography of the residue over silica gel with methylene chloride–hexene (1:4) as the eluent gave 656 mg (48%) of **24**, mp >205 °C dec; ^{1}H NMR δ 3.84 (s, 4 H), 5.52 (s, 2 H), 7.03 (dd, 2 H), 7.11 (dd, 2 H), 7.21 (dd, 2 H), 7.36 (s, 2 H) 7.38 (dd, 2 H), 7.40 (dd, 2 H), 7.87 (s, 2 H), 7.93 (dd, 2 H), 8.22 (s, 2 H); mass spectrum, *m/e* (relative intensity) 456 (M^+, 53), 455 (59), 454 (80), 453 (100), 452 (45), 374 (2), 227 (35), 226 (52), 225 (36), 210 (28), 194 (2), 151 (2), 121 (4).

7,16[1′,2′]-Benzeno-7,16-dihydroheptacene (2). A solution of **24** (547 mg, 1.2 mmol) in 20 mL of mesitylene containing 80 mg of 10% Pd/C was heated at reflux for 60 h. The hot solution was filtered, and the filtrate was concentrated to give 528 mg (97%) of **2** as pale yellow crystals, mp >360 °C dec; ^{1}H NMR δ 5.68 (s, 2 H), 7.11 (dd, 2 H), 7.41 (dd, 4 H), 7.52 (dd, 2 H), 7.93 (dd, 4 H), 7.98 (s, 4 H), 8.28 (s, 4 H); ^{13}C NMR δ 53.30, 121.66, 123.95, 125.02, 125.72, 126.24, 127.99, 130.69, 131.71, 140.35, 143.35; mass spectrum, *m/e* (relative intensity) 454 (M^+, 59), 453 (35), 452 (24), 290 (4), 274 (13), 227 (100), 226 (97), 213 (34), 197 (11), 165 (6), 149 (6), 105 (5); UV (cyclohexane) λ_{max} 378 nm (ε 14 298), 358 (14 480), 342 (14 361), 325 (14 217), 283 (31 700), 254 (20 762), 212 (15 070). Anal. Calcd for $C_{36}H_{22}$: C, 95.12; H, 4.88. Found: C, 94.87; H, 5.04.

Heptiptycene 25.[8] A mixture of **2** (227 mg, 0.5 mmol), benzenediazonium-2-carboxylate hydrochloride (222 mg, 1.2 mmol) and propylene oxide (2 mL) in 20 mL of 1,2-dichloroethane was heated at reflux for 5 h. Diethylcarbitol (4 mL) was added, and the solvent was distilled until the head temperature reached 150 °C. Maleic anhydride (55 mg) was added to remove unreacted **2**, and the mixture was heated at reflux for 15 min. To the cooled mixture was added 0.2 g of KOH in 3 mL of methanol–water (2:1). The mixture was chilled in ice and the resulting solid was filtered, washed with methanol–water (4:1), and dried. Recrystallization from chloroform gave 152 mg (50%) of **25**, whose ^{1}H NMR spectrum was identical with that reported.[8]

Acknowledgment. We thank the National Aeronautics and Space Administration (NAG 3-670) and the National Science Foundation (CHE 83-19578) for grants in support of this research.

Registry No. **2**, 110372-75-3; **3**, 110391-11-2; **5a**, 87207-46-3; **5s**, 87248-22-4; **6**, 110372-76-4; **7**, 110454-01-8; **8**, 110391-12-3; **9**, 40476-38-8; **10**, 22187-13-9; **11**, 110372-77-5; **12**, 20244-36-4; **13**, 135-48-8; **14**, 573-57-9; **15**, 106750-88-3; **16**, 110372-78-6; **17**, 110372-79-7; **18**, 959-02-4; **19**, 110372-80-0; **20**, 92-24-0; **21**, 110372-81-1; **22**, 110372-82-2; **23**, 110454-02-9; **24**, 110372-83-3; **25**, 87207-52-1; benzenediazonium-2-carboxylate hydrochloride, 4661-46-5; benzocyclobutene, 4026-23-7; propylene oxide, 75-56-9.

Highly Stereocontrolled Synthesis of Some Polyfunctionalized Cyclohexenes. A Short Formal Total Synthesis of (±)-Chorismic Acid

Gary H. Posner,*‡ Alberto Haces, Wayne Harrison, and Chris M. Kinter

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Received June 23, 1987

Lewis acid catalysis or high pressure is an effective means for promoting stereocontrolled 2 + 4 cycloaddition between pyrone sulfoxide **1** and vinyl ethers and vinyl thioethers. The bridged, bicyclic lactone cycloadducts are versatile synthons carrying much structural and stereochemical information. The allylic sulfoxide groups in such cycloadducts are used ultimately in [2,3]-sigmatropic rearrangements to generate allylic alcohols, and the phenylthio group in cycloadduct **10** is used, after oxidation, to generate the second double bond in 1,3-cyclohexadiene **17**, which is a key intermediate in a total synthesis of chorismic acid.

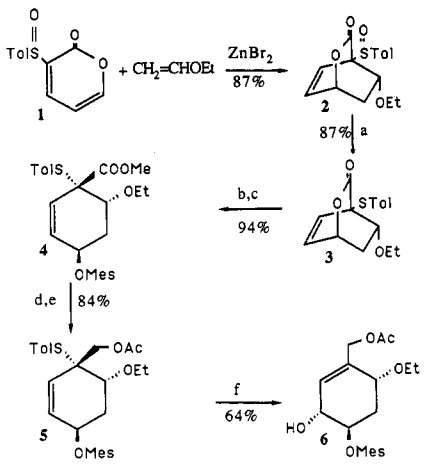
We have reported recently that some pyridone[1] and pyrone[2] sulfones 2 + 4 cycloadd to vinyl ethers under mild conditions to produce stable, bridged, bicyclic lactams and lactones in very good to excellent yields; cleavage of the

‡ 1987 Maryland Chemist of the Year Awardee.

(1) Posner, G. H.; Switzer, C. *J. Org. Chem.* **1987**, *52*, 1642.

0022-3263/87/1952-4836$01.50/0

Scheme I[a]



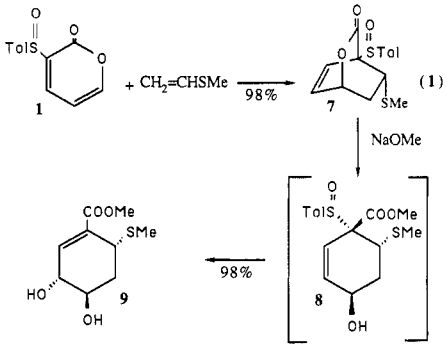
[a] (a) $(CF_3CO)_2O$, Me_2S, (b) NaOMe, (c) 2,4,6-$Me_3C_6H_2COCl$, (d) $LiAlH_4$, (e) AcCl, and (f) *m*-CPBA.

hetero bridge produces some regiospecifically and stereospecifically polysubstituted cyclohexyl systems. The usefulness of this protocol for efficient preparation of complex organic compounds was illustrated by an asymmetric total synthesis of (−)-methyl triacetyl-4-epishikimate.[2b] We have reported also that a pyrone sulfoxide likewise undergoes diastereoselective Diels–Alder cycloaddition with 1,1-dimethoxyethylene.[3] If this type of inverse-electron-demand Diels–Alder cycloaddition could be achieved by using a pyrone sulfoxide with less electron-rich vinyl ether (CH_2=CHOR) and vinyl thioether (CH_2=CHSR) dienophiles, then the bicyclic lactone sulfoxide cycloadducts might be useful ultimately for [2,3]-sigmatropic rearrangements;[4] oxidation of the sulfide group introduced via the vinyl thioether could then be followed by thermolysis as a means of regiospecific olefin formation.[5] We record here some successful examples of this protocol (a) by using a Lewis acid and separately by using high pressure to facilitate the 2 + 4 cycloaddition reactions and (b) subsequently by using the sulfoxide functionality to place an allylic hydroxyl group regiospecifically and stereospecifically on a cyclohexyl ring and separately by using a different sulfoxide group to form a carbon–carbon double bond pyrolytically. A short formal total synthesis of chorismic acid highlights this methodology.

Results and Discussion

Pyrone sulfoxide 1[6] reacted with ethyl vinyl ether in the presence of zinc dibromide at room temperature for 3 days to form bicyclic lactone sulfoxide **2** as a 10:1 endo/exo mixture in very high yield. Methanolysis of the lactone bridge under a variety of conditions leading to a cyclohexenyl allylic sulfoxide failed to produce acceptable yields of an allylic alcohol via a [2,3]-sigmatropic rearrangement.[7] Therefore an indirect path was explored. Reduction of bicyclic sulfoxide **2** to bicyclic sulfide **3** proceeded smoothly.[8] Methanolysis and mesitoylation gave polysubstituted cyclohexene **4** cleanly and in high yield. Reduction of the methyl ester and acetylation produced protected allylic sulfide **5**. Sulfide → sulfoxide oxidation with *m*-chloroperbenzoic acid and spontaneous [2,3]-sigmatropic rearrangement gave allylic alcohol **6** (Scheme I). The overall yield of allylic alcohol **6** in eight steps from pyrone sulfoxide **1** was 38%. *This regiospecifically tetrasubstituted, stereospecifically trioxygenated cyclohexene represents a complex, versatile synthon in which four hydroxyl groups are present in different forms (i.e., free OH, ether, acetate ester, and mesitoate ester), and therefore these four oxygen functionalities can be manipulated independently.*

Medium and high pressures usually facilitate reactions with negative volumes of activation such as Diels–Alder cycloadditions.[9] Although pyrone sulfoxide **1** failed to react with methyl or phenyl vinyl *thio*ethers in the presence of zinc dibromide at room temperature, highly successful room temperature 2 + 4 cycloaddition occurred at 6.8 kbar, as illustrated by eq 1, with methyl vinyl thioether.[10] Only the *endo*-methylthio cycloadduct **7** was produced. Methanolysis of the bridged bicyclic lactone sulfoxide **7** produced in situ allylic sulfoxide **8**, which spontaneously underwent an efficient [2,3]-sigmatropic rearrangement to polysubstituted cyclohexene *trans*-diol **9** in only two steps and in 96% overall yield from pyrone sulfoxide **1**. *This two-step, exceptionally high yield procedure represents an effective conversion of an α-pyrone into a regiospecifically tetrasubstituted, stereospecifically trans-dihydroxylated cyclohexene.*



Phenyl vinyl thioether also underwent highly diastereoselective albeit somewhat longer room temperature, 6.8 kbar, 2 + 4 cycloaddition with pyrone sulfoxide **1** (eq 2). Only the *endo*-phenylthio adduct **10** was formed. Methanolysis was followed in situ by spontaneous [2,3]-sigmatropic rearrangement to form (phenylthio)cyclohexene *trans*-diol **11** in 66% overall yield from pyrone sulfoxide **1**. All attempts failed to derivatize the secondary hydroxyl group liberated by methanolysis of the lactone *before*

(2) (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. *Acc. Chem. Res.* **1987**, *20*, 72.

(3) Posner, G. H.; Harrison, W. *J. Chem. Soc., Chem. Commun.* **1985**, 1786.

(4) (a) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100; (b) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147; (c) Masaki, Y.; Sakuma, K.; Kaji, K. *Chem. Pharm. Bull.* **1985**, *33*, 2531.

(5) (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887; (b) Trost, B. M., *Chem. Revs.*, **1978**, *78*, 363.

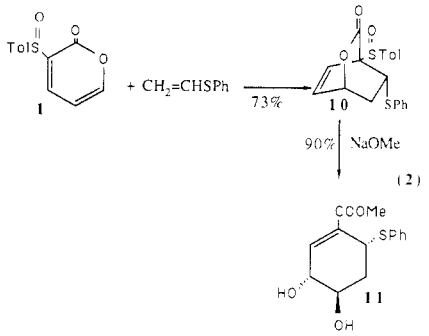
(6) Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1986**, *50*, 5041.

(7) For examples of successful [2,3]-sigmatropic rearrangement of α-sulfinyl-β,γ-ethylenic carbonyl compounds, see: (a) Satoh, T.; Motohashi, S.; Yamakawa, K. *Tetrahedron Lett.* **1986**, *27*, 2889. (b) Kosugi, H.; Kitaoka, M.; Takahashi, A.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1986**, 1268.

(8) Drabowicz, J.; Oae, S. *Synthesis* **1977**, 404.

(9) (a) Dauben, W. G.; Gerdes, J. M.; Smith, D. B.; *J. Org. Chem.* **1985**, *50*, 2576 and references cited therein. (b) Dauben, W. G.; Drabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 282. (c) Le Noble, W. J. *Prog. Phys. Org. Chem.* **1967**, *5*, 207. (d) Le Noble, W. J.; Asano, T. *Chem. Rev.* **1978**, *78*, 407. (e) Isaacs, S. N.; Rannala, E. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1555. (f) Gladysz, J. A.; Lee, S. J.; Tomasello, J. A. V.; Yu, Y. S. *J. Org. Chem.* **1977**, *42*, 4170.

(10) Prepared according to Regel E. K.; Botts, M. F., U.S. Patent 3416912, 1968; *Chem. Abstr.* **1969**, *71*, 22185g.

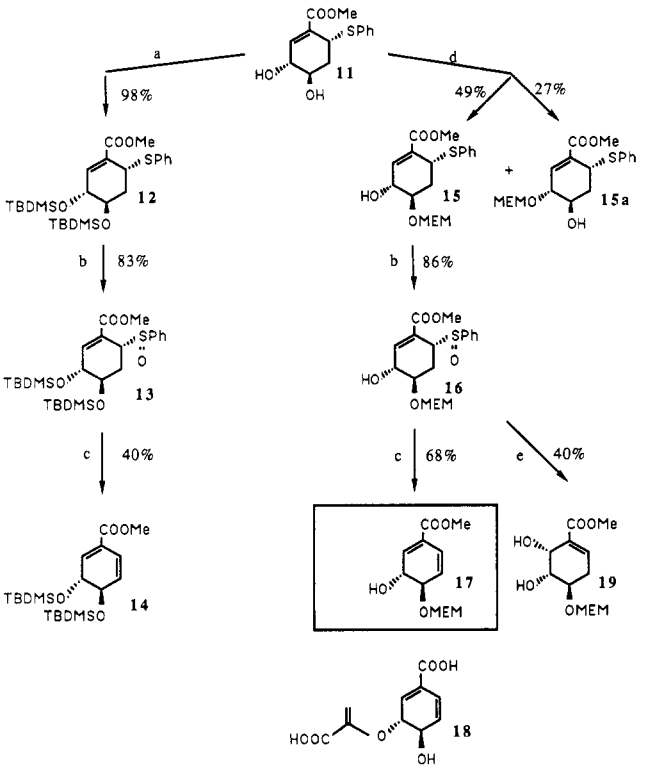


[2,3]-sigmatropic rearrangement. Having used the sulfinyl group in pyrone sulfoxide **1** as a precursor to the allylic hydroxyl group in *trans*-diol **11**,[11] we now wanted to use the phenylthio group from the phenyl vinyl thioether as a precursor to a regiospecifically placed carbon–carbon double bond[12] with the aim of preparing a chorismic acid intermediate; sulfide → sulfoxide oxidation followed by pyrolysis was thought to meet these requirements, but first protection of the diol funtionality was carried out.

Bis-silylation proceeded without difficulty (Scheme II). Peracid oxidation led cleanly to sulfoxide **13**, which was pyrolyzed in methanol at 75 °C to form cycloxadiene *trans*-diol derivative **14**. Selective monoprotection of the homoallylic hydroxyl group in *trans*-diol **11** led to MEM ether derivative **15**, which was oxidized into sulfoxide **16**. Pyrolysis of this cyclohexadienyl sulfoxide in methanol at 75 °C led to monoprotected cyclohexadiene *trans*-diol **17**, which has previously been converted into chorismic acid (**18**),[13] a key intermediate in the shikimate biosynthetic pathway that bacteria and lower plants use to convert carbohydrates into aromatic compounds.[14] The 400-MHz ^{1}H NMR spectrum of our synthetic chorismic acid intermediate **17** was identical with an NMR spectrum of this compound provided by Professor Ganem. Preparation of diol **17** in only five steps and in 19% overall yield from pyrone sulfoxide **1** represents a short formal total synthesis of chorismic acid. It is noteworthy that pyrolysis of allylic sulfoxide **16** in benzene instead of in methanol produced mainly triol **19** via a [2,3]-sigmatropic rearrangement rather than producing cyclohexadiene **17** via a syn elimination; this is a dramatic and useful solvent effect allowing selective [2,3]-rearrangement *or* 1,2-elimination of an allylic sulfoxide.[15]

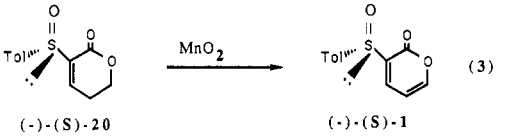
Having established that pyrone sulfoxide **1** undergoes diastereoselective 2 + 4 cycloadditions, we sought to prepare enantiomerically pure sulfoxide **1** so that it could be used in eq 2 and in Scheme II to prepare chorismic acid intermediate **17** in high enantiomeric purity. Homochiral dihydropyrone sulfoxide, (–)-(*S*)-**20**,[16] was dehydrogenated

Scheme II[a]



[a] (a) TBDMS–OTf; (b) *m*-CPBA; (c) MeOH, 75 °C; (d) MEM–Cl; (e) benzene, 85 °C.

under several conditions (e.g. DDQ, NiO_2, Se, MnO_2).[17] Only manganese dioxide successfully produced pyrone suloxide (–)-(*S*)-**1** (eq. 3);[17b] 400-MHz ^{1}H NMR spectroscopy using a homochiral shift reagent [Eu(hfc)$_3$] showed pyrone sulfoxide (–)-(*S*)-**1** to be >98% enantiomerically pure, in comparison with racemic pyrone sulfoxide **1** and the shift reagent. Unfortunately, the reaction represented by eq 3 was capricious,[17] and we could never obtain more than a few milligrams of homochiral pyrone sulfoxide (–)-(*S*)-**1**.



In conclusion, we have demonstrated here (1) that a Lewis acid or high pressure is an effective means of promoting 2 + 4 cycloadditions beteen pyrone sulfoxide **1** and vinyl ethers and vinyl thioethers, (2) that the bridged, bicyclic lactone cycloadducts are stable, richly functionalized, and versatile synthons having fixed stereochemistry, (3) that the sulfoxide groups in such cycloadducts can be used ultimately for stereospecific introduction of allylic hydroxyl groups, and (4) that the latent sulfoxide (i.e., the phenylthio) group in cycloadducts such as **10** can be used ultimately for regiospecific introduction of a second olefinic bond to form the 1,3-cyclohexadiene structural unit characteristic of chorismic acid.

(11) For a related (but unsuccessful) strategy, see: Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854.

(12) For a related strategy using a selenoxide pyrolysis, see: Schlessinger, R. H.; Lopes, A. *J. Org. Chem.* **1981**, *46*, 5252. Hoare, J. H.; Policastro, P. O.; Berchtold, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6264.

(13) (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.

(14) (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) Lesuisse, D.; Berchtold, G. A. *J. Org. Chem.* **1985**, *50*, 888 and references therein.

(15) For a related example, see Overman, L. E.; Petty, C. B.; Ban, T.; Huang, G. T. *J. Am. Chem. Soc.* **1983**, *105*, 6335.

(16) Posner, G. H.; Weitzberg, M.; Hamill, T. G.; Asirvatham, E.; Cun-Leng, H.; Clardy, J. *Tetrahedron* **1986**, *42*, 2919.

(17) (a) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. (b) Fatiadi, A. J. *Synthesis* **1976**, 65.

Experimental Section[18]

Diels–Alder Reaction of Pyrone Sulfoxide 1 with Ethyl Vinyl Ether. To 0.015 g (0.064 mmol) of pyrone sulfoxide 1 in 0.13 mL of tetrahydrofuran was added 0.050 mL of a 1.29 M solution of zinc dibromide in 2,5-dimethyltetrahydrofuran (0.064 mmol) and 0.055 g (0.76 mmol) of ethyl vinyl ether. The reaction mixture was stirred at room temperature for 3 days, diluted with dichloromethane, washed with saturated ammonium chloride, dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC with double elution with ether–hexanes (2:1) to provide 0.019 g (0.062 mmol, 97%) of the Diels–Alder adduct **2** (R_f 0.09) with an endo/exo ratio of ~10:1 as determined by ^1H NMR analysis: ^1H NMR ($CDCl_3$) δ 1.14 (t, 3 H, J = 7.0 Hz, CH_3 endo), 1.30 (t, 3 H, J = 7.0 Hz, CH_3 exo), 1.67 (d, 1 H, J = 13.7 Hz, CH endo), 2.41 (s, 3 H, CH_3), 2.62 (ddd, 1 H, J = 13.7, 7.3, 3.7 Hz, CH exo), 3.50–3.62 (m, 2 H, OCH_2), 4.43 (d, 1 H, J = 7.3 Hz, C*H*OEt), 5.20–5.22 (m, 1 H, CH bridgehead), 6.43 (d, 1H, J = 8.0 Hz, =CH), 6.64 (dd, 1 H, J = 8.0, 5.2 Hz, HC=), 7.31 (d, 2 H, J = 8.0 Hz, Ar), 7.75 (d, 2 H, J = 8.0 Hz, Ar); IR (CCl_4) 1745 (C=O) cm^{-1}; mass spectrum (low resolution) 306 (M^+), 262 ($M^+ - CO_2$), 234 ($M^+ - H_2C$=CHOEt). The diastereomeric excess of the reaction was determined from the ratio of the integration of the diastereomeric tolyl signals [doublet at δ 7.75 (major) and doublet at δ 7.83 (minor)] and was calculated to be ~60%.

Reduction of Sulfoxide 2 to Sulfide 3. To 0.050 g (0.163 mmol) of sulfoxide **2** in 2 mL of dichloromethane were added 0.330 g (5.3 mmol) of dimethyl sulfide and 0.580 g (7.3 mmol) of pyridine. The reaction mixture was cooled to 0 °C and 0.156 g (0.74 mmol) of trifluoroacetic anhydride was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and 5 h at room temperature, then cooled to 0 °C, and quenched by the addition of 2 mL of saturated sodium bicarbonate. The resulting mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate, dried ($MgSO_4$), and concentrated. The concentrate was purified by preparative TLC with hexanes–ethyl acetate (1:1) as the eluent to yield 0.041 g (0.141 mmol, 87%) of sulfide **3** (R_f 0.42): ^1H NMR ($CDCl_3$) δ 1.17 (t, 3 H, J = 7.0 Hz, CH_3), 1.71 (d, 1 H, J = 14.0 Hz, CH endo), 2.33 (s, 3 H, CH_3), 2.58 (ddd, 1 H, J = 14.0, 7.8, 3.8 Hz, CH exo), 3.30–3.55 (m, 2 H, OCH_2), 3.62 (d, 1 H, J = 7.8 Hz, CHOEt), 5.12–5.16 (m, 1 H, CH bridgehead), 6.21 (d, 1 H, J = 8.0 Hz, =CH), 6.55 (dd, 1 H, J = 8.0, 5.3 Hz, HC=), 7.13 (d, 2 H, J = 8.0 Hz, Ar), 7.63 (d, 2 H, J = 8.0 Hz, Ar); IR (CCl_4) 1765 (C=O) cm^{-1}. There was no evidence of the exo product from NMR analysis. HRMS, m/z calcd for $C_{16}H_{18}O_3S$ 290.0977, found 290.0998.

Reaction of Sulfide 3 with Sodium Methoxide and Then Mesitoyl Chloride. To a 0 °C solution of 0.047 g (0.162 mmol) of sulfide **3** in 2 mL of methanol–tetrahydrofuran (1:1) was added 0.40 mL of a 25% sodium methoxide in methanol solution. The reaction mixture was stirred at 0 °C for 40 min, quenched with 1 mL of saturated ammonium chloride, extracted with 20 mL of dichloromethane, and a catalytic amount (~0.1 equiv) of 4-(dimethylamino)pyridine was added. The solution was cooled to 0 °C, and 0.190 g (2.41 mmol) of pyridine was added followed by 0.235 g (1.29 mmol) of 2,4,6-trimethylbenzoyl chloride. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 16 h, quenched with 1 mL of saturated ammonium chloride, extracted with 25 mL of dichloromethane, dried ($MgSO_4$), and concentrated. The concentrate was purified by preparative TLC with hexanes–ethyl acetate–1,2-dichloroethane (10:1:1) as the eluant to provide 0.071 g (0.152 mmol, 94%) of mesitoate sulfide **4** (R_f 0.30): ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7.0 Hz, CH_3), 1.65–1.85 (m, 1 H, CH), 2.29 (br s, 9 H, CH_3), 2.36 (s, 3 H, CH_3), 2.52–2.78 (m, 1 H, CH), 3.53 (s, 3 H, OCH_3), 3.55–3.78 (m, 2 H, OCH_2), 4.23–4.40 (m, 1 H, CHOEt), 5.62–5.77 (m, 1 H, CHOCOAr), 5.81–5.86 (m, 2 H, HC=CH), 6.85 (br s, 2 H, Ar), 7.13 (d, 2 H, J = 8.0 Hz, Ar), 7.48 (d, 2 H, J = 8.0 Hz, Ar); IR (CCl_4) 1720 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{27}H_{32}O_5S$ 468.1971, found 468.1978.

Lithium Aluminum Hydride Reduction of Ester 4 Followed by Acetylation. To a suspension of 0.006 g (0.16 mmol) of lithium aluminum hydride in 1 mL of ether at −20 °C was added a solution of 0.057 g (0.124 mmol) of ester **4** in 2 mL of ether. The reaction mixture was stirred for 2 h at −20 °C, quenched by the addition of saturated ammonium chloride in aqueous tetrahydrofuran, diluted with 30 mL of dichloromethane, and washed with 15 mL of saturated ammonium chloride (containing 1 mL of 10% hydrochloric acid). The aqueous layer was reextracted with 15 mL of dichloromethane, and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was reacted with 10 equiv of acetyl chloride and pyridine in dichloromethane to provide 0.050 g (0.104 mmol, 84%) of acetate **5**, isolated by preparative TLC with double elution with hexanes–ethyl acetate–1,2-dichloroethane (10:1:1), R_f 0.35: ^1H NMR ($CDCl_3$) δ 1.22 (t, 3 H, J = 7.0 Hz, CH_3), 1.62–1.82 (m, 1 H, CH), 1.96 (s, 3 H, $COCH_3$), 2.31 (br s, 9 H, CH_3), 2.36 (s, 3 H, CH_3), 2.45–2.72 (m, 1 H, CH), 3.33–4.10 (m, 3 H, OCH_2 and CHOEt), 4.37 (br s, 2 H, CH_2OAc), 5.31 (d, 1 H, J = 10.2 Hz, HC=), 5.57–5.72 (m, 1 H, CHOCOAr), 5.92 (dd, 1 H, J = 10.2, 4.8 Hz, =CH), 6.85 (br s, 2 H, Ar), 7.08 (d, 2 H, J = 8.0 Hz, Ar), 7.45 (d, 2 H, J = 8.0 Hz, Ar); IR (CCl_4) 1740 (C=O), 1720 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{28}H_{34}O_5S$ 482.2127, found 482.2112.

Reaction of Sulfide 5 with *m*-Chloroperbenzoic Acid. To a −20 °C solution of 0.050 g (0.103 mmol) of **5** in 2 mL of dichloromethane was added a solution of 0.020 g of 90% *m*-chloroperbenzoic acid (0.104 mmol) in 1 mL of dichloromethane. The reaction mixture was stirred at −20 °C for 2 h, diluted with dichloromethane, washed with saturated sodium bicarbonate, dried ($MgSO_4$), and concentrated. The hydroxy compound **6** could be isolated in pure form by preparative TLC with double elution with hexanes–ethyl acetate–1,2-dichloroethane (4:1:1), R_f 0.30: yield 0.025 g (0.066 mmol, 64%); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.0 Hz, CH_3), 1.75–1.81 (m, 1 H, CH), 2.10 (s, 3 H, $COCH_3$), 2.29 (s, 3 H, CH_3), 2.34 (s, 6 H, CH_3), 2.41–2.46 (m, 1 H, CH), 3.44–3.77 (m, 2 H, OCH_2), 3.96 (dd, 1 H, J = 3.6, 3.2 Hz, CHOEt), 4.29 (d, 1 H, J = 8.0 Hz, C*H*OH), 4.59 (d, 1 H, J = 13.4 Hz, CH_2OAc), 4.72 (d with fine coupling, 1 H, J = 13.4 Hz, CH_2OAc), 5.28 (ddd, 1 H, J = 11.6, 8.0, 4.0 Hz, CHOCOAr), 5.82–5.83 (m, 1 H, =CH), 6.88 (br s, 2 H, Ar); IR (CCl_4) 1740 (C=O), 1725 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{21}H_{28}O_6$ ($M^+ - H_2O$) 358.1768, found 358.1780.

Diels–Alder Preparation of Bicyclic Lactone 7. A solution of pyrone sulfoxide 1 (75 mg, 0.32 mmol) in methyl vinyl sulfide (1 mL) was pressurized at 6.8 kbar and room temperature for 24 h. Excess methyl vinyl sulfide was removed in vacuo, and the residue was purified by PTLC (10% EtOAc–ether, R_f 0.45) to produce pure *endo*-methylthio lactone **7** (98 mg, 98%) as a mixture of sulfoxide diastereomers (7.7:1 from ^1H NMR): ^1H NMR ($CDCl_3$) δ 1.83 (ddd, 1 H, J = 14.2, 3.4, 1.5 Hz, CH endo), 2.24 (s, 3 H, SCH_3), 2.40 and 2.41 (2 s 7.7:1 ratio, 3 H, CH_3), 2.89 (ddd, 1 H, J = 14.3, 8.0, 3.9 Hz, CH exo), 3.40 (dd, 1 H, J = 8, 3.4 Hz, SC*H*), 5.14 (m, 1 H, CH bridgehead), 6.68 (dd, 1 H, J = 8.3, 5.1 Hz, =CH), 6.92 (d, 1 H, J = 7.5 Hz, =CH), 7.29 and 7.92 (pair of d, 4 H, J = 7.9 Hz, Zr); IR ($CDCl_3$) 1750 (C=O) cm^{-1}; HRMS, m/z calcd fo$C_{15}H_{16}O_3S_2$ 308.0541, found 308.0545.

Methanolysis of Cycloadduct 7. To a cooled (0 °C) solution of lactone **7** (17 mg, 0.055 mmol) in dry methanol (1 mL) was added sodium methoxide (25 mg, 100 μL, 25% solution in methanol), and the resulting solution was stirred for 1 h. The reaction was quenched with aqueous ammonium chloride (2 mL, 20%) and extracted with chloroform (4 × 10 mL). The organic

(18) Melting points were determined by using a Sybron/Thermolyne Model MP-12615 melting point apparatus; melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 559B spectrometer and were calibrated by using the 1601-cm^{-1} polystyrene absorption as reference. ^1H NMR spectra were recorded by using a Varian XL-400 spectrometer operating at 400 MHz. Chemical shifts are reported in parts per million (ppm) downfield from a tetramethylsilane (Me_4Si) internal standard, and the resonances are noted as being a singlet (s), a doublet (d), a triplet (t), or a multiplet (m). Specific rotations were determined with a Perkin-Elmer 141 variable-wavelength polarimeter with a thermostated 1-dm quartz window cell of 1-mL capacity. Concentrations (*c*) for specific rotations are reported in units of g/100 mL. Mass spectra were performed by the mass spectrometry service laboratory at the University of Minnesota, Minneapolis and by in-house services. Elemental analyses were performed by Atlantic Microlab, Atlantic, GA. The following solvents were distilled from sodium/benzophenone before use: diethyl ether and tetrahydrofuran. Pyridine and triethylamine were distilled from calcium hydride; dichloromethane and chloroform were distilled from phosphorus pentoxide. Methanol was distilled from magnesium. All other reagents and solvents were used as received. Phenyl vinyl thioether was used as received from Aldrich. A Leco Corp. Model PG-100-HPC 7-kbar apparatus was used for the high-pressure experiments.

layer was dried ($MgSO_4$) and filtered, and the solvent was removed. Preparative TLC of the residue (silica gel, ethyl acetate, R_f 0.65) afforded pure diol **9** (10.1 mg, 98%): mp 52–54 °C; ^1H NMR ($CDCl_3$) δ 2.93 (m, 1 H, CH), 2.28 (br s, 4 H, SCH_3 and CH), 3.78 (s, 4 H, OCH_3 and *H*CSCH$_3$), 4.08 (m, 1 H, *H*COH), 4.18 (m, 1 H, *H*COH allylic), 6.69 (d, 1 H, J = 2.4 Hz, =CH); IR ($CDCl_3$) 3360 (OH), 1710 (C=O) cm^{-1}; HRMS, m/z calcd for $C_9H_{14}O_4S$ 218.0613, found 218.0618.

Diels–Alder Preparation of Bicyclic Lactone 10. A solution of pyrone sulfoxide **1** (100 mg, 0.42 mmol) in phenyl vinyl sulfide (1 mL) was pressurized at 6.8 kbar for 3 days at room temperature. Excess phenyl vinyl sulfide was removed by short path silica gel chromatography (10% ether–low boiling petroleum ether), and then the crude product was recovered by further elution with EtOAc. Preparative TLC (silica gel, 10% EtOAC–ether, R_f 0.5) afforded *endo*-phenylthio adduct **10** (115 mg, 73%) as a mixture of sulfoxide diastereomers (16:1 by ^1H NMR): ^1H NMR ($CDCl_3$) δ 1.92 (ddd, 1 H, J = 13.5, 3.1, 0.5 Hz, CH endo), 2.42 (s, 3 H, CH_3), 2.74 (ddd, J = 13.5, 7.9, 3.9 Hz, CH exo), 3.92 (dd, 1 H, J = 7.9, 3.3 Hz, C*H*S C_6H_5), 5.13 and 5.20 (16:1 ratio, m, 1 H, CH bridgehead), 6.73 (dd, 1 H, J = 7.9, 3.4 Hz, HC=), 6.96 (d, J = 7.9 Hz, =CH), 7.27–7.44 (m, 7 H, Ar), 7.97 (d, 2 H, J = 7.9 Hz, tolyl); IR ($CDCl_3$) 1750 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{20}H_{18}O_3S_2$ 370.0697, found 370.0692.

Methanolysis of Bicylic Lactone 10. To a cooled (0 °C) suspension of lactone **10** (133 mg, 0.36 mmol) in methanol (5 mL) under N_2 was added sodium methoxide (50 μL, 25% in methanol), and the resulting mixture was stirred for 40 min. The reaction was quenched with Sat NH_4Cl (2 mL), followed by extraction with chloroform (3 × 5 ml) and ethyl acetate (3 × 5 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed. The residue was purified by preparative TLC (silica gel, 100% ether, R_f ~0.25) to afford pure **11** (90 mg, 90%): mp 107–109 °C; H^1 NMR ($CDCl_3$) δ 2.0 (ddd, 1 H, J = 13.8, 9.8, 3.9 Hz, CH), 2.27 (ddd, 1 H, J = 13.8, 3.5, 1.3 Hz, CH), 3.80 (s, 3 H, CH_3), 4.13–4.25 (m, 2 H, C*H*OH and C*H*SC_6H_5), 4.29 (br s, 1 H, C*H*OH allylic), 6.79 (d, 1 H, J = 1.8 Hz, =CH); IR ($CDCl_3$) 3580 (OH), 1715 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{14}H_{16}O_4S$ 280.0769, found 280.0766.

Bis-TBDMS Derivative 12. To a cooled (0 °C) solution of diol **11** (77 mg, 0.27 mmol) in dry chloroform (1 mL) under nitrogen were added triethylamine (435 mg, 4.2 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (345 mg, 1.3 mmol), and the resulting solution was stirred for 30 min at 0 °C and then for 21 h at room temperature. The reaction was quenched with aqueous ammonium chloride (5 mL) and extracted with chloroform (3 × 15 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed. Preparative TLC of the residue (silica gel, 10% ether–1bpe, R_f 0.5) afforded pure **12** (137 mg, 98%): ^1H NMR ($CDCl_3$) δ 0.12 (2 pair of s, 12 H, $Si(CH_3)_2$), 0.92 (pair of s, 18 H, $SiC(CH_3)_3$), 1.91 (m, 1 H, CH), 2.12 (m, 1 H, CH), 3.79 (s, 3 H, CO_2CH_3), 4.12 (m, 2 H), 4.20 (m, 1 H), 6.27 (d, 1 H, J = 2.1 Hz, C=CH), 7.30 and 7.53 (m, 5 H, Ar); IR ($CDCl_3$) 1705 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{26}H_{44}O_4Si_2S$ 508.2499, found 508.2504.

Sulfoxide 13. To a cooled (0 °C) solution of sulfide **12** (61.5 mg, 0.12 mmol) in dry chloroform (3 mL) under nitrogen was added *m*-CPBA (25 mg, 0.12 mmol, 83%, 10% solution in chloroform), and the resulting solution was stirred for 3 h. The reaction was quenched with aqueous $NaHCO_3$ (5 mL) and extracted with chloroform (3 × 10 mL). The organic layer was dried ($MgSO_4$) and filtered, and solvent was removed to afford pure sulfoxides **13** (53 mg, 83%). Preparative TLC (silica gel, 1bpe–ether, 2:1) of a portion of the crude gave pure **13a** (R_f 0.4) and **13b** (R_f 0.35). **13a**: ^1H NMR ($CDCl_3$) δ 0.15 (2 pair of s, 12 H, $Si(CH_3)_2$), 0.92 (2 s, 18 H, $SiC(CH_3)_3$), 1.57 (ddd, 1 H, J = 13.8, 10.6, 6.3 Hz, CH), 2.24 (ddd, 1 H, J = 13.8, 3.1, 3.1 Hz, CH), 3.73 (m, 1 H, OCH), 3.77 (s, 3 H, CH_3), 4.04 (ddd, 1 H, J = 6.8, 2.3, 2.3 Hz, SC*H*), 4.20 (ddd, 1 H, J = 10.6, 6.0, 3.9 Hz, OCH), 6.94 (d, 1 H, J = 2.8 Hz, =CH), 7.5 and 7.72 (m, 5 H, Ar); IR ($CDCl_3$) 1710 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{26}H_{44}O_5Si_2SC_6H_5SOH$ 398.2309, found 398.2309. **13b**: ^1H NMR ($CDCl_3$) δ 0.07 (2 pair of s, 12 H, $Si(CH_3)_2$), 0.86 (2 s, 18 H, $SiC(CH_3)_3$), 1.96 (m, 1 H, CH), 2.07 (m, 1 H, CH), 3.52 (m, 1 H, OCH), 3.80 (s, 3 H, CO_2CH_3), 3.98 (m, 1 H, CH), 4.34 (m, 1 H, CH), 6.80 (d, 1 H, J = 3.1 Hz), 7.5 (m, 5 H, Ar).

Thermolysis of Bis-TBDMS Derivative 13. A solution of sulfoxides **13a** and **13b** (15 mg, 0.03 mmol) in methanol (1 mL, hydrolysis tube) was heated at 75 °C for 1 day. The solvent was removed, and the residue was purified by preparative TLC (silica gel, 10% ether–1bpe, R_f 0.6) to afford pure **14** (4.5 mg, 40%): ^1H NMR ($CDCl_3$) δ 0.12 (2 pair of s, 12 H, $Si(CH_3)_2$), 0.92 (2 s, 18 H, $SiC(CH_3)_3$), 3.78 (s, 3 H, Me), 4.48 (dd, 1 H, J = 14.6, 2.3 Hz, OCH), 4.57 (dd, 1 H, J = 14.6, 2.76 Hz, OCH), 5.85 (dd, 1 H, J = 11.8, 2.1 Hz, =CH), 6.26 (d, 1 H, J = 11.4 Hz, =CH), 6.77 (s, 1 H, C=CH); IR ($CDCl_3$) 1715 (C=O); HRMS, m/z calcd for $C_{20}H_{36}O_4Si_2$ 398.2309, found 398.2307.

MEM Derivative 15. To a cooled (0 °C) suspension of diol **11** (28.2 mg, 0.09 mmol) in dry $CHCl_3$ (200 μL) under nitrogen was added diisopropylethylamine (58 mg, 0.46 mmol), and the mixture was stirred for 10 min. MEMCl (14.9 mg, 0.11 mmol) was added, and the resulting solution was stirred for 42 h at 65 °C. The reaction mixture was cooled (0 °C), quenched with aqueous $NaHCO_3$ (1 mL, 20%), and extracted with $CHCl_3$ (4 × 10 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed. Preparative TLC (silica gel, ether) of the residue afforded **15** (19 mg, R_f 0.5, 49%) and **15a** (7.3 mg, R_f 0.45, 19%). **15**: ^1H NMR ($CDCl_3$), δ 1.95 (ddd, 1 H, J = 15, 9.8, 3.9 Hz, CH), 2.20 (ddd, 1 H, J = 15, 6.7, 1.3 Hz), 3.40 (s, 3 H, CH_3OCH_2), 3.54–3.64 (m, 2 H, OCH_2CH_2O), 3.69 and 3.89 (m, 2 H, OCH_2CH_2O), 3.78 (s, 3 H, CO_2Me), 3.97 (m, 1 H, C_6H_5SCH), 4.26 (m, 2 H, C*H*O and C*H*OR), 4.84 (s, 2 H, OCH_2O), 6.82 (d, 1 H, J = 3.1 Hz, =CH), 7.28 and 7.52 (m, 5 H, Ar); IR ($CDCl_3$) 3400 (OH), 1713 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{18}H_{24}O_6S$ 368.1294, found 368.1292. **15a**: ^1H NMR ($CDCl_3$) 1.94 (ddd, 1 H, J = 13.8, 11.8, 3.9 Hz, CH), 2.3 (m, 1 H, CH), 3.43 (s, 3 H, OCH_3), 3.62 (t, 2 H, OCH_2CH_2), 3.79 and 3.94 (m, 2 H, CH_2CH_2O), 3.8 (s, 3 H, CO_2CH_3), 4.07 (m, 1 H, C*H*SC_6H_5), 4.25 (m, 2 H, CHO), 4.88 (AB, 2 H, J = 7.0 Hz, OCH_2O), 6.75 (d, 1 H, J = 3.9 Hz, =CH), 7.32 and 7.56 (m, 5 H, Ar); IR ($CDCl_3$) 3400 (OH), 1715 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{18}H_{24}O_6S$ 368.1294, found 368.1292.

Sulfoxides 16a and 16b. To a cooled (0 °C) solution of sulfide **15** (20 mg, 0.05 mmol) in dry chloroform (0.6 mL) under nitrogen was added *m*-CPBA (11.2 mg, 0.05 mmol, 83%, 10% solution in chloroform), and the resulting solution was stirred for 3 h. The reaction was quenched with 10% $NaHCO_3$ solution (2 mL) and extracted with chloroform (3 × 5 mL). The organic layer was dried ($MgSO_4$) and filtered and the solvent was removed. Preparative TLC of the residue (silica gel, 20% EtOAC–ether) afforded pure sulfoxides **16a** and **16b** (9.9 mg, R_f 0.45, 47.4%) and (8 mg, R_f 0.35, 38%). **16a**: ^1H NMR ($CDCl_3$) δ 1.72 (m, 1 H, CH), 2.38 (m, 1 H, CH), 3.40 (s, 3 H, CH_3), 3.57 (m, 2 H, CH_2CH_2), 3.65 (m, 1 H, CH_2CH_2), 3.77 (s, 3 H, CO_2CH_3), 3.83 (m, 2 H), 4.19 (m, 2 H), 4.82 (AB, J = 6.3 Hz, OCH_2O), 7.22 (s, 1 H, =CH), 7.53 and 7.72 (m, 5 H, Ar); IR ($CDCl_3$) 3390 (OH), 1712 (C=O), 1045 (S–O) cm^{-1}; HRMS, m/z calcd for $C_{18}H_{24}O_7S$ 384.1243, found 384.1237. **16b**: ^1H NMR ($CDCl_3$) δ 1.94 (m, 1 H, CH), 2.57 (m, 1 H, CH), 3.37 (s, 3 H, CH_3), 3.5–3.64 (m, 3 H), 3.69 (s, 3 H, CO_2Me), 3.77 (m, 3 H), 4.06 (d, 1 H, J = 7.9 Hz), 4.26 (d, 1 H, J = 7.9 Hz), 4.56 (AB, J = 7.9 Hz, OCH_2O), 7.07 (d, 1 H, J = 3.1 Hz, =CH), 7.52 (m, 5 H, Ar); IR ($CDCl_3$) 3390 (OH), 1715 (C=O), 1055 (S–O); HRMS, m/z calcd for $C_{18}H_{24}O_7S$ 384.1243, found 384.1284.

Thermolysis of Sulfoxides 16a and 16b. A. In Methanol. A solution of sulfoxides **16a** and **16b** (4.3 mg, 0.01 mmol) in methanol (1 mL in a hydrolysis tube) was heated at 75 °C for 2 days. The solvent was removed, and the residue was purified by preparative TLC (silica gel, 10% EtOAC–ether, R_f 0.6) to afford pure **17** (2 mg, 68%): ^1H NMR ($CDCl_3$) δ 3.40 (s, 3 H, CH_3), 3.52–3.88 (m, 4 H, CH_2CH_2), 3.77 (s, 3 H, CO_2CH_3), 4.47 (d, 1 H, J = 13.2 Hz, C*H*OH), 4.75 (d, 1 H, J = 13.2 Hz, C*H*OR), 4.82 and 4.92 (AB, 2 H, J = 7.9 Hz, OCH_2O), 5.86 (d, 1 H, J = 10.5 Hz, C=CH), 6.32 (d, 1 H, J = 10.5 Hz, C=CH), 6.92 (s, 1 H, C=CH); IR ($CDCl_3$) 3400 (OH), 1715 (C=O) cm^{-1}. HRMS, m/z calcd for $C_{12}H_{18}O_6$ 258.1103, found 258.1093. These data matched identically with those reported by Ganem for this compound.

B. In Benzene. A solution of sulfoxides **16a** and **16b** (4 mg, 0.01 mmol) and triethylamine (72 mg, 0.71 mmol) in dry benzene (1 mL in a hydrolysis tube) was warmed to 85 °C for 4 h. The solvent was removed, and the residue was separated by preparative TLC (silica gel, 10% EtOAC–ether, R_f 0.25) to afford diol **19** (1.2 mg, 40%): ^1H NMR δ 2.29 (ddd, 1 H, J = 19.7, 8.5, 2.6 Hz, CH),

2.80 (ddd, 1 H, J = 19.7, 4.6, 4.6 Hz, CH), 3.40 (s and m, 4 H, CH_3O and HCO), 3.58 (t, 2 H, J = 4.3 Hz, CH_2CH_2), 3.75 (m, 2 H, CH_2CH_2), 3.79 (s, 3 H, CO_2CH_3), 3.99 (m, 1 H, HCOMEM), 4.74 (d, 1 H, J = 4.1 Hz, HCO allylic), 4.84 (AB, 2 H, J = 7.2 HZ, OCH_2O), 6.98 (dd, 1 H, J = 4.6, 2.3 Hz, C=CH); IR ($CDCl_3$) 3400 (OH), 1710 (C=O) cm^{-1}; HRMS, m/z calcd for $C_{12}H_{20}O_7 \cdot H_2O$ 258.1103, found 258.1105.

Dehydrogenation of (−)-(*S*)-20. To 20.2 mg (0.086 mmol) of dihydropyrone sulfoxide (−)-**20** in 10 mL of benzene was added 200 mg of active manganese dioxide.[19] The reaction mixture was heated at reflux in a 90 °C oil bath. Heating was continued until the reaction was complete (TLC 1:1 CH_2Cl_2–Et_2O). When the mixture had cooled to room temperature, the brownish-black suspension was filtered through a pad of Celite and washed exhaustively with 100 mL of each of the following solvents: benzene, dichloromethane, chloroform, ethyl acetate, and acetone. Concentration afforded 5 mg of crude product, which was purified by preparative TLC with dichloromethane–ethyl ether (1:1) as the eluent yielding 4.5 mg (0.019 mmol, 22%): $[\alpha]^{25}_D$ −136.9° (c 0.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.38 (s, 3 H, CH_3), 6.49 (dd, 1 H, J = 6.7, 5.1 Hz, H-5), 7.26 (d, 2 H, J = 8.0 Hz, Ar), 7.54 (dd, 1 H, J = 5.1, 2.1 Hz, H-6), 7.70 (d, 2 H, J = 8.0 Hz, Ar), 8.08 (dd, 1 H, J = 6.7, 2.1 Hz, H-4).

The enantiomeric purity of (−)-(*S*)-**1** was determined by using the chiral shift reagent Eu(hfc)$_3$. Complexation of racemic pyrone sulfoxide **1** with 0.58 equiv of Eu(hfc)$_3$ produced two diastereotopic signals of equal intensity for H-4 at δ 15.34 and δ 15.01. Complexation of pyrone sulfoxide (−)-(*S*)-**1** with 0.58 equiv of Eu(hfc)$_3$ produced a similar downfield shift with only one diastereotopic resonance present.

(19) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. H.; Hams, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.

Acknowledgment. We thank the NIH (Grant GM 30052) for financial support. Purchase of a 400-MHz NMR spectrometer was made possible by the NIH (Grant 1510 RR01934) and by the NSF (Grant PCM-83-03776). We also thank Professor Bruce Ganem (Cornell University) for kindly providing an NMR spectrum of cyclohexadiene **17**.

Total Synthesis of 11-Deoxydaunomycinone and Analogues by a Tandem Claisen–Diels–Alder Strategy

George A. Kraus* and Soon Hyung Woo

Department of Chemistry, Iowa State University, Ames, Iowa 50011

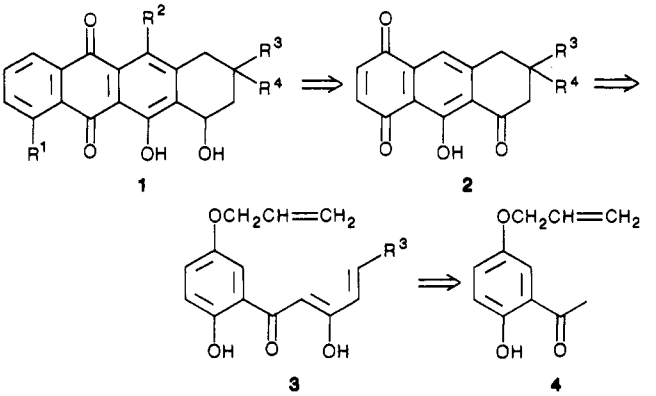
Received April 9, 1987

11-Deoxydaunomycinone (**6**), its 4-deoxy analogue **5**, and 1-methoxy-4,11-dideoxyduanomycinone were prepared by a sequence involving an intramolecular acyl transfer reaction followed by a tandem Claisen–Diels–Alder reaction. The resulting diketone could be oxidized to naphthoquinone **11** with DDQ. This quinone was then treated with either 1-[(trimethylsilyl)oxy]butadiene or 1-methoxy-1,3-cyclohexadiene to provide adducts that could be transformed into **5** and **6**. Unfortunately, the presence of the C-7 carbonyl group *decreased* the regioselectivity of **11** in Diels–Alder reactions.

After more than a decade of intense activity, the synthesis of anthracycline antibiotics remains an active area of research.[1] In large part, this is due to the isolation and characterization of new and highly active anthracyclines. Compounds such as 11-deoxyduanomycin, aclacinomycin, and nogalomycin are perhaps the most active of the newer anthracyclines.[2] One structural feature that these compounds have in common is that the hydroxyl group that is present at C-11 in most anthracyclines has been replaced by a hydrogen atom. These compounds exhibit dramatically lower cardiac toxicities than their 11-hydroxy counterparts. As a consequence, aclacinomycin has become a clinically useful drug.[3]

While many elegant solutions to the synthesis of anthracyclines have been advanced, some problems still remain. For example, the C-7 hydroxyl group (anthracycline numbering) is almost always introduced by way of the solvolysis of a benzylic halide. This method is often inefficient, especially on a large scale. A better strategy would be to incorporate a hydroxyl group or its precursor into a synthetic intermediate at a much earlier stage. Additionally, the recent interest[4] in anthracyclines that are halogenated in the D ring has increased the need for a direct synthetic route that allows rapid entry to a variety of D ring modified compounds.

Scheme I



(1) *Tetrahedron Symposium in Print No. 17*, **1984**, 40. Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790.

(2) Arcamone, F. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic: New York, 1980; Chapter 1.

(3) Tone, H.; Nishida, H.; Takeuchi, T.; Umezawa, H. *Drugs Exp. Clin. Res.* **1985**, *11*, 9. Tone, H.; Takeuchi, T.; Umezawa, H. *Curr. Chemother. Immunother. Proc. Int. Congr. Chemother., 13th, 1983* **1983**, *12*, 211/1.

(4) Morrow, G. W.; Swenton, J. S.; Filppi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* **1987**, *52*, 713.

0022-3263/87/1952-4841$01.50/0