A Remarkably Simple, Highly Efficient, and Stereoselective Synthesis of Steroids and Other Polycyclic Systems. Total Synthesis of Estra-1,3,5(10)-trien-17-one via Intramolecular Capture of *o*-Quinodimethanes Generated by Cheletropic Elimination of SO_2

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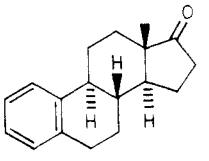
The synthesis of polycycles based on the intramolecular capture of *o*-quinodimethanes generated by cheletropic elimination of SO_2 from strategically designed and easily accessible precursors requiring no catalysts or high-dilution conditions is presented. The methodology involves the monoalkylation of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**2**) employing potassium hydride as base and bromides, iodides, tosylates, or mesylates as alkylating agents, followed by the thermolysis of the substituted sulfones in solution or in the vapor phase. As an application of this novel methodology, a stereoselective total synthesis of *dl*-estra-1,3,5(10)-trien-17-one (**1**), representing one of the simplest and shortest routes to steroidal systems and demonstrating the simplicity and practicality of the reported technology, is included.

Introduction

Despite the several years elapsed since their discovery and initial synthesis, the steroid hormones continue to occupy focal points in biological, clinical, and chemical research due to their important physiological role and challenging structures.[2] Their widespread usage in human contraception and medicine earns them a favorite-target status among synthetic chemists.[2] Among the most recent and elegant syntheses of steroidal systems are the ones of Vollhardt,[3] Oppolzer,[4] and Kametani[5] based on the intramolecular capture of *o*-quinodimethanes[6] generated from benzocyclobutenes by thermolysis to produce the polycyclic frameworks. The benzocyclobutene precursors, however, are usually synthesized by multistep and low overall yield procedures. Vollhardt's elegant, cobalt-catalyzed synthesis of benzocyclobutenes[7] from acetylenes, which was modified to produce polycycles[8] including steroids[3] directly from acetylenic precursors under high-dilution conditions, constitutes a considerable improvement. This *o*-quinodimethane-based methodology to polycyclic frameworks from benzocyclobutenes (Scheme I) has been successfully applied to other complex systems besides steroids and today constitutes one of the most practical and elegant routes to polycycles.[6]

To increase the potential value of this concept, we embarked on a program directed toward new methodology for the generation and intramolecular trapping of *o*-quinodimethanes from precursors other than benzocyclobutenes. We now wish to report the construction of estra-1,3,5(10)-trien-17-one (**1**) and other polycycles by intramolecular capture of *o*-quinodimethanes generated by *cheletropic elimination*[9] *of sulfur dioxide from strategically designed and easily accessible precursors requiring no catalysts or high-dilution conditions.* In developing this novel and practical methodology leading to polycycles, we were guided by the pioneering work of Cava in the 1950's on the pyrolytic generation of *o*-quinodimethanes from 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides[10] and our crucial observation that the readily available sulfone **2** can be alkylated quite efficiently under appropriate conditions. The strategy of this new route to polycycles involves (a) alkylation of sulfone **2** to give the requisite sulfone precursors and (b) pyrolysis of the substituted sulfones to produce directly the polycyclic frameworks via *o*-quinodimethanes.



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Alkylation of 1,3-dihydrobenzo[*c*]thiophene 2,2-Dioxide (2)

The successful alkylation of sulfone **2** is depicted in Scheme II. Thus, treatment of **2** with KH (1.1 equiv) in DME at 0 °C resulted in rapid formation of the anion **3** as a yellow solution stable at 25 °C for relatively prolonged periods of time. This anion can then be alkylated with a variety of alkylating agents such as bromides, iodides, tosylates, and mesylates at 25 °C (12–24 h) to give rise predominantly to monoalkylated products (**5–7**, 60–80%) together with varying amounts of dialkylated materials (Table I). For optimum yields it was found beneficial to use 2 equiv of anion **3** and 1 equiv of alkylating agent. Dialkylation proceeded overwhelmingly in a 1,3 rather than 1,1 fashion as shown by the examples (**5a–7a**) of Table I. This efficient alkylation reaction of sulfone **2** provided the crucial artery to a number of sulfones with the appropriate substitution to serve as precursors to polycyclic frameworks. The utilization of NaH or LDA as bases for the alkylation of **2**, although successful, proved somewhat less satisfactory than the KH procedure.

(1) Fellow of the Alfred P. Sloan Foundation, 1979–1981.
(2) Nakanishi, K. In "Natural Products Chemistry", Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S., Eds; Academic Press: New York, 1974; Vol. 1, Chapter 6. Akhrem, A. A.; Titov, Y. A. "Total Steroid Synthesis", Plenum Press: New York, 1970.
(3) (a) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1979**, *101*, 215. (b) Funk, R. L.; Vollhardt, K. P. C. *Ibid.* **1977**, *99*, 5483.
(4) (a) Oppolzer, W.; Battig, K.; Petrzilka, M. *Helv. Chim. Acta.* **1978**, *61*, 1945. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.
(5) Kametani, T.; Matsumoto, H.; Nemoto, H.; Funkumoto, K. *J. Am. Chem. Soc.* **1978**, *100*, 6218. Kametani, T.; Nemoto, H.; Ishikawa, H.; Shirayama, K.; Matsumoto, H.; Fukumoto, K. *Ibid.* **1977**, *99*, 3401.
(6) For a pertinent recent review, see: Oppolzer, W. *Synthesis* **1978**, 793.
(7) Hillard, R. L., III; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1977**, *99*, 4058. Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1.
(8) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1976**, *98*, 6755.
(9) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie, Academic Press: New York, 1971; p 152.
(10) Cava, M. P.; Deana, A. A. *J. Am. Chem. Soc.* **1959**, *81*, 4266. Cava, M. P.; Mitchell, M. J.; Deana, A. A. *J. Org. Chem.* **1960**, *25*, 1481.

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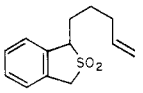
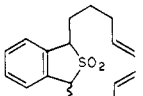
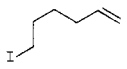
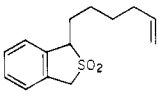
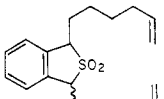
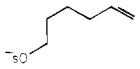
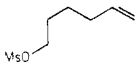
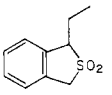
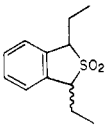
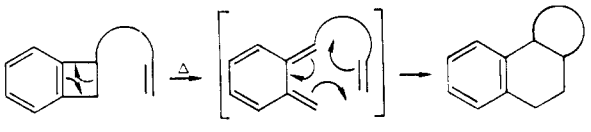
Table I. Alkylation of Sulfone 2 via Anion 3[a]

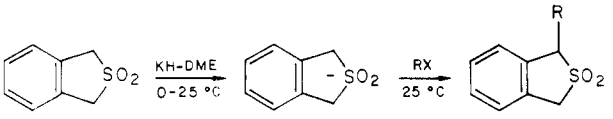
entry	alkylating agent	monoalkylation product	yield,[b] %	dialkylation product	yield,[b,c] %
1		 5	66	 5a	32
2		 6	75	 6a	24
3			71		20
4			67		18
5		 7	60	 7a	28
6			70		30

[a] Reactions were carried out on a 2-mmol sulfone scale in DME with 1 equiv of alkylating agent. [b] Yields are based on alkylating agent and refer to chromatographically isolated and pure materials. [c] The yields of the dialkylated products reflect the utilization of 2 mol of alkylating agent and should be halfed to reflect the molar ratio of monoalkylated to dialkylated materials.

Scheme I. Synthesis of Polycycles from Benzocyclobutenes via *o*-Quinodimethanes



Scheme II. Alkylation of 1,3-Dihydrobenzo[*c*]thiophene 2,2-Dioxide (2)



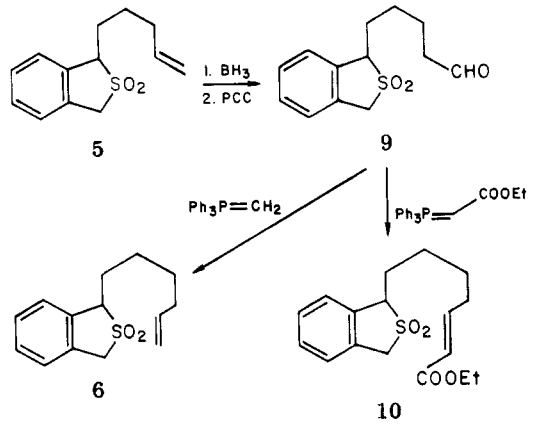
2 3 4

Thermolysis of Alkylated Sulfones to Polycyclic Frameworks

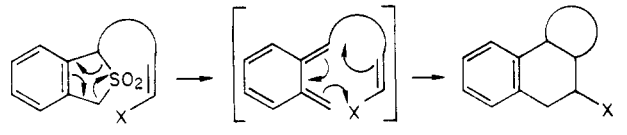
The substituted sulfones shown in Table II were utilized in the pyrolysis experiments to produce polycycles. Sulfones **5** and **6** were obtained by direct alkylation as described above. Sulfone **6** was also prepared from **5** by one-carbon extension, as indicated in Scheme III, via aldehyde **9** which served as a precursor to the ester sulfone **10** as well. Thus hydroboration of the olefin **5** [(1) BH_3, THF, 0–25 °C; (2) $NaOH–H_2O_2$)] led to the corresponding alcohol (**8**) which was converted by oxidation (CrO_3·pyr·HCl, CH_2Cl_2, 25 °C) to the aldehyde **9** (78% overall yield). Condensation of **9** with methylenetriphenylphosphorane afforded **6** (58%), whereas (carbethoxymethylene)triphenylphosphorane led to the unsaturated ester **10** in 78% yield.

Thermolysis of these substituted sulfones (Table II) at 210 °C in di-*n*-butyl phthalate solution (ca. 0.5 M) (method A) generated the corresponding *o*-quinodimethanes by cheletropic elimination of SO_2 and led to the indicated polycycles by intramolecular [4 + 2] cycloaddition as shown in Scheme IV. The same transformations could

Scheme III. Preparation of Substituted Sulfones 6 and 10

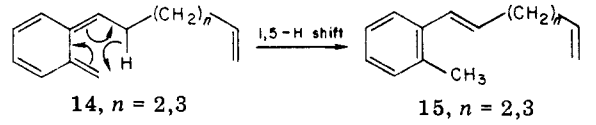


Scheme IV. Construction of Polycycles by Intramolecular Trapping of *o*-Quinodimethanes Generated by Cheletropic Elimination of SO_2



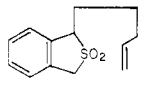
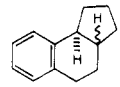
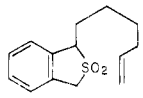
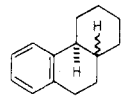
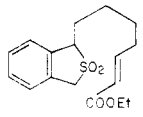
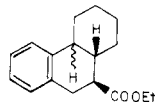
be carried out by dripping a solution of the precursor sulfones in an inert solvent such as ethyl acetate down a quartz hot tube at 300 °C and collecting the condensate (method B).

2-Methylstyrenes (**15**, n = 2,3) were observed in small amounts in the formation of polycycles **11** and **12** due to a second pathway of the reaction involving 1,5-hydride shift as shown in structure **14**.[11]



14, n = 2,3 15, n = 2,3

Table II. Synthesis of Polycyclic Frameworks by Thermolysis of Substituted Sulfones[a]

entry	sulfone precursor	polycycle	yield, %[b]
1			65, method A 80, method B
		11ab, isomeric ratio ca. 3:1	
2			42, method A 65, method B
		12ab, trans:cis ca. 11:1	
3			70, method A 75, method B
		13ab, trans:cis ca. 11:1	

[a] Reactions were carried out on a 1-mmol scale. [b] Yields refer to chromatographically homogeneous materials. Method A: ca. 0.5 M di-*n*-butyl phthalate solution at 210 °C. Method B: quartz tube at 300 °C.

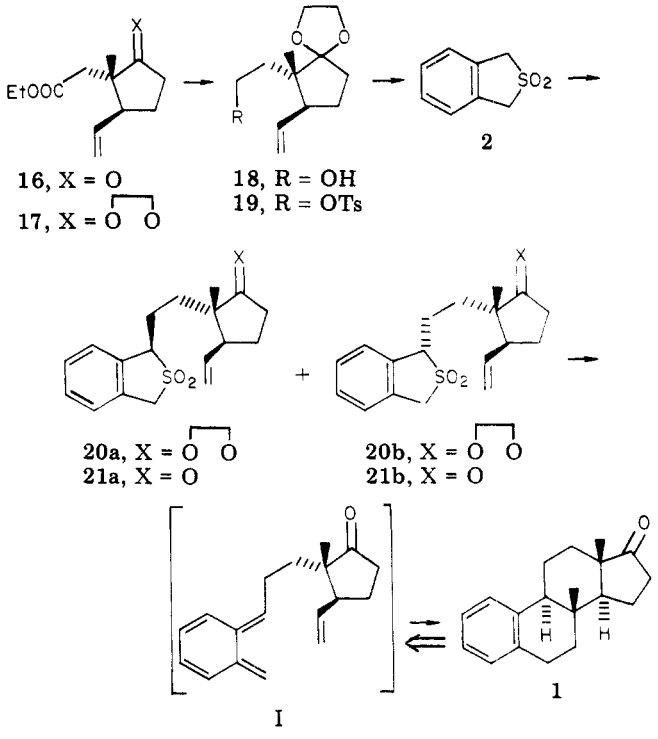
Synthesis of Estra-1,3,5(10)-trien-17-one (1)

It is apparent that the reported methodology for the synthesis of polycycles is of high potential value in the construction of steroids and other complex natural products. Our initial studies resulted in a remarkably simple and highly efficient synthesis of estra-1,3,5(10)-trien-17-one (1). The retrosynthetically conceived plan for this total synthesis is depicted in Scheme V. The actual synthesis proceeded smoothly according to plan and is described in detail below. Reaction of 2-methylcyclopentenone[12] with vinylmagnesium bromide (1.5 equiv)/cuprous iodide (1.5 equiv) in THF (−60 to −40 °C) followed by quenching with ethyl bromoacetate (4 equiv) in HMPA (−20 to 25 °C) resulted in predominant formation of the ester **16** together with its epimer (ca. 3.5:1 by ^{1}H NMR, τ 9.15 and 8.87 for the methyl group) in 69% total yield. Ketalization of this mixture ($HOCH_2CH_2OH$, *p*-TsOH, refluxing benzene) furnished **17** and its epimer. Reduction with $LiAlH_4$ in ether at 0 °C produced a mixture of the two alcohols from which the desired isomer **18** was separated by column chromatography (75% yield). The tosylate **19** was then prepared (TsCl, pyridine, 25 °C) in 80% yield, as a colorless crystalline solid mp 86–87 °C (ether–hexane).

The assembly of the completed precursor for the steroidal structure was achieved by coupling the tosylate **19** (1 equiv) with the anion of sulfone **2** (2 equiv) (KH, DME, 0–25 °C, 5 min) at 25 °C (15 h). The coupling product was obtained in 77% yield based on tosylate **19** (87% based on consumed sulfone **2**) as a mixture of diastereoisomers **20a** and **20b** (1:1 by ^{1}H NMR spectroscopy). Deketalization of the mixture of **20a** and **20b** (AcOH–THF–H_2O, 3:2:2, 45 °C, 24 h) furnished quantitatively the diastereomeric mixture of ketones **21a** and **21b** (1:1 by ^{1}H NMR spectroscopy) which could be separated chromatographically (silica, ether–petroleum ether, 1:1): R_f 0.14, oil; R_f 0.18, colorless crystals, mp 138–139 °C (ether–hexane).

Finally, thermolysis of either diastereoisomer **21a** or **21b** or a mixture of the two in di-*n*-butyl phthalate at 210 °C for 8 h led, after chromatography (silica, 3% ether in benzene, R_f 0.26), to the isolation of estra-1,3,5(10)-trien-17-one (1) in 85% yield. ^{1}H NMR spectroscopic analysis (360 MHz) of the steroidal product formed in these reactions revealed the presence of ca. 5–7% of what was assumed to be the cis-anti-trans C-9 epimer of **1** (τ 9.08 and 9.02 for **1** and its epimer, respectively, for the methyl group). One recrystallization from ether–hexane furnished isomerically pure *dl*-estratrienone **1**, mp 109–110 °C (lit.[36] mp 107–109 °C), spectroscopically and chromatographically identical with an authentic sample.[13] Authentic estratrienone **1** was prepared from estrone[14] by hydrogenolysis of its *N*-phenyltetrazoyl ether (**22**) over 10% Pd–C in THF.[15]

Scheme V. Total Synthesis of Estra-1,3,5(10)-trien-17-one (1)



The remarkable stereoselectivity of this steroidal-forming reaction was anticipated on the basis of previous *o*-quinodimethane-based syntheses,[3-5] and it reveals a rapid geometrical isomerization of the *o*-quinodimethane (com-

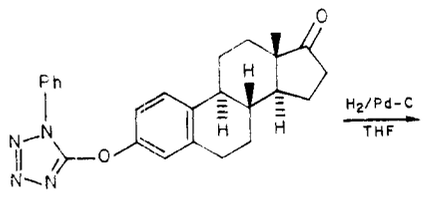
(11) Kametani, T.; Tsubuki, M.; Shiratori, Y.; Kato, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K.; Satoh, F.; Inoue, H. *J. Org. Chem.* **1977**, *42*, 2672.

(12) Gassman, P. G.; Pascone, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 7801.

(13) We thank Dr. F. Li, Syntex Research Laboratories, Palo Alto, CA, for an authentic sample of *d*-estra-1,3,5(10)-trien-17-one.

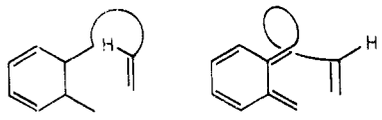
(14) We thank Professor M. P. Cava for a generous gift of estrone.

(15) Musliner, W. J.; Gates, J. W., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 4271.



22

pared to the cycloaddition step) and a distinct preference for the exo (Ia) rather than the endo (Ib) transition state in the [4 + 2] cycloaddition reaction. The high yield [4 + 2] cycloaddition step reveals a degree of rigidity favoring the intramolecular trapping of the *o*-quinodimethane.



Ia Ib

Conclusion

We have demonstrated that *o*-quinodimethanes can be efficiently generated and trapped from suitably substituted sulfones to lead to polycyclic frameworks. A key issue in this new methodology is the successful monoalkylation of the readily available 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**2**) employing potassium hydride as the base to form the anion which undergoes smooth alkylation with a variety of electrophiles.

The usefulness of the reported methodology, which is characterized by high simplicity and practicality, was demonstrated by a total synthesis of estra-1,3,5(10)-trien-17-one (**1**). To our knowledge the present construction of this polycyclic system represents one of the simplest and shortest stereoselective syntheses of the steroid nucleus. Furthermore, the readily available starting materials and reagents employed and the high overall yield (51% from **18**) make this route highly efficient and economically attractive. It is anticipated that further and useful applications of the reported methodology in the synthesis of complex molecules will be found. The construction of the female hormone estrone and several other steroidal and nonsteroidal naturally occurring substances along the reported lines is now in progress in these laboratories.[16]

Experimental Section

General Procedures. Melting points were recorded on a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 360-MHz NMR spectrometer in $CDCl_3$ unless otherwise stated and are reported in τ from Me_4Si. ^{13}C NMR were recorded on a Varian XL100 NMR spectrometer in $CDCl_3$ and are reported in δ from Me_4Si. IR spectra were obtained with a Perkin-Elmer Model 237 spectrophotometer and ν_{max} are reported in cm^{-1}. Mass spectra were provided by the Mass Spectral Service of the Chemistry Department, University of Pennsylvania, and are within acceptable limits unless otherwise stated. Microanalyses were performed by Galbraith Laboratories.

Thin-layer chromatography (TLC) was carried out on 0.25-mm Merck precoated silica gel plates (60F–254) with UV light and/or 7% polyphosphomolybdic acid in ethanol-heat as developing agent. Preparative-layer chromatography (PLC) was performed on 0.25, 0.5, 1, or 2 mm × 20 cm × 20 cm Merck precoated silica gel plates (60F-254). For column chromatography Merck silica gel (60, particle size 0.063–0.200 mm) was used.

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Ethereal and hydrocarbon solvents were dried and distilled under argon from sodium benzophenone ketyl. Methylene chloride was distilled under argon from calcium hydride. Reaction temperatures were measured externally. NMR multiplicities are reported by using the following abbreviations: s singlet, d doublet, t triplet, q quartet, m multiplet, br broad, J coupling constant (Hz). Only the strongest and/or structurally most important peaks are reported for the IR and mass spectra. Yields refer to chromatographically and spectroscopically pure compounds.

Alkylation of 1,3-Dihydrobenzo[*c*]thiophene 2,2-Dioxide (2). General Procedure. Potassium hydride (205 mg, 40% oil dispersion, 2 mmol) was suspended in anhydrous DME (6 mL) and cooled in an ice bath under argon. 1,3-Dihydrobenzo[*c*]thiophene 2,2-dioxide (**2**) (336 mg, 2 mmol) was added portionwise, accompanied by evolution of hydrogen. The ice bath was removed, and the resulting solution stirred for 5 min under argon. The alkylating agent (bromide, iodide, tosylate, mesylate; 1 mmol) was added rapidly in anhydrous DME (1 mL), and the resulting mixture was stirred at room temperature under argon for 12–24 h, the progress of the reaction being followed by TLC. The reaction mixture was then diluted with ether (75 mL), washed with water (25 mL), and dried over anhydrous $MgSO_4$. Removal of the solvents under reduced pressure followed by column chromatography (silica, 25% ethyl acetate in hexane) yielded the pure monoalkylated and dialkylated products in the yields indicated.

1,3-Dihydro-1-(4-pentenyl)benzo[*c*]thiophene 2,2-Dioxide (5): from bromide, 66%; oil; R_f 0.25 (silica, 25% ethyl acetate in hexane); IR (liquid film) ν_{max} 3050, 2970, 2930, 2860, 1640 (vinyl), 1475, 1440, 1315, 1220, 1125, 1030, 915, 845, 780, 715 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 2.65 (m, 2 H, aromatic), 2.73 (m, 2 H, aromatic), 4.20 (m, 1 H, vinylic), 4.98 (m, 2 H, vinylic), 5.72 (s, 2 H, CH_2SO_2), 5.82 (dd, 1 H, J = 9, 6 Hz, $CHSO_2$), 7.83 (m, 2 H, allylic), 7.88 (m, 1 H, CH_2), 8.02 (m, 1 H, CH_2), 8.25 (m, 2 H, CH_2); mass spectrum, m/e (relative intensity) 236 (M^+, 0.1%), 172 ($M - SO_2$, 20%), 168 ($C_8H_8SO_2$, 3.3%), 129 (base peak), 104 (C_8H_8, 31.8%). Anal. ($C_{13}H_{16}O_2S$) C, H.

1,3-Dihydro-1,3-bis(4-pentenyl)benzo[*c*]thiophene 2,2-Dioxide (5a): from bromide, 32%; oil; R_f 0.42 (silica, 25% ethyl acetate in hexane); IR (liquid film) ν_{max} 3050, 2980, 2920, 2850, 1640 (vinyl), 1445, 1300, 1200, 1110, 990, 865, 750 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 2.67 (m, 2 H, aromatic), 2.73 (m, 2 H, aromatic), 4.18 (m, 2 H, vinylic), 4.95 (m, 4 H, vinylic), 5.87 (m, 2 H, CH_2SO_2), 7.82 (m, 4 H, allylic), 7.92 (m, 2 H, CH_2), 8.05 (m, 2 H, CH_2), 8.23 (m, 4 H, CH_2); mass spectrum m/e (relative intensity) 304 (M^+, 0.5%), 240 ($M - SO_2$, 2.2%), 171 (39.9%), 169 (18.4%), 130 (18.3%), 129 (base peak); exact mass calcd for $C_{18}H_{24}O_2S$ 304.1496, found 304.1475.

1,3-Dihydro-1-(5-hexenyl)benzo[*c*]thiophene 2,2-Dioxide (6): from iodide, 75%; from tosylate, 71%; from mesylate, 67%; oil; R_f 0.25 (25% ethyl acetate in hexane); IR (liquid film) ν_{max} 3050, 2950, 2925, 2845, 1640 (vinyl), 1430, 1400, 1230, 1150, 1105, 990, 865, 775 cm^{-1}; ^{1}H NMR τ 2.65 (m, 2 H, aromatic), 2.73 (m, 2 H, aromatic), 4.20 (m,

(16) Preliminary communication: (a) Partly reported in July 1979 at the Cambridge (England) 6th International Symposium on Synthesis in Organic Chemistry; Professor W. Oppolzer informed us at that occasion of similar work in his laboratories. (b) Nicolaou, K. C.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1979**, 1119. After the submission of our manuscript similar independent work appeared in the literature: Oppolzer, W.; Roberts, D. A.; Bird, T. G. C. *Helv. Chim. Acta* **1979**, *62*, 2017.

1 H, vinylic), 5.02 (m, 2 H, vinylic), 5.70 (s, 2 H, CH_2SO_2), 5.83 (dd, J = 9, 6 Hz, 1 H, $CHSO_2$), 7.83 (m, 1 H, CH_2), 7.88 (m, 2 H, allylic), 8.03 (m, 1 H, CH_2), 8.33 (m, 2 H, CH_2), 8.48 (m, 2 H, CH_2); mass spectrum, m/e (relative intensity) 250 (M^+, 0.7%), 186 (M - SO_2, 46.9%), 168 ($C_8H_8SO_2$, 7.1%), 167 ($C_8H_7SO_2$, 3.7%), 91 (62.8%), 51 (base peak). Anal. ($C_{14}H_{18}O_2S$) C, H.

1,3-Dihydro-1,3-bis(5-hexenyl)benzo[*c*]thiophene 2,2-Dioxide (6a): from iodide, 24%; from tosylate, 20%; from mesylate, 18%; oil; R_f 0.45 (25% ethyl acetate in hexane); IR (liquid film) ν_{max} 3050, 2960, 2920, 2850, 1640 (vinyl), 1455, 1190, 1110, 990, 755 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.68 (m, 2 H, aromatic), 2.75 (m, 2 H, aromatic), 4.18 (m, 2 H, vinylic), 5.02 (m, 4 H, vinylic), 5.90 (m, 2 H, $CHSO_2$), 7.80 (m, 1 H, CH_2), 7.88 (m, 4 H, allylic), 7.95 (m, 1 H, CH_2), 8.07 (m, 1 H, CH_2), 8.18 (m, 1 H, CH_2), 8.32 (m, 4 H, CH_2), 8.48 (m, 4 H, CH_2); mass spectrum m/e (relative intensity) 332 (M^+, 0.7%), 268 (M - SO_2, 4.7%), 171 (43%), 168 ($C_8H_8SO_2$, 11.3%), 57 (base peak); exact mass calcd for $C_{20}H_{28}O_2S$ 332.1809, found 332.1789.

1,3-Dihydro-1-ethylbenzo[*c*]thiophene 2,2-Dioxide (7): from iodide, 60%; from tosylate, 70%; oil; R_f 0.21 (25% ethyl acetate in hexane); IR (liquid film) ν_{max} 3050, 2950, 2920, 1480, 1400, 1310, 1200, 1105, 900, 800, 750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.65 (m, 2 H, aromatic), 2.73 (m, 2 H, aromatic), 5.72 (s, 2 H, CH_2SO_2), 5.90 (dd, J = 9, 6 Hz, 1 H, $CHSO_2$), 7.83 (m, 1 H, CH_2), 7.93 (m, 1 H, CH_2), 8.78 (t, J = 8 Hz, 3 H, CH_2CH_3); mass spectrum, m/e (relative intensity) 196 (M^+, 0.1%), 132 (M - SO_2, 46.8%), 131 (17.5%), 118 (10.6%), 117 (base peak); exact mass calcd for $C_{10}H_{12}O_2S$ 196.0557, found 196.0570.

1,3-Dihydro-1,3-diethylbenzo[*c*]thiophene 2,2-Dioxide (7a): from iodide, 28%; from tosylate, 30%; oil; R_f 0.40 (25% ethyl acetate in hexane); IR (liquid film) ν_{max} 3050, 3020, 2950, 2930, 2860, 1460, 1345, 1220, 1165, 1115, 1075, 915, 790, 735 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.65 (m, 2 H, aromatic), 2.75 (m, 2 H, aromatic), 5.93 (m, 2 H, $CHSO_2$), 7.90 (m, 4 H, CH_2CH_3), 8.70 (t, J = 8 Hz, 2.58 H, CH_2CH_3), 8.78 (t, J = 8 Hz, 3.42 H, CH_2CH_3); mass spectrum, m/e (relative intensity) 224 (M^+, 0.1%), 161 (5.3%), 160 (M - SO_2, 36.9%), 133 (16.3%), 131 (base peak); exact mass calcd for $C_{12}H_{16}O_2S$ 224.0871, found 224.0825.

1,3-Dihydrobenzo[*c*]thiophene-1-pentanol 2,2-Dioxide (8). 1,3-Dihydro-1-(4-pentenyl)benzo[*c*]thiophene 2,2-dioxide (**5**) (2.36 g, 10 mmol) was dissolved in anhydrous THF (30 mL), and the solution was cooled to 0 °C under argon. Borane–THF complex (15 mL, 1 M solution in THF, 15 mmol) was added dropwise with stirring. The reaction mixture was then allowed to warm up to room temperature and stirred for 15 min when TLC indicated completion of the reaction. After the solution was cooled to 0 °C, the excess borane was quenched with water (0.5 mL). The borane complex was then oxidized by the slow, simultaneous addition of 3 M NaOH (8 mL) and 30% H_2O_2 (8 mL). Dilution with ether (100 mL), washing with water (20 mL), 10% sodium thiosulfate solution (20 mL), and water (20 mL), drying over anhydrous $MgSO_4$, and removal of the solvents under reduced pressure afforded an oily residue. Purification by column chromatography (silica, 5% methanol in ether) yielded **8** as an oil (2.06 g, 81%): R_f 0.42 (5% methanol in ether); IR (liquid film) ν_{max} 3450, 3050, 2920, 2860, 1475, 1400, 1230, 1160, 1110, 1055, 965, 875, 755; ^1H NMR (360 MHz, $CDCl_3$) τ 2.63 (m, 2 H, aromatic), 2.72 (m, 2 H, aromatic), 5.70 (s, 2 H, CH_2SO_2), 5.80 (dd, J = 8, 6 Hz, 1 H, $CHSO_2$), 6.33 (t, J = 6 Hz, 2 H, CH_2O), 7.83 (m, 1 H, CH_2), 8.00 (m, 1 H, CH_2), 8.33 (m, 5 H, CH_2), 8.47 (m, 3 H, CH_2); mass spectrum, m/e (relative intensity) 254 (M^+, 2.9%), 236 (M - H_2O, 4.1%), 190 (M - SO_2, 1.8%), 168 ($C_8H_8SO_2$, 3.0%), 131 (53.8%), 129 (base peak). Anal. ($C_{13}H_{18}O_3S$) C, H.

1,3-Dihydrobenzo[*c*]thiophene-1-pentanal 2,2-Dioxide (9). Pyridinium chlorochromate (1.070 g, 4.98 mmol) was suspended in anhydrous CH_2Cl_2 (8 mL). 1,3-Dibenzo[*c*]thiophene-1-pentanol 2,2-dioxide (**8**) (843 mg, 3.32 mmol) was added in CH_2Cl_2 (2 mL), and the mixture stirred for 2 h under argon. Ether (100 mL) was added and the solution was filtered through a layered plug of Celite and anhydrous $MgSO_4$. Removal of the solvents on the rotary evaporator furnished crude aldehyde **9** (602 mg, 72%) which was used directly without further purification: oil; R_f 0.50 (5% methanol in ether); IR (liquid film) ν_{max} 3050, 3000, 2920, 2850, 2820 (aldehyde), 2700 (aldehyde), 1720 (aldehyde), 1460, 1310, 1195, 1125, 1030, 900, 810, 750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 0.25 (s, 1 H, CHO), 2.65 (m, 2 H, aromatic), 2.72 (m, 2 H, aromatic), 5.70 (s, 2 H, CH_2SO_2), 5.82 (m, 1 H, $CHSO_2$), 7.25 (m, 2 H, CH_2CHO), 7.88 (m, 1 H, CH_2), 8.00 (m, 1 H, CH_2), 8.28 (m, 4 H, CH_2); mass spectrum m/e (relative intensity) 252 (M^+, 1.0%), 188 (M - SO_2, 2.8%), 168 ($C_8H_8SO_2$, 1.2%), 84 (base peak); exact mass calcd for $C_{13}H_{16}O_3S$ 252.0819, found 252.0793.

Ethyl (*E*)-7-(1,3-Dihydrobenzo[*c*]thien-1-yl)-2-heptenoate *S,S*-Dioxide (10). Crude 1,3-Dihydrobenzo[*c*]thiophene-1-pentanal 2,2-dioxide (**9**) (602 mg, 2.4 mmol) was dissolved in anhydrous benzene (10 mL). (Carbethoxymethylene)triphenylphosphorane (1.002 g, 2.88 mmol) was added, and the solution stirred at room temperature under argon overnight. The solvent was removed under reduced pressure, and purification by column chromatography (silica, 25% ethyl acetate in hexane) yielded the ester **10** as an oil (543 mg, 78%): R_f 0.14 (silica, 25% ethyl acetate in hexane); IR (liquid film) ν_{max} 3050, 2960, 2920, 2850, 1720 (ester), 1650 (olefin), 1460, 1320, 1245, 1140, 1105, 985, 865, 775, 715 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.70 (m, 2 H, aromatic), 2.77 (m, 2 H, aromatic), 3.10 (dt, J = 15, 6 Hz, 1 H, CH=CHCOOEt), 4.20 (d, J = 15 Hz, 1 H, CHCOOEt), 5.73 (s, 2 H, CH_2SO_2), 5.85 (q, J = 7 Hz, 2 H, OCH_2), 5.87 (m, 1 H, $CHSO_2$), 7.75 (m, 2 H, allylic), 7.87 (m, 1 H, CH_2), 8.03 (m, 1 H, CH_2), 8.33 (m, 2 H, CH_2), 8.43 (m, 2 H, CH_2), 8.72 (t, J = 7 Hz, 3 H, CH_3); mass spectrum m/e (relative intensity) 322 (M^+, 0.2%), 276 (M - CH_3CH_2OH, 2.2%), 238 (M - SO_2, 0.5%), 168 ($C_8H_8SO_2$, 2.7%), 57 (base peak). Anal. ($C_{17}H_{22}O_4S$) C, H.

Pyrolysis of Alkylated 1,3-Dihydrobenzo[*c*]thiophene 2,2-Dioxides. General Procedure. Method A. The sulfone was dissolved in di-*n*-butyl phthalate (1 mmol in 2 mL) and the solution degassed with argon. The solution was then heated at 210 °C under argon, and the progress of the reaction monitored by TLC. Once the reaction was complete (1–8 h), the products were isolated directly by column chromatography in the yields indicated.

Method B. The sulfone (1 mmol) was dissolved in ethyl acetate (100 mg/5 mL) and passed through a quartz tube (12 × 1 in.) heated to 300 °C. The condensate was collected and the solvent removed under reduced pressure. Purification by column chromatography or preparative layer chromatography furnished the pure products in the yields indicated.

***cis*- and *trans*-2,3,3a,4,5,9b-Hexahydro-1*H*-benzo[*c*]indenes (11ab)**: method A, 80%; method B, 65%; 3:1 trans/cis by GC (unassigned); oil; R_f 0.36 (silica, hexane); IR (liquid film) ν_{max} 3050, 3000, 2940, 2860, 1480, 1450, 1040, 765, 740 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.95 (m, 4 H, aromatic), 7.07 (m, 2 H, $ArCH_2$), 7.37 (m, 1 H, Ar-

$CH_{tert}CH_{tert}$), 7.67 (m, 1 H, $ArCH_{tert}$), 7.70–8.83 (m, 8 H, CH_2); ^{13}C NMR (25.2 MHz, $CDCl_3$) δ 141.25, 140.67, 136.87, 136.59, 128.93, 128.26, 125.76, 125.65, 125.38, 125.19, 124.93, 47.50, 43.93, 42.60, 37.39, 35.10, 32.48, 30.78, 30.02, 29.20, 28.56, 28.15, 27.45, 24.42, 22.71; mass spectrum, *m/e* (relative intensity) 172 (M^+, 56.2%), 144 (79.9%), 143 (54.8%), 129 (base peak), 128 (37.5%), 115 (30%), 91 (26.7%); exact mass calcd for $C_{13}H_{16}$ 172.1252, found 172.1249.

***cis*- and *trans*-1,2,3,4,4a,9,10,10a-Octahydrophenanthrenes (12ab)**: method A, 65%; method B, 42%; mixture of trans and cis isomers; ca. 5:1 trans/cis (^1H NMR trans τ 7.77 (0.83 H, $ArCH_{tert}$); cis τ 7.63 (0.17 H, $ArCH_{tert}$); the remaining cis isomer proton signals were obscured due to considerable overlap with the signals of the trans isomer); oil; R_f 0.36 (silica, hexane); IR (liquid film) ν_{max} 3050, 2990, 2925, 2860, 1475, 1440, 780, 765, 755, 735 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.77 (m, 1 H, aromatic), 2.98 (m, 3 H, aromatic), 7.22 (m, 2 H, $ArCH_2$), 7.58 (br dd J = 12, 3 Hz, 1 H, $ArCH_{tert}CH_{tert}$), 7.77 (br dd, J = 12, 6 Hz, 1 H, $ArCH_{tert}$), 8.17 (m, 5 H, CH_2), 8.53 (m, 5 H, CH_2); ^{13}C NMR (25.2 MHz, $CDCl_3$) cis isomer δ 141.63, 135.82, 128.42, 125.20, 33.82, 32.53, 31.71, 29.37, 26.86, 26.05, 23.82, 21.48; trans isomer δ 140.33, 136.69, 128.72, 125.20, 43.70, 40.14, 34.28, 30.83, 30.60, 29.78, 26.86, 26.22; mass spectrum *m/e* (relative intensity) 186 (M^+, base peak), 143 (76.9%), 129 (83.1%), 128 (39.5%), 115 (34.2%), 104 (33.6%); exact mass calcd for $C_{14}H_{18}$ 186.1408, found 186.1418.

***trans*-Ethyl 4b,5,6,7,8,8a,9,10-Octahydro-9-phenanthrenecarboxylate (13a,b)**: method A, 71%; method B, 80%; 11:1 trans/cis (^1H NMR trans τ 6.88 (0.92H, $ArCH_2$); cis τ 7.23 (0.08 H, $ArCH_2$)). Recrystallization from *n*-hexane yielded pure trans compound: mp 58.5–60 °C (hexane); R_f 0.23 (silica, 5% ether in hexane); IR (CCl_4) ν_{max} 3050, 3025, 2960, 2940, 2860, 1740 (ester), 1490, 1460, 1410, 1360, 1335, 1275, 1240, 1215, 1150, 1100, 1045, 875 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.75 (m, 1 H, aromatic), 2.93 (m, 3 H, aromatic), 5.83 (m, 2 H, OCH_2), 6.88 (dd, J = 18, 12 Hz, 1 H, $ArCH_2$), 7.08 (dd, J = 18, 6 Hz, 1 H, $ArCH_2$), 7.48 (m, 1 H, CHCOOEt), 7.55 (m, 1 H, $ArCH_{tert}CH_{tert}$), 7.67 (br t, J = 12 Hz, 1 H, $ArCH_{tert}$), 8.10 (br d, J = 12 Hz, 1 H, CH_2), 8.22 (br d, J = 12 Hz, 2 H, CH_2), 8.43 (br q, J = 10 Hz, 1 H, CH_2), 8.68 (m, 4 H, CH_2), 8.73 (t, J = 6 Hz, 3 H, CH_3); ^{13}C NMR (25.2 MH_2, $CDCl_3$) δ 174.87, 138.98, 134.29, 128.27, 125.63, 125.41, 124.84, 59.72, 46.48, 42.70, 42.32, 32.82, 31.01, 30.78, 26.34, 25.64, 14.00; mass spectrum *m/e* (relative intensity) 258 (M^+, 10.8%), 184 (base peak), 141 (66.8%), 128 (52.4%). Anal. ($C_{17}H_{22}O_2$) C, H.

Ethyl *cis*- and *trans*-1-Methyl-2-oxo-5-vinylcyclopentaneacetates (16). 2-Methylcyclopentenone[12] (1.92 g, 20 mmol) was dissolved in anhydrous THF (125 mL). CuI (5.7 g, 30 mmol) was added and the mixture cooled to −60 °C under argon. Vinylmagnesium bromide (25 mL of a 1.2 M solution in THF, 30 mmol) was added dropwise with stirring over a 15-min period, and the mixture was then allowed to warm up to −40 °C over a 30-min period. The mixture was then cooled back to −60 °C and ethyl bromoacetate (13.4 g, 8.9 mL, 80 mmol) in HMPA (150 mL) was added dropwise over a 10-min period. Stirring was continued and the mixture was allowed to warm up to room temperature over 15 h. The reaction mixture was poured into saturated NH_4Cl solution (300 mL) and extracted with ether (3 × 100 mL). The combined extracts were washed with saturated NH_4Cl solution (50 mL) and water (50 mL) and dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure and purification by column chromatography (silica, 20% ether in hexane R_f 0.23) yielded 2.9 g (69%) of a colorless liquid consisting of a mixture of the desired ketone **16** and its diastereomer [3.5:1 by ^1H NMR (360 MHz, $CDCl_3$) τ 9.15 (s, CH_3) for **16** and 8.87 (s, CH_3) for its diastereomer]; IR (liquid film) ν_{max} 3080, 2950, 2930, 2850, 1730 (C=O, COOEt), 1630 (vinyl), 1405, 1345, 1200, 1095, 1030, 920 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.22 (m, 1 H, vinylic), 4.85 (m, 2 H, vinylic), 5.90 (q, J = 8 Hz, 2 H, CH_2O), 7.04 (m, 1 H, allylic), 7.32 (m, 1 H, CH_2), 7.58 (m, 3 H, CH_2), 7.90 (m, 1 H, CH_2), 8.13 (m, 1 H, CH_2), 8.77 (t, J = 8 Hz, 3 H, CH_3CH_2O), 8.87 (s, 0.66 H, CH_3), 9.15 (s, 2.34 H, CH_3); mass spectrum, *m/e* (relative intensity) 210 (M^+, 3%), 195 (M − CH_3, 8.7%), 165 (M − OEt, 15%), 149 (10.8%), 137 (M − COOEt, 17.7%), 136 (5.8%), 123 (base peak), 122 (20%), 121 (8.9%). Anal. ($C_{12}H_{18}O_3$) C, H.

Ethyl *cis*- and *trans*-6-Methyl-7-vinyl-1,4-dioxaspiro[4.4]nonane-6-acetate (17). Ethyl *cis*- and *trans*-1-methyl-2-oxo-5-vinylcyclopentaneacetate (**16**) (3.5:1 mixture, 1.20 g, 5.7 mmol) was dissolved in anhydrous benzene (28 mL). Ethylene glycol (3.5 g, 3.2 mL, 57 mmol) and *p*-toluenesulfonic acid (22 mg, 2 mmol %) were added, and the mixture was refluxed for 12 h while water was azeotropically removed from the reaction mixture by a Dean–Stark trap. The reaction mixture was diluted with ether (100 mL), washed with 5% $KHCO_3$ (25 mL) and water (25 mL), and dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure and purification by column chromatography (silica, ether–hexane 1:1) yielded the ketal **17** together with its stereoisomer (1.32 g, 91%): R_f 0.23 (silica, 20% ether in hexane); IR (liquid film) ν_{max} 3050, 2950, 2860, 1740 (COOEt), 1640 (vinyl), 1410, 1340, 1265, 1120, 1050, 1000, 915, 735 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.22 (m, 1 H, vinylic), 4.93 (m, 2 H, vinylic), 5.90 (q, J = 8 Hz, 2 H, CH_2O), 6.08 (m, 4 H, ketal), 7.18 (q, J = 9 Hz, 1 H, allylic), 7.47 (q, J = 8 Hz, 0.22 H, CH_2), 7.57 (q, J = 8 Hz, 0.22, CH_2), 7.70 (d, J = 12 Hz, 0.78 H, CH_2), 7.78 (d, J = 12 Hz, 0.78 H, CH_2), 8.13 (m, 3 H, CH_2), 8.40 (m, 1 H, CH_2), 8.75 (t, J = 8 Hz, 3 H, CH_3CH_2O), 8.78 (s, 0.66 H, CH_3), 9.00 (s, 2.34 H, CH_3); mass spectrum, *m/e* (relative intensity) 254 (M^+, 0.2%), 209 (M − OEt, 4.6%), 181 (M − COOEt, 0.4%), 99 (base peak), 86 (22%); exact mass calcd for $C_{14}H_{22}O_4$ 254.1517, found 254.1513.

***trans*-6-Methyl-7-vinyl-1,4-dioxaspiro[4.4]nonane-6-ethanol (18) and Its Cis Diastereomer.** Lithium aluminum hydride (LAH) (350 mg, 9.2 mmol) was suspended in anhydrous ether (50 mL). Ethyl *cis*- and *trans*-6-methyl-7-vinyl-1,4-dioxaspiro[4.4]nonane-6-acetate (**17**) (1170 mg, 4.6 mmol) in anhydrous ether (10 mL) was added dropwise with stirring under argon. After the addition was complete, the mixture was stirred for an additional 15 min. Excess $LiAlH_4$ was quenched with water and the mixture was stirred for 3 h with anhydrous $MgSO_4$. Filtration, removal of solvent under reduced pressure, and purification by medium-pressure column chromatography (silica, 25% hexane in ether) yielded *trans*-6-methyl-7-vinyl-1,4-dioxaspiro[4.4]nonane-6-ethanol (**18**) (more polar, 735 mg, 75%) and its cis diastereomer (210 mg, 22%, less polar). Trans isomer (**18**): R_f 0.31 (silica, ether); IR (liquid film) ν_{max} 3340 (OH), 3050, 2950, 2860, 1635 (vinyl), 1430, 1375, 1300, 1155, 1090, 1040, 995, 945 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.26 (m, 1 H, vinylic), 4.93 (m, 2 H, vinylic), 6.03 (m, 4 H, ketal), 6.33 (m, 2 H, CH_2OH), 7.41 (br s, 1 H, OH), 7.50 (q, J = 9 Hz, 1 H, allylic), 8.17 (m, 4 H, CH_2), 8.35 (m, 1 H, CH_2), 8.50 (dt, J = 14, 7 Hz, 1 H, CH_2), 9.05 (s, 3 H, CH_3); mass spectrum *m/e* (relative intensity) 212 (M^+, 0.8%), 197 (0.2%), 184 (0.6%), 181 (0.5%), 167 1.3%), 151 (4.4%), 139 (11.3%), 123 (3.3%), 113 (8.4%), 100 (26.3%), 99 (base peak), 86 (36.4%). Anal. ($C_{12}H_{20}O_3$) C,

H. Cis isomer: R_f 0.40 (silica, ether); IR (liquid film) ν_{max} 3400 (OH), 3050, 2960, 2860, 1670 (vinyl), 1425, 1345, 1210, 1140, 1040, 950 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.20 (m, 1 H, vinylic), 4.98 (m, 2 H, vinylic), 6.05 (m, 4 H, ketal), 6.23 (m, 1 H, CH_2O), 6.37 (br s, 1 H, CH_2O), 6.88 (br s, 1 H, OH), 7.53 (q, J = 8 Hz, 1 H, allylic), 8.03 (m, 1 H, CH_2), 8.17 (m, 2 H, CH_2), 8.32 (m, 1 H, CH_2), 8.38 (m, 1 H, CH_2), 8.52 (dt, J = 14, 7 Hz, 1 H, CH_2), 9.03 (s, 3 H, CH_3); mass spectrum m/e (relative intensity) 212 (M^+, 0.7%), 139 (11%), 113 (12.1%), 100 (29.2%), 99 (base peak), 86 (37.4%); exact mass calcd for ($C_{12}H_{20}O_3$) 212.1412, found 212.1390.

***trans*-6-Methyl-7-vinyl-1,4-dioxaspiro[4.4]nonane-6-ethanol *p*-Toluenesulfonate (19).** *trans*-6-Methyl-7-vinyl-1,4-dioxaspiro[4.4]nonane-6-ethanol (18) (212 mg, 1 mmol) was dissolved in anhydrous pyridine (1 mL). *p*-Toluenesulfonyl chloride (228 mg, 1.2 mmol) was added and the mixture stirred at room temperature under argon for 2 h. The reaction mixture was diluted with ether (50 mL), washed with water (2 × 10 mL), 10% $CuSO_4$ (3 × 10 mL), water (1 × 10 mL), and 5% $KHCO_3$ (10 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure and crystallization from ether–hexane (1:1) furnished the tosylate **19** (293 mg, 80%) as a white crystalline solid: mp 86–87 °C (ether–hexane); R_f 0.28 (silica, ether–hexane 1:1), IR ($CHCl_3$) ν_{max} 3050, 3000, 2950, 2940, 2860, 1600 (vinyl), 1355, 1280, 1190, 1100, 1025, 955, 845, cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.28 (d, J = 8 Hz, 2 H, aromatic), 2.71 (d, J = 8 Hz, 2 H, aromatic), 4.40 (m, 1 H, vinylic), 5.05 (m, 2 H, vinylic), 5.89 (m, 2 H, CH_2O), 6.22 (m, 4 H, ketal), 7.58 (s, 3 H, aromatic, CH_3), 7.61 (q, J = 8 Hz, 1 H, allylic), 8.10–8.55 (m, 6 H, CH_2), 9.17 (s, 3 H, CH_3); mass spectrum, m/e (relative intensity) 366 (M^+, 0.1%), 194 (M – TsOH, 4.9%), 155 (28.7%), 135 (45.9%), 91 (base peak), 79 (43.1%); exact mass calcd for $C_{19}H_{26}O_5S$ 366.1500, found 366.1485.

***trans*-6-[2-(1,3-Dihydrobenzo[*c*]thien-1-yl)ethyl]-6-methyl-7-vinyl-1,4-dioxaspiro[4.4]nonane *S*,*S*-Dioxide (20a,b).** Potassium hydride (205 mg, 40% oil dispersion, 2 mmol) was suspended in anhydrous DME (6 mL) and the mixture cooled in an ice bath under argon. 1,3-Dihydrobenzo[*c*]thiophene 2,2-dioxide (**2**) (336 mg, 2 mmol) was added portionwise, and the resulting solution stirred at room temperature for 5 min under argon. *trans*-6-Methyl-7-vinyl-1,4-dioxaspiro[4.4]nonane-6-ethanol *p*-toluenesulfonate (**19**) (366 mg, 1 mmol) was added and the mixture was stirred at room temperature under argon for 12 h. The reaction mixture was diluted with ether (75 mL), washed with water (25 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure and purification by medium-pressure column chromatography (silica, 1% acetone in CH_2Cl_2) afforded the coupling product **20a,b** (279.4 mg, 77%) as a mixture of diastereomers (1:1): oil; R_f 0.14 (silica, 1% acetone in CH_2Cl_2); IR (liquid film) ν_{max} 3050, 2950, 2930, 2870, 1640 (vinyl), 1460, 1210, 1155, 1070, 1000, 915 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.68 (m, 4 H, aromatic), 4.24 (m, 1 H, vinylic), 4.95 (m, 2 H, vinylic), 5.72 (m, 2 H, CH_2SO_2), 5.95 (m, 1 H, $CHSO_2$), 6.14 (m, 4 H, ketal), 7.48 (m, 1 H, allylic), 7.65–8.47 (m, 8 H, CH_2), 9.05 (s, 3 H, CH_3); mass spectrum, m/e (relative intensity) 362 (M^+, 0.4%), 298 (M – SO_2, 1.7%), 195 (M – $C_8H_7SO_2$, 1.8%), 181 (1.5%), 168 ($C_8H_8SO_2$, 1.0%), 167 ($C_8H_7SO_2$, 3.7%), 139 (7.2%), 117 (4.8%), 99 (base peak), 86 (21.3%). Anal. ($C_{20}H_{26}O_4S$) C, H. S.

(2*R,3*R**)-2-[2-[(*R**)- and -(*S**)-1,3-Dihydrobenzo[*c*]thien-1-yl]ethyl]-2-methyl-3-vinylcyclopentanone *S*,*S*-Dioxides (21a and 21b).** *trans*-6-[2-(1,3-Dihydrobenzo[*c*]thien-1-yl)ethyl]-6-methyl-7-vinyl-1,4-dioxaspiro[4.4]nonane *S*,*S*-dioxide (**20a,b** mixture of diastereomers) (362 mg, 1 mmol) was dissolved in a mixture of HOAc–THF–H_2O (3:2:2) (10 mL) and stirred at 45 °C under argon for 12 h. The solvents were removed under reduced pressure, and purification by column chromatography (silica, ether) afforded the ketone **21a,b** (311 mg, 98%) as a 1:1 mixture of diastereomers, which were separated by preparative layer chromatography (silica, ether–hexane 1:1, 3 developments).

Less polar isomer: colorless crystals; R_f 0.18 (silica, ether–heane 1:1); mp 138–139 °C (ether–hexane); IR ($CHCl_3$) ν_{max} 3050, 2900, 2850, 2825, 1730 (C=O), 1635 (vinyl), 1460, 1375, 1225, 1125, 1105, 1075, 925 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.64 (m, 2 H, aromatic), 2.72 (m, 2 H, aromatic), 4.18 (m, 1 H, vinylic), 4.97 (m, 2 H, vinylic), 5.66 (d, J = 15 Hz, 1 H, CH_2SO_2), 5.72 (d, J = 15 Hz, 1 H, CH_2SO_2), 5.84 (dd, J = 8, 2 Hz, 1 H, $CHSO_2$), 7.22 (m, 1 H, allylic), 7.54 (dd, J = 18, 8 Hz, 1 H, CH_2CO), 7.87 (m, 3 H, CH_2), 8.14 (m, 4 H, CH_2), 9.08 (s, 3 H, CH_3); mass spectrum, m/e (relative intensity) 318 (M^+, 11%), 254 (M – SO_2, 5.8%), 168 ($C_8H_8SO_2$, 4.4%), 167 ($C_8H_7SO_2$, 6.0%), 123 (base peak). Anal. ($C_{18}H_{22}O_3S$) C, H.

More polar isomer: oil; R_f 0.14 (silica, ether–hexane 1:1); IR (liquid film) ν_{max} 3050, 2950, 2925, 1730 (C=O), 1635 (vinyl), 1460, 1375, 1260, 1155, 1105, 1025, 955, 870, 810, 740 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.66 (m, 4 H, aromatic), 4.22 (m, 1 H, vinylic), 4.86 (m, 2 H, vinylic), 5.70 (s, 2 H, CH_2SO_2), 5.86 (dd, J = 7,6 Hz, 1 H, $CHSO_2$), 7.33 (m, 1 H, allylic), 7.58 (dd, J = 18, 8 Hz, 1 H, CH_2CO), 7.85 (m, 4 H, CH_2), 8.17 (m, 2 H, CH_2), 8.28 (m, 1 H, CH_2), 9.10 (s, 3 H, CH_3); mass spectrum, m/e (relative intensity) 318 (M^+, 11.7%), 254 (M – SO_2, 5.4%), 168 ($C_8H_8SO_2$, 5.9%), 167 ($C_8H_7SO_2$, 10.4%), 123 (base peak). Anal. ($C_{18}H_{22}O_3S$) C, H.

***dl*-Estra-1,3,5(10)-trien-17-one (1).** The sulfone **21a** or **21b** or a mixture of both diastereomers **21a,b** (318 mg, 1 mmol) was dissolved in di-*n*-butyl phthalate (1.62 mL, giving a ca. 0.5 M solution) and degassed with argon. The solution was heated at 210 °C under argon for 8 h. The reaction mixture was then purified directly by medium-pressure column chromatography (silica, 3% ether in benzene), followed by recrystallization (hexane), to yield the product as a white crystalline solid (215 mg, 85%), mp 109–110 °C, chromatographically and spectroscopically identical with an authentic sample: R_f 0.26 (silica, 3% ether in benzene); IR (CCl_4) ν_{max} 3060, 3030, 2930, 2855, 1740 (C=O), 1460, 1390, 1215, 1050, 970, 915 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.72 (m, 1 H, aromatic), 2.88 (m, 3 H, aromatic), 7.07 (m, 2 H, CH_2Ar), 7.49 (dd, J = 18, 8 Hz, 1 H, CH_2CO), 7.56 (br dd, J = 12, 3 Hz, 1 H, $ArCH_{tert}CH_{tert}$), 7.67 (br dd, J = 12, 1 Hz, 1 H, $ArCH_{tert}$), 7.84 (dd, J = 18, 8 Hz, 1 H, CHCO), 7.97 (m, 3 H, CH, CH_2), 8.45 (m, 6 H, CH, CH_2), 9.08 (s, 3 H, CH_3); mass spectrum, m/e (relative intensity) 254 (M^+, base peak), 210 (47.1%), 197 (41.9%), 142 (48.8%), 129 (52.4%), 128 (55.4%); exact mass calcd for $C_{18}H_{22}O$ 254.1670, found 254.1662. The 360-MHz ^1H NMR spectrum of the steroidal product after chromatographic isolation and before recrystallization revealed the presence of the cis-anti-trans C-9 epimer of **1** (ca. 5–7% τ 9.08 (s, CH_3) for **1** and τ 9.02 (s, CH_3) for its epimer).

Preparation of *d*-Estra-1,3,5(10)-trien-17-one (1) from *d*-Estrone. *d*-Estrone (54 mg, 0.2 mmol), 5-chloro-1-phenyltetrazole (360 mg, 2 mmol), and potassium carbonate (560 mg, 4 mmol) were heated in methyl ethyl ketone (2 mL) at 90 °C. After 6 h the solvent was removed under reduced pressure, and the crystalline residue pu-

rified by column chromatography (silica, 5% methanol in CH_2Cl_2, R_f 0.57) to yield the phenol derivative as white crystals (68 mg, 82%), mp 191–193 °C (ether–pentane). The tetrazolyl ether (41 mg, 0.1 mmol) was then dissolved in THF (5 mL) and hydrogenated over 10% palladium on charcoal (10 mg) at room temperature and atmospheric pressure for 48 h. Filtration of the catalyst and removal of the solvent under reduced pressure followed by preparative layer chromatography (silica, 10% ether in hexane, R_f 0.13, 3 developments) yielded *d*-estratrienone 1 as a white crystalline solid (15 mg, 60%), mp 135–136.5 °C, chromatographically and spectroscopically indentical with our synthetic sample and an authentic sample provided by Syntex.[13]

Acknowledgment. We thank Professor M. P. Cava and Dr. F. Li, Syntex Research Laboratories, for generous gifts of estrone and estra-1,3,5(10)-trien-17-one, respectively. The 360-MHz ^1H NMR spectra were recorded at the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania directed by Dr. G. McDonald. Financial support of this work was provided by Merck, Sharp, and Dohme, USA, Grunenthal Chemie, West Germany, and the University of Pennsylvania.

Registry No. *d*-1, 53-45-2; (±)-1, 69515-99-7; *epi*(*C*-9)-1, 72984-28-2; 2, 2471-91-2; 5, 72939-06-1; 5a, 72953-43-6; 6, 72939-07-2; 6a, 72939-08-3; 7, 72939-09-4; 7a, 72938-78-4; 8, 72938-79-5; 9, 72938-80-8; 10, 72938-81-9; 11a, 71721-30-7; 11b, 71721-31-8; 12a, 20480-66-4; 12b, 20480-67-5; 13a, 72938-82-0; 13b, 72938-83-1; (±)-*cis*-16, 72938-84-2; (±)-*trans*-16, 72938-85-3; (±)-*cis*-17, 72938-86-4; (±)-*trans*-17, 72938-87-5; (±)-*cis*-18, 72938-88-6; (±)-*trans*-18, 72938-89-7; (±)-*trans*-19, 72938-90-0; (±)-20a, 72938-91-1; (±)-20b, 72984-25-9; (±)-21a, 72938-92-2; (±)-21b, 72984-26-0; 22, 26435-99-4; 5-bromo-1-pentene, 1119-51-3; 6-iodo-1-hexene, 18922-04-8; 5-hexen-1-ol tosylate, 18922-06-0; 5-hexen-1-ol mesylate, 64818-36-6; ethyl iodide, 75-03-6; ethanol tosylate, 22381-54-0; (carbethoxymethylene)triphenylphosphorane, 1099-45-2; 2-methylcyclopentenone, 1120-73-6; vinyl bromide, 593-60-2; ethyl bromoacetate, 105-36-2; 5-chloro-1-phenyltetrazole, 14210-25-4.

Total Synthesis of the Major Metabolite of Methoxsalen

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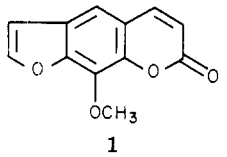
The total synthesis of the 6-coumarinylacetic acid (**15**), the major metabolic isolate of methoxsalen (**1**), starting from umbelliferone (**5**) is described. Several derivatives of a second metabolite, **4**, were also prepared from the common intermediate aldehyde **13**. This preparation involves a novel rearrangement of the bromoacetate **20** to the acetoxyphenol **21**. A mechanism for the displacement reactions of the metabolite **4** and its derivative **21** implicating the transient enone **24** is presented.

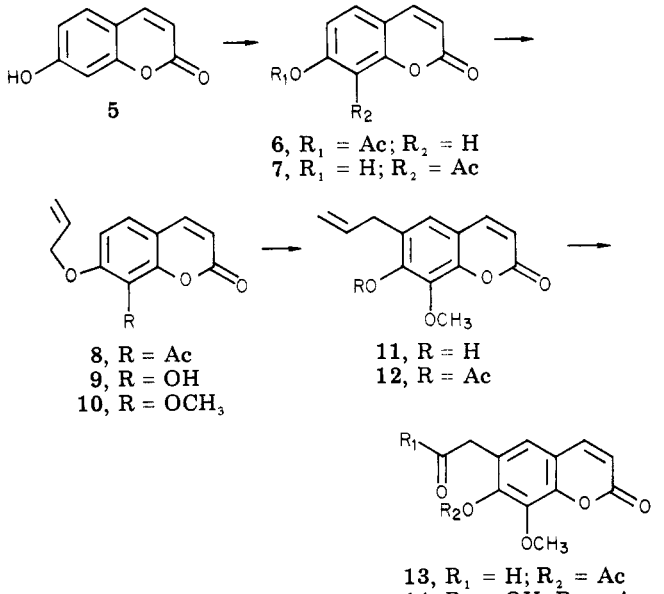
Extracts of the flowering plant *Ammi majus* Linn (family Umbelliferae),[2] a common annual herbaceous plant indigenous to the Nile Delta region, have been employed in the treatment of leukodermia in the form of an ocher powder known as "ameum" since the time of Charles the Great.[3] The active principle was isolated in 1947 by Fahmy and Abu-Shady[4] and was named "ammoidin". An elucidation of the structure was presented by Schönberg[5] in 1950 and shown to be identical with xanthotoxin, a furocoumarin previously reported by Thomas.[6] A number of total syntheses of this substance have since appeared.[7]

A renewed interest in this compound has been ignited by the disclosure that ammoidin (now primarily designated as methoxsalen (**1**) in the literature) is an effective photochemotherapeutic agent for the treatment of psoriasis.[8]



1

Scheme I



5

6, R_1 = Ac; R_2 = H
7, R_1 = H; R_2 = Ac

8, R = Ac
9, R = OH
10, R = OCH_3

11, R = H
12, R = Ac

13, R_1 = H; R_2 = Ac
14, R_1 = OH; R_2 = Ac
15, R_1 = OH; R_2 = H
16, R_1 = OCH_3; R_2 = H

We have recently published[9] the isolation and structure determination of the major metabolites of methoxsalen (**1**) and wish to report herein the total synthesis of metabolite A (**3**) and a derivative of metabolite B (**4**). Metabolism

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