New Synthetic Reactions. A Chemoselective Approach to Cleavage α to a Carbonyl Group via β-Keto Sulfides. Preparation of 1,2-Diketones

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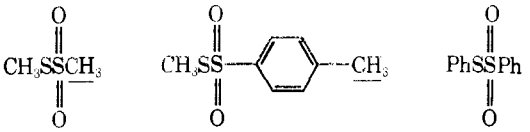
Abstract: β-Keto sulfides, available by the direct sulfenylation of enolates with diphenyl disulfide or phenyl benzenethiosulfonate, are acetoxylated by lead tetraacetate in warm benzene. The β-keto acetoxy sulfides represent a monoprotected form of a 1,2-dicarbonyl compound. Oxidation and sulfoxide pyrolysis produce regiospecifically the monoenol acetate of the diketone. Treatment with iodine in methanol gives the monoketal. Exposure to basic hydrogen peroxide leads directly to the ring cleaved diacids. Alternatively, the β-keto sulfide upon subjection to basic hydrogen peroxide is directly converted to the ring cleaved diacids. Interestingly, this cleavage also succeeds with potassium superoxide in the absence of any crown compounds. Thus, the β-keto sulfides provide direct and easy access to 1,2-dicarbonyl compounds or a route for ring cleavage of cyclic ketones. The chemoselectivity of the approach is discussed.

Strategy in the total synthesis of natural products and theoretically important molecules frequently focuses on ring cleavage reactions. Problems in controlling stereochemistry of acyclic and large ring compounds[1] are particularly resolved by this approach. Acyclic dicarboxylic acids have oftentimes served as important synthetic intermediates. For example, 3-benzyladipic acids are important starting materials in the total synthesis of tetracyclines.[2,3] Adjustment of ring sizes by oxidative cleavage followed by reclosure has played an important role—e.g., in creation of the *trans*-hydrindan system.[4] The importance of such synthetic design requires the development of general but chemoselective approaches for such reactions. Cleavage of olefins either directly or indirectly via vicinal glycols constitutes an important solution. Carbonyl compounds have been less useful in such reactions. Classically, rearrangements like the Baeyer–Villiger or Beckmann reactions can ultimately lead to ring cleaved products of the type desired. Conversion of a carbonyl compound into an enol derivative and treatment of the latter as a reactive olefin has had some success.[5] Oxidative cleavage of α-formyl or α-arylidene ketones has had limited success.[3b,6] Recently, several significant approaches have evolved. Most noteworthy are the second-order Beckmann fragmentation of oximes of α-thioketones,[7] hydroxide induced cleavage of α,α-dithianyl ketones,[8] nitrosolysis of ketones,[9] and superoxide cleavage of α-halo ketones.[10] The limitations of such methods makes the development of alternative solutions highly desirable.

The discovery of chemoselective sulfenylation of carbonyl partners[11,12] suggests the potential utility of these intermediates in selective ring cleavage sequences. Indeed, we previously found that conversion of β-keto sulfides to the β-hydroxy sulfides followed by treatment with lead tetraacetate was an excellent approach provided that some ring strain existed (e.g., four- and five-membered rings).[13] The inapplicability of this strategy to six or larger membered cycloalkanones encouraged us to seek alternatives. One successful technique involved cleavage of 1-hydroxy-2-trimethylenedithiocycloalkanes, which provided not only ring cleavage but also adjustment of the oxidation level of more remote carbons. However, a more direct approach was clearly required.[14] In this paper, we wish to report two new solutions to this problem. In addition, this chemistry provided a new entry into 1,2-dicarbonyl compounds. A resurgence of interest in such compounds has led to the development of several new approaches.[15] Bissulfenylation provides one such entry but has been somewhat limited in scope and/or has involved difficultly accessible reagents.[11b,c,16] The approach reported herein appears to overcome some of these limitations. These two new reactions of β-keto sulfides further expand the synthetic utility of this increasingly versatile type of intermediate.

Sulfenylation. The ready availability of sulfenylated ketones led us to consider chemoselective approaches utilizing the sulfenylation reaction as the initiating step (see Tables I and II). While in most instances diphenyl disulfide (**1**) was employed for sulfenylations, further exploration of the use of thiosulfonates was undertaken.[11c] In our hands, methyl methanethiosulfonate (**2**) and methyl *p*-toluenesulfonate were not particularly effective sulfenylating agents for carbanions.[17]



2 **3** **4**

The problem that concerned us was the acidity of the methyl groups activated by the thiosulfonate group (underlined in the structures). For this reason and the intrinsic higher reactivity of phenylsulfenylating agents, phenyl benzenethiosulfonate (**4**)[18,19] was most extensively explored. The rapidity of the sulfenylation of ketones with this latter reagent makes a stoichiometric reaction (~1:1:1 ratio of base, ketone, and **4**) feasible. The reactions are somewhat cleaner and less odoriferous than with diphenyl disulfide (**1**). While it is readily accessible by oxidation of **1** with 30% aqueous hydrogen peroxide in acetic acid (see Experimental Section), it is somewhat less accessible than **1**, which is commercially available, and its higher reactivity can lead to polysulfenylation. Thus, both reagents seem to have applicability in synthesis.

It is interesting to note that with ketones **7** and **9** regiospecific sulfenylation was achieved. In both cases, not only is a single regioisomer of the product evident but also only a single stereoisomer appears to be present. Thus, **13** shows only one proton α to sulfur at δ 4.04 as a dd (J = 11.1, 6.0 Hz) and **15** shows this proton at δ 4.00 as a dd (J = 13.0, 6.2 Hz)—a pattern indicative of an axial proton (therefore phenylthio is equatorial). This stereochemistry may be a result of thermodynamic equilibration of the product since sulfenylation of **5** and **8** with **4** using stoichiometric amounts of base led only to the phenylthio group being axial. The proton at C(2) appears at δ 3.60 as a broad absorption ($W_{1/2}$ = 6 Hz) for **11** and at δ 3.79 as a broad absorption ($W_{1/2}$ = 6 Hz) for **14**—an observation supporting the equatorial nature of this proton. As previously noted, the 6-axial proton is deshielded by the axial phenylthio group and appears at δ 2.98 (td, J = 13.6, 5.8 Hz) and 3.07 (m) for **11** and **14**, respectively. The axial sulfenylations are anticipated on the basis of kinetic control. Thus, while with **1** as sulfenylating agent equilibration may occur, with **4**

Table I. Acetoxylation and Subsequent Ring Cleavage of β-Keto Sulfides

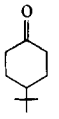
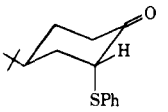
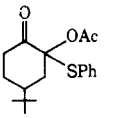
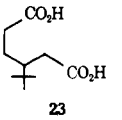
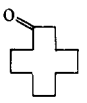
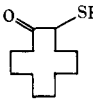
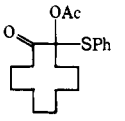
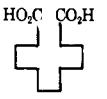
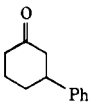
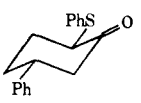
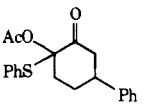
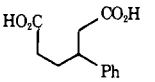
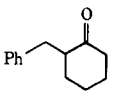
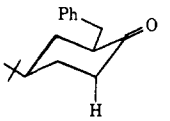
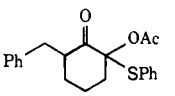
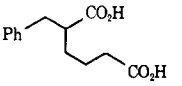
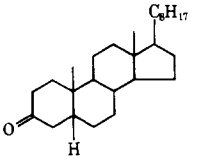
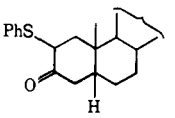
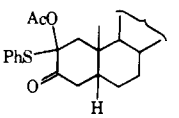
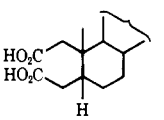
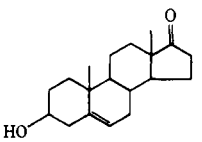
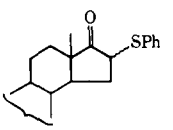
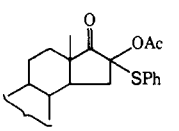
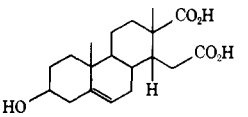
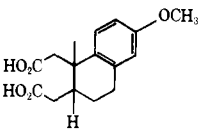
Entry	Ketone	Keto sulfide	Acetoxylated keto sulfide	Yield, %	Ring cleavage	Yield, %
1	 5	 11	 17	95	 23	67
2	 6	 12	 18	55	 24	99
3	 7	 13	 19	90	 25	80
4	 8	 14	 20	71	 26	85
5	 9	 15	 21	99	 27	65
6	 10	 16	 22	91		

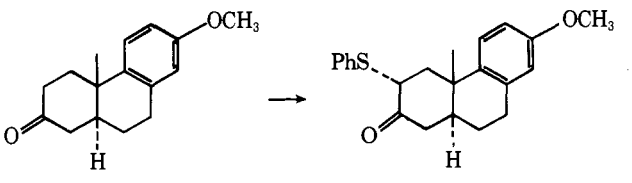
Table II. Direct Oxidative Cleavage of β-Keto Sulfides

Entry	Ketone	β-Keto sulfide	Conditions[a]	Product	Yield,[b] %
1	5	11	50 °C, 3 h AMB,[d] 12 h	23	69[c] overall from 5
2	6	12	Reflux, 60 h	24	83
3	7	13	70 °C, 16 h	25	67
4	8	14	AMB,[d] 15 h 55 °C, 14 h	26	63[c] overall from 8
5	9	15	65 °C, 15 h	27	94
6	10	16	Reflux, 16 h		67
7	28a	28b	AMB,[d] 12 h 50 °C, 16 h		55

[a] All reactions were performed in 1:1 THF–water except entries 2 and 7, which required 1:1 methanol–water. [b] All yields are for isolated, recrystallized diacids. In most cases yields before recrystallization were substantially higher. [c] In this case, the crude sulfenylated ketone was directly employed in the ring cleavage reaction and thus the yield represents the conversion from starting ketone. [d] AMB = ambient temperature.

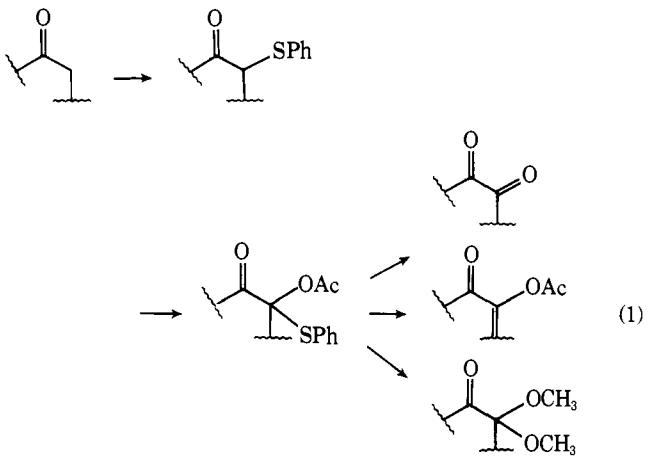
kinetics seem to dominate. It should be noted, however, that ketone **28a** only gives the isomer **28b** with the phenylthio group being equatorial with **4**. Keto sulfide **16** appears to be a 1.7:1 mixture of stereoisomers tentatively assigned the 16β (16 proton α, t, $J \sim 8$ Hz) and 16α (16 proton β, dd, $J = 7, 4$ Hz) isomers, respectively.

Acetoxylation Cleavage. 1,2-Dicarbonyl Compounds. Our



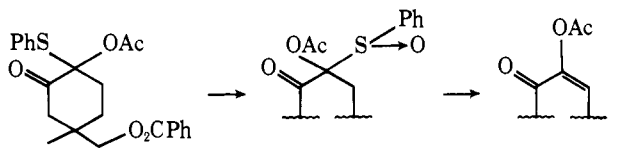
28a **28b**

initial approach to ring cleavage centered upon the known cleavage of 1,2-diketones with basic hydrogen peroxide.[20] While generation of such systems via bissulfenylation is feasible, such reactions are not easily achieved in ketones compared to esters and are somewhat capricious.[11b,c] Treatment of the β-keto sulfides with lead tetraacetate in hot benzene leads to the α-acetoxy-α-phenylthioketones normally in over 90% yields (see eq 1 and Table I).[21,22] For the five- and six-

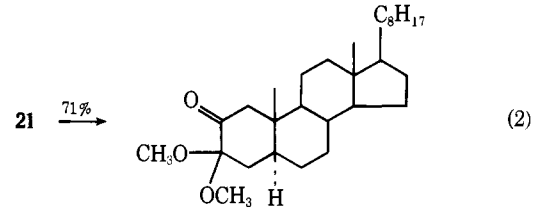


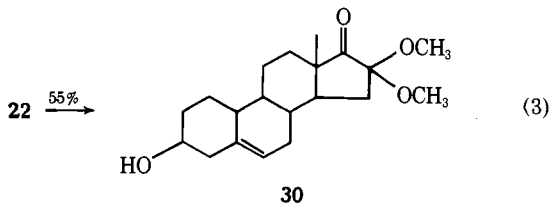
membered ring systems reaction is complete between 0.5 and 3 h, whereas the cyclododecanone system was much more sluggish. In **16** the free hydroxyl group at C(3) was best protected as its trifluoroacetate for this step. For the acetoxylation reaction it is not necessary to purify the intermediate β-keto sulfide. Indeed, this acetoxylation appears to be much more facile and general than the direct acetoxylation of simple ketones.[23]

The high yields and facility of this reaction clearly attest to its usefulness as a synthesis of 1,2-diketones which are available by hydrolytic methods. More significantly, these intermediates can be converted directly to more stable monoprotected forms of the diketone system. For example, we previously showed that oxidation to the sulfoxide followed by pyrolysis leads in high yield to the enol acetate.[22] Thus, this approach allows the

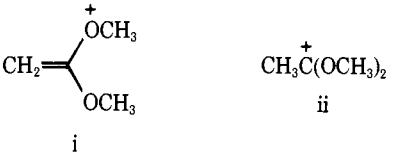


maintenance of differentiation between the two carbonyl groups. Alternatively, treatment with iodine in methanol leads to the monoketal (eq 2 and 3). The conversion of **10** to **30** at-

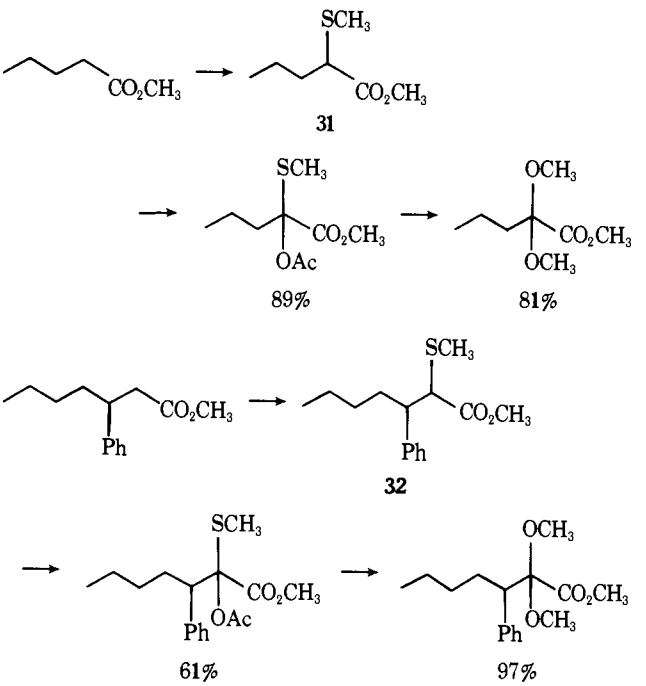




tests to the mildness of this approach. The obtention of **29** rather than the ketal at C(2) was assigned on the basis of the appearance of the protons α to the carbonyl group as a simple AB pattern with no further splitting at δ 2.40 and 2.33 (J = 12.3 Hz) which is in accord with protons at C(1), not C(4). The melting point and mass spectrum also correspond to those reported for **29**. Since this is also the product formed upon selective ketalization of the diketone it appears that this reaction may involve the diketone as an intermediate. The presence of the ketal at C(16) in **30** is assigned on the basis of the 270-MHz NMR spectrum, which shows no protons α to a carbonyl group, and the mass spectrum, which has its base peak at *m/e* 88 and an intense peak at *m/e* 89 corresponding to fragments i and ii.



We briefly explored the extension of the chemistry to sulfenylated esters **31** and **32**.[24] The acetoxylation was consid-



erably slower and required 35–45 h for completion. The slower rate may be attributed to the lower acidity of these sulfenylated derivatives compared to the β-keto sulfides. Nevertheless, the reactions were clean and good yields were obtained. Conversion to the methyl ketals proceeded smoothly as before.

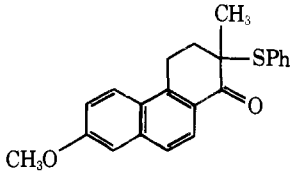
For ring cleavage, the unmasking of the diketones proceeds well from the crude acetoxy sulfides in the presence of the cleaving reagent. Thus, direct treatment of the acetoxy sulfides with basic hydrogen peroxide smoothly leads to the desired ring cleaved dicarboxylic acids as shown in Table I. The reactions proceed at room temperature in every case. Ring size did not pose any limitation as in the previous approach.[13] Considering the likelihood of the diketone as an intermediate, such an observation is expected. For this ring cleavage, it is unnecessary to purify any intermediates and most frequently the sequence from cyclic ketone to dicarboxylic acid was performed in such a manner. The structures of the products were evident from their spectral properties and comparison of their physical properties to those of the literature.

Direct Cleavage. The success of the above three-step procedure led us to consider the possibility of in situ oxidation of

the β-keto sulfide to 1 equiv of an α-diketone and cleavage. It can be envisioned that hydroxylation of the anion of the β-keto sulfide would provide such an entry to the diketone and ultimately ring cleavage. In the event, treatment of the β-keto sulfide with aqueous basic hydrogen peroxide–THF at 50–80 °C leads to the biscarboxylic acids as summarized in Table II. In several cases (Table II, entries 2 and 6), the reactions were extraordinarily slow under these conditions. In these instances, switching to an aqueous methanolic solvent clearly facilitated ring cleavage. For this sequence as well, purification of the intermediate sulfide was unnecessary. Entries 1 and 4 led nicely to ring cleavage in 63–69% overall yield without purifying any intermediates. Synthetically, such a procedure is preferred because the final product (a diacid) is so easily separated from the neutral by products such as unsulfenylated starting material.

The mildness of the reaction conditions is highlighted by several of the examples. Thus, the homoallylic alcohol portion of the epidehydroandrosterone **10** can be carried through both steps without any protecting groups. This fact contrasts with the first approach, which required protection of the alcohol for the lead tetraacetate reaction. The sensitive electron-rich aromatic ring of tricyclic ketone **28** survives unscathed. It appears that this approach has a sufficiently high degree of chemoselectivity to recommend it as a method of choice.

The mechanism of this reaction is quite obscure; however, several observations provide some insight. There is a requirement for the presence of a proton on the carbon bearing sulfur. For example, keto sulfide **33** is recovered totally unchanged.



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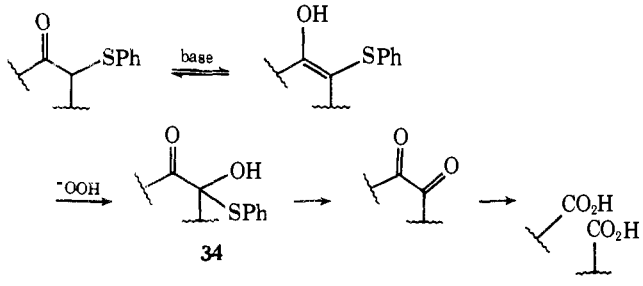
It is particularly striking to note that no sulfoxide is observed in this case or in any other case even when the reaction is run to partial completion. α,β-Unsaturated ketones, the product of thermal decomposition of such sulfoxides, also are never observed. Thus, it seems unlikely that the reaction is initiated by attack at sulfur. On this basis, Pummerer-related processes are eliminated. Addition of hydrogen peroxide anion to the carbonyl group followed by a Grob-type fragmentation also seems unlikely owing to the inertness of keto sulfides like **33.**



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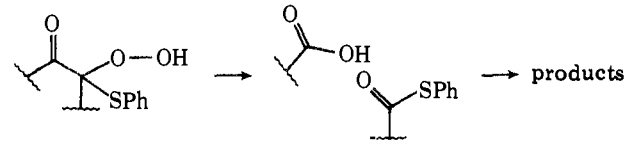
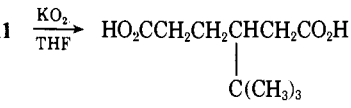
A reasonable rationale mimics the two-step process reported in the first part of this paper. Thus, hydroxylation of the enol form of the β-keto sulfide in a slow step ultimately to generate the diketone is analogous to the facile acetoxylation with lead



tetraacetate. The 1,2-diketones have been shown to fragment rapidly under these conditions. Invoking a hydroperoxide related to **34** (i.e., **35**) which could undergo nucleophilic initiated fragmentation cannot be ruled out although hydroxylation seems more likely.[10b,c]

Reaction of the β-keto sulfide with potassium superoxide may be envisioned to generate an intermediate like **35.** Indeed, treatment of **11** with excess potassium superoxide in anhydrous THF in the presence (somewhat faster) or absence of sodium hydride at room temperature or below leads to the ring cleaved product **23.** It is striking to note the facility of this reaction in



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the absence of any crown compounds in contrast to the usual chemistry of this reagent. This reaction may be particularly compared to the recent report of the cleavage of α-halo ketones with potassium superoxide which required the use of crown compounds, an observation which demonstrates the advantage of the keto sulfide substrate.[10a] The role that sulfur plays in "activating" the superoxide toward direct reactions remains to be established.

An intermediate such as **35** appears most reasonable for the superoxide reaction. Thus, either pathway is viable. Synthetically, the superoxide reaction is less clean, less chemoselective, and more tedious—drawbacks that do not appear to be counterbalanced by any outstanding advantages. For this reason it was not explored further.

Both approaches to ring cleavages developed herein appear useful. The main advantage of the two-stage process stems from the shorter reaction times and lower temperatures required for the hydrogen peroxide reaction. The one-step reaction gains from its directness and does not appear to suffer any obvious complications from the somewhat more strenuous conditions for ring cleavage. Both sequences possess good chemoselectivity, although the case of the *trans*-dehydroandrosterone **10** suggests a higher degree for the direct approach. The high ability to control the regioselectivity of the sulfenylation reaction translates into an excellent ability to control the regioselectivity of ring cleavage via this approach.

This method nicely complements the lead tetraacetate cleavage of the β-hydroxy sulfides.[13] The latter reaction maintains a chemical differentiation between the two ends of the newly created chain whereas this method does not. However, such differentiation in the diacids can frequently be achieved in highly unsymmetrical molecules and is not necessary in many applications. The greater range of ring sizes susceptible to ring cleavage via the methods reported herein offer a decided advantage.

The methodology reported herein offers several advantages over existing methods. In the synthesis of 1,2-dicarbonyl compounds, differentiation of the two carbonyl groups is maintained. Thus, regiospecific generation of diosphenols and a 1,2-alkylative carbonyl transposition are possible. The mildness of the oxidizing agents allows tolerance of a wide variety of functional groups in the ring cleavage. Thus, the direct chemoselective cleavage of **10** is most noteworthy in this regard. The ease of manipulation allows easy scale-up. Furthermore, tedious purification of any intermediates is unnecessary since impurities do not impede the reactions and the final products are easily isolated. The availability of the β-keto sulfides by other routes (e.g., by displacement of α-halo ketones, etc.) expands the applicability of this approach. These new reactions of β-keto sulfides further attest to their tremendous versatility as intermediates in organic synthesis.

Experimental Section

General. Melting points were taken on a Thomas-Hoover melting point apparatus. All melting and boiling points are uncorrected. Unless otherwise stated, infrared spectra were determined in carbon tetrachloride or chloroform solution on a Beckman IR-8 or Perkin-Elmer 267 spectrophotometer. NMR spectra were determined in carbon tetrachloride solution on a jeolco MH-100 or Brucker 270-MHz spectrometer; chemical shifts are given in δ with Me_4Si as the internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; b, broad; m, multiplet; p, pseudo. Coupling constants are given in hertz. Mass spectra were taken on an AEI MS-902 high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 98 mA. All exact mass determinations were obtained on the MS-902 instrument. Rotations were determined on a Perkin-Elmer Model 141 polarimeter.

All experiments were carried out under an atmosphere of dry nitrogen. In experiments requiring dry solvent, ether, tetrahydrofuran, and dimethoxyethane were distilled from sodium–benzophenone. Methylene chloride was distilled from calcium hydride. Apparatus for experiments requiring dry conditions were dried by flaming in a nitrogen stream.

During workup of the reactions, general drying of the solvent was performed over anhydrous magnesium sulfate or anhydrous sodium sulfate as indicated. Thin layer or preparative thick layer plates were made of E. Merck AG Darmstadt silica gel PF-254 activated by drying for 2 h at 140 °C. Removal of material from the silica gel was accomplished by successive washings with ether. Column silica gel was obtained from W. R. Grace and Co.

The lithium dialkylamides were prepared by adding 1 equiv of *n*-butyllithium to a solution of 1 equiv of dialkylamine (distilled from potassium hydroxide pellets) in THF or DME at −78 °C. After 15 min of stirring, the solutions were ready for use.

Sulfenylations. Preparation of Phenyl Benzenethiosulfonate. To a suspension of 54.5 g (250 mmol) of commercially available diphenyl disulfide in 200 mL of glacial acetic acid was added dropwise 57 g (510 mmol) of 30% aqueous hydrogen peroxide over a 30-min period. After stirring for 24 h at room temperature, cooling precipitated 4.5 g of product. Dilution of the mother liquors with 100 mL of water caused an oil to separate which was decanted off. The oil and crystals were combined and dissolved in 100 mL of chloroform. After washing with aqueous saturated sodium bicarbonate and drying (sodium sulfate), evaporation left 60.4 g of an oil. Filtration through 600 g of silica gel (7 × 90 cm column) with 1 L of 4:1 hexane–benzene gave 12.6 g (23% recovery) of diphenyl disulfide and then 1 L of benzene gave 34.6 g (72%) of phenyl benzenethiosulfonate. Recrystallization from methanol gave 30.5 g of colorless crystals, mp 36–37 °C.

Preparation of 11. To a solution of lithium cyclohexylisopropylamide (from 0.31 mL (1.74 mmol) of amine and 1.74 mmol of *n*-butyllithium) in 2 mL of dry THF was added a solution of 240 mg (1.55 mmol) of 4-*tert*-butylcyclohexanone in 1.5 mL of dry THF. After 10 min at −78 °C and 10 min at 0 °C, the enolate solution was transferred by syringe into a solution of 380 mg (1.55 mmol) of phenyl benzenethiosulfonate in 2 mL of dry THF. After 3 min a white precipitate formed. The resulting suspension was poured into a separatory funnel containing ether and 1 N aqueous hydrochloric acid. The aqueous layer was extracted with 2 × 20 mL of ether; the organic layers were combined, washed with aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). Evaporation of the solvent in vacuo leaves 388 mg (96%) of sulfenylated ketone **11** which was homogeneous and used directly in subsequent reactions without further purification. Its spectral properties are identical with those of an authentic sample.[11c]

Preparation of 13. To a solution of 7.5 mmol of lithium cyclohexylisopropylamide in 5 mL of dry THF at −78 °C was added 1.18 g (6.8 mmol) of 3-phenylcyclohexanone in 2 mL of dry THF. After 15 min at −78 °C and 1 h at room temperature, 1.63 g (7.5 mmol) of diphenyl disulfide was added rapidly. After 5 min, the reaction was quenched by pouring into aqueous dilute hydrochloric acid. The aqueous layer was extracted with 2 × 25 mL of ether and the combined ether layers were washed with aqueous sodium bicarbonate and brine and then dried (magnesium sulfate). Evaporation in vacuo gave 1.90 g of crude oil. Crystallization from hexane gave 371 mg, mp 104–107 °C, of colorless crystals of the trans isomer. Chromatographic purification of the mother liquors on 80 g of silica gel (2.8 × 25 cm column) with 1 L of 1:1 hexane–benzene gave diphenyl disulfide, with 500 mL of benzene gave 346 mg of sulfenylated ketone as a cis–trans mixture, and with an additional 500 mL of benzene gave 450 mg (38% recovery) of starting ketone. The total yield of β-keto sulfide is 717 mg (62%). Recrystallization of the trans isomer raised the melting point to 112 °C: IR ($CHCl_3$) 1710, 1600, and 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.1–7.5 (m, 10 H), 4.01 (ddd, J = 7.6, 5.7, 1.2 Hz, 1 H), 3.09 (m, 1 H), 2.85 (ddd, J = 13.4, 4.3, 2.0 Hz, 1 H), 2.64 (ddd, J = 13.4, 12.3, 1.2 Hz, 1 H), 2.39 (m, 1 H), 2.13 (m, 1 H), 1.94 (m, 1 H), 1.86 (m, 1 H); MS *m/e* (rel %) 284 (6), 283 (21), 282 (100), 218 (23), 173 (83), 172 (51), 149 (81), 145 (25), 144 (30), 136 (25), 131 (27), 129 (20), 110 (42), 109 (36), 105 (23), 104 (26), 91 (89), 77 (26), 69 (39), 65 (24), 57 (96), and 56 (65). Calcd for $C_{18}H_{18}OS$: 282.1078. Found: 282.1084.

Preparation of 14. Utilizing the procedure described for **11**, 188 mg (1.0 mmol) of 2-benzylcyclohexanone in 3.5 mL of THF, 1.1 mmol of lithium cyclohexylisopropylamide, and 250 mg (1.0 mmol) of phenyl benzenethiosulfonate produced 310 mg (quantitative) of crude product utilized directly for subsequent transformations: IR (CCl_4) 1710, 1602, 1580, 1493, 700, and 690 cm^{-1}; NMR (CCl_4) δ 6.9–7.7 (m, 10 H), 3.75 (broad, 1 H), 2.9–3.5 (m, 2 H), 1.0–2.6 (m, 7 H).

Preparation of 15. Utilizing the procedure described for **13**, 1.00 g (2.60 mmol) of 5α-cholestan-3-one was converted to its enolate utilizing 2.73 mmol of amide base in 8 mL of dry HMPA and 5 mL of dry THF by reacting for 30 min at −78 °C and 2 h at room temperature. Sulfenylation utilized 566 mg (2.60 mmol) of diphenyl disulfide for 2 h at room temperature. Workup gave 1.63 g of crude oil which deposited 410 mg of long, colorless needles upon dissolution in 10 mL of hexane. The mother liquors were concentrated and the residue purified by PLC ($CHCl_3$) to give 493 mg of product (t_R ~0.6) which deposited 180 mg of crystals upon dissolution in hexane and 122 mg (t_R ~0.7) of recovered cholestan-3-one (12%). The combined product, 903 mg (81%), gave 590 mg after recrystallization: mp 167–168 °C; $[\alpha]^{26}_D$ −40° (c 0.90, $CHCl_3$); IR ($CHCl_3$) 1715, 1583, 1485, 1392, and 1378 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.5 (m, 5 H), 4.00 (dd, J = 13, 6 Hz, 1 H), 2.1–2.5 (m, 5 H), 1.0–2.1 (m, 24 H), 1.02 (s, 3 H), 0.85 (d, J = 7 Hz, 9 H), 0.65 (s, 3 H); MS *m/e* (rel %) 496 (11), 495 (36), 494 (100), 386 (4), 163 (4), 135 (5), 123 (5), 121 (6), 110 (11), 109 (10), 95 (12), 81 (11), and 57 (12). Calcd for $C_{33}H_{50}OS$: 494.3582. Found: 494.3582.

Preparation of 16. Utilizing the procedure described for **13**, 1.00 g (3.48 mmol) of androst-5-en-3β-ol-17-one (**10**) was converted to the enolate alkoxide utilizing 7.3 mmol of amide base in 5 mL of dry HMPA and 10 mL of dry THF by reacting for 10 min at −78 °C and 2 h at room temperature. Sulfenylation utilized 760 mg (3.48 mmol) of diphenyl disulfide with a reaction time of 45 min at room temperature. Usual workup gave 1.33 g of pale yellow oil that gave 1.212 g (88%) of colorless crystals, mp 106–109 °C, from a mixture of benzene and hexane: IR ($CHCl_3$) 3590, 3460, 1735, and 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.6 (m, 5 H), 5.35 (m, 1 H), 3.92 (dd, J = 6, 3 Hz, 0.3 H), 3.5 (m, 1.7 H), 1.0–2.5 (m, 1 H), 1.02 (s, 3 H), 0.92 (s, 0.9 H), 0.78 (s, 2.1 H); MS *m/e* (rel %) 396 (50), 199 (3), 159 (3), 145 (4), 137 (11), 136 (100), 109 (4), 105 (5), 91 (6), and 55 (9). Calcd for $C_{25}H_{32}O_2S$: 396.2123. Found: 396.2125.

Sulfenylation of 28. Utilizing the procedure described for **11**, 244 mg (1.0 mmol) of ketone **28** and 1.1 mmol of amide base in 4 mL of dry THF was sulfenylated with 250 mg (1.0 mmol) of phenyl benzenethiosulfonate in 0.7 mL of dry THF. Usual workup gave 503 mg of crude oil that was purified by PLC (chloroform, t_R ~0.6) to give 155 mg (44%) of product: IR ($CHCl_3$) 1710, 1608, 1580, and 1500 cm^{-1}; NMR ($CDCl_3$) δ 7.0–7.6 (m, 6 H), 6.6 (m, 2 H), 3.73 (s, 3 H), 3.54 (d, J = 11 Hz, 1 H), 2.1–3.1 (m, 6 H), 1.4–2.1 (m, 3 H), 1.22 (s, 3 H); MS *m/e* (rel %) 354 (8), 353 (26), 352 (100), 351 (26), 335 (14), 296 (24), 241 (27), 227 (39), 187 (29), 174 (23), 173 (33), 110 (20), 109 (15), and 55 (17). Calcd for $C_{22}H_{24}O_2S$: 352.1497. Found: 352.1466.

Acetoxylations. General Procedure. Preparation of 20. A solution of 420 mg (1.42 mmol) of the crude keto sulfides and 1.63 g (~3.6 mmol) of lead tetraacetate stabilized by ~5% acetic acid (available from G. F. Smith Chemical Co.) in 15 mL of benzene was refluxed for 3 h, during which time a precipitate of lead diacetate formed. At the end of this period, 5 mL of ethylene glycol was added and the solution kept warm until all solids dissolved. The benzene layer was washed twice with brine, dried (sodium sulfate), filtered, and evaporated in vacuo. The crude oil, 470 mg, crystallizes from 1:1 benzene–hexane to give 320 mg of colorless crystals, mp 135 °C. PLC (chloroform, t_R ~0.25) of the mother liquors gave an additional 45 mg of

Table III. Experimental Details for Acetoxylation Reaction

	Keto sulfide (wt, mmol)	$Pb(OAc)_4$[a] wt (mmol)	PhH, mL	Temp, °C	Time, h	Ethylene glycol, mL	Acetoxy keto sulfide[c] wt (% yield)
11	(388 mg, 1.48)	1.63 g (3.68)	15	80	2	1.0	**17:** 471 mg (99)[d]
12	(897 mg, 3.10)	13.7 g (31)	15	80	8	10.0	**18:** 593 mg (55)[e]
13	(94 mg, 0.33)	370 mg (0.83)	1	70	30 min	0.5	**19:** 102 mg (90)[f]
14	See detailed procedure						
15	(175 mg, 0.355)	470 mg (~1.0)	1.5	70	45 min	1.0	**21:** 195 mg (99)[d]
16	See detailed procedure						
31	(1.52 g, 10)	11.5 g (26)	50	75	42	7.5	1.96 g (89)[g]
32	(194 mg, 0.723)	1.132 mg (2.5)[b]	5	Reflux	35	2	142 (61)[f]

[a] In each case, lead tetraacetate contained approximately 5% by weight of acetic acid as a stabilizer. [b] In this case, initially 832 mg was added and after a reaction time of 16 h an additional portion of 300 mg was added. [c] It is not necessary to purify the acetoxy keto sulfide for further transformations. [d] In this case the crude product was not further purified. [e] Recrystallized from acetone–hexane, mp 118–119 °C. [f] Purified by PLC utilizing chloroform. [g] Purified by Kugelrohr distillation at 50 °C (bath temp), 0.1 mm.

product for a total yield of 365 mg (73%): IR ($CHCl_3$) 1740, 1720, 1600, 1582, 1573, 1493, and 1370 cm^{-1}; NMR ($CDCl_3$) δ 7.0–7.6 (m, 10 H), 3.1 (m, 2 H), 2.05 (s, 3 H) superimposed upon 1.1–2.7 (m, 7 H); MS *m/e* (rel %) 354 (23), 294 (5), 203 (24), 185 (46), 157 (33), 152 (45), 91 (100), and 43 (96). Calcd for $C_{21}H_{22}O_3S$: 354.1288. Found: 354.1309.

The details for the remaining examples are accumulated in Table III except for entry 6, Table I, which appears below in the preparation of the monoketal of the 16,17-diketo steroid **30.**

Spectral Properties of β-Keto Acetoxy Sulfides. 17: NMR (CCl_4) δ 7.0–7.6 (m, 5 H), 2.1–2.5 (m, 2 H), 2.00 and 2.05 (two s, 3 H), 1.3–2.1 (m, 5 H), 0.90 and 0.85 (two s, 9 H).

18: IR ($CHCl_3$) 1740, 1720, and 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.1–7.6 (m, 5 H), 2.7 (m, 2 H), 2.11 (s, 3 H), 1.0–2.2 (m, 18 H); MS *m/e* (rel %) 348 (9), 305 (63), 288 (9), 239 (63), 169 (16), 152 (63), 98 (18), 55 (18), and 43 (100). Calcd for $C_{20}H_{28}O_3S$: 348.1757. Found: 348.1759.

19: IR ($CHCl_3$) 1745, 1725, 1597, 1579, and 1485 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.6 (m, 10 H), 1.90–3.25 (m, 10 H), 2.10 and 2.16 (two s, ratio ~3:2, 3 H).

21: IR ($CHCl_3$) 1745, 1720, 1580, and 1480 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.6 (m, 5 H), 0.8–2.9 (m, 29 H), 2.00 and 2.05 (two s, ratio ~3:2, 3 H), 1.25 (s, 3 H), 0.85 (d, J = 7 Hz, 9 H), 0.64 and 0.67 (two s, ratio ~2:3, 3 H).

Methyl 2-acetoxy-2-methylthiopentanoate: IR (CCl_4) 2880, 1755, 1745 cm^{-1}; ^1H NMR (CCl_4) δ 3.75 (s, 3 H), 2.40 (m, 1 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.90 (m, 1 H), 1.45 (m, 2 H), 0.90 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 169.3 (s), 168.5 (s), 86.7 (s), 52.5 (q), 36.7 (t), 20.7 (quart), 17.2 (t), 13.9 (t), 12.1 (q); MS *m/e* (rel %) 161 (16), 115 (12), 101 (16), 83 (21), 73 (17), 69 (100), 59 (24), and 55 (38). Calcd for $C_7H_{13}O_2S$ (M − OAc): 161.0635. Found: 161.0635.

Methyl 2-acetoxy-2-methylthio-3-phenylheptanoate: IR ($CHCl_3$) 2868, 2860, 1740, 1600, and 1492 cm^{-1}; NMR (CCl_4) δ 7.28 (ps, 5 H), 3.68 (s, 3 H), 3.20 (dd, J = 10.5, 5 Hz, 1 H), 2.05 and 2.15 (two s, 3 H), 1.70 and 2.10 (two s, 3 H), 1.84 (m, 2 H), 1.18 (m, 4 H), 0.80 (t, J = 7 Hz, 3 H); MS *m/e* (rel %) 324 (3), 277 (1), 264 (5), 234 (12), 190 (18), 177 (30), 147 (56), 135 (50), 134 (43), 129 (11), 117 (15), 115 (25), 105 (25), 103 (18), 91 (93), and 43 (100). Calcd for $C_{17}H_{24}O_4S$: 324.1395. Found: 324.1361.

Preparation of Monoketal of 1,2-Dicarbonyl Compounds. 3β-Hydroxy-16,16-dimethoxyandrost-5-en-17-one (30). To a solution of the keto sulfide **16** (176 mg, 0.445 mmol) in 5 mL of methylene chloride at room temperature was added 1 mL (7.0 mmol) of trifluoroacetic anhydride. After 5 min, the solution was evaporated to dryness in vacuo; 5 mL of benzene was added and the evaporation repeated. One obtained 215 mg of the trifluoroacetate as a pale yellow oil which was used without further purification: IR ($CHCl_3$) 1775, 1735 cm^{-1}; NMR ($CDCl_3$) δ 5.4 (m, 1 H), 4.8 (m, 1 H), 3.95 (bdd, J = 7, 3 Hz, 0.4 H), 3.60 (bt, J = 6 Hz, 0.6 H), 1.02 (s, 3 H), 0.93 and 0.75 (two s, 3 H). After dissolution of the trifluoroacetate in 4 mL of benzene and addition of 496 mg (~1.1 mmol) of lead tetraacetate, the resulting solution was heated for 30 min at 70 °C. Then 1 mL of ethylene glycol was carefully added and the reaction maintained hot until all the precipitate dissolved. The mixture was diluted with 10 mL of ether and washed with 5 mL of brine to give after usual further workup 227 mg of acetoxy sulfide as its trifluoroacetate **22:** IR ($CHCl_3$) 1775, 1750, 1735 cm^{-1}; NMR ($CDCl_3$) δ 5.47 (m, 1 H), 4.83 (m, 1 H), 2.07 and 2.02 (two s, 3 H), 1.10 and 1.32 (two s, 6 H). The crude product was dissolved in 10 mL of methanol to which has been added 256 mg (1.13 mmol) of iodine and the resulting mixture maintained at 45 °C for 48 h. After cooling, 1 g of sodium thiosulfate pentahydrate in 5 mL of water was added and the methanol removed in vacuo. The residue was diluted with 10 mL of brine and extracted with 2 × 10 mL of chloroform. After drying (sodium sulfate) and evaporation, the crude oil (225 mg) was eluted through 5 g of alumina with benzene (40 mL) to remove diphenyl disulfide, with 1:1 benzene–chloroform (40 mL), and then with chloroform (20 mL) to give 140 mg (90%) of titled product **30**, mp 176–177 °C and $[\alpha]^{25}_D$ +6.0° (*c* 1.0, $CHCl_3$), after recrystallization from ethyl acetate: IR ($CHCl_3$) 3590, 3450, 1750, and 1663 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 5.37 (m, 1 H), 3.53 (m, 1 H), 3.34 (s, 6 H), 1–2.4 (m, 18 H), 1.03 (s, 3 H), 1.01 (s, 3 H); MS *m/e* (rel %) 348 (0.1), 320 (1), 317 (2), 288 (3), 203 (2), 199 (2), 159 (2), 145 (2), 143 (2), 118 (10), 105 (5), 89 (96), 88 (100), 81 (5), 79 (6), 70 (9), 61 (11), and 58 (13). Calcd for $C_{21}H_{32}O_4$: 348.2301. Found: 348.2290.

Preparation of 29. As above, 226 mg (0.41 mmol) of acetoxy sulfide **21** was reacted with 230 mg (1.02 mmol) of iodine in 15 mL of methanol for 15 h. After workup as above, the crude oil was directly crystallized from methanol to give 141 mg (78%), mp 106 °C (lit.[25] mp 105–106 °C), after an additional recrystallization from methanol, optical rotation $[\alpha]^{25}_D$ +81° (*c* 0.93, $CHCl_3$) (lit.[25] +70° (*c* 0.3, $CHCl_3$)).

Preparation of Methyl 2,2-Dimethoxypentanoate. As above, 1.136 g (5.18 mmol) of methyl 2-acetoxy-2-phenylthiopentanoate in 10 mL of methanol was reacted with 2.92 g (12.9 mmol) of iodine for 39 h at room temperature. After the usual workup and removal of solvents by distillation through a 15-cm Widmer column at atmospheric pressure, the residue was distilled on a Kugelrohr apparatus at 12 mm and the fraction distilling at a pot temperature of 40–65 °C was collected to give 739 mg (81%) of product as a colorless oil: IR (CCl_4) 2885, 2835, and 1745 cm^{-1}; NMR (CCl_4) δ 3.70 (s, 3 H), 3.15 (s, 6 H), 1.70 (m, 2 H), 1.15 (m, 2 H), 0.90 (t, J = 7 Hz, 3 H).

Preparation of Methyl 2,2-Dimethoxy-3-phenylheptanoate. As above, 142 mg (0.436 mmol) of methyl 2-acetoxy-2-phenylthio-3-phenylheptanoate and 246 mg (1.09 mmol) of iodine in 5 mL of methanol for 16 h at room temperature gave 118 mg (97%) of product as a colorless oil after the usual workup: IR (CCl_4) 2845, 2862, 2880, and 1750 cm^{-1}; NMR (CCl_4) δ 7.14 (ps, 5 H), 3.54 (s, 3 H), 3.30 (s, 3 H), 3.25 (s, 3 H), 3.02 (dd, J = 10, 4 Hz, 1 H), 1.77 (m, 2 H), 0.95–1.4 (m, 4 H), 0.80 (t, J = 7 Hz, 3 H).

Ring Cleavages via Acetoxy Keto Sulfides. Preparation of 3-*tert*-Butyladipic Acid (23). To a solution of 471 mg (1.47 mmol) of the acetoxy sulfides in 10 mL of THF was added a preformed solution of 600 mg (15 mmol) of sodium hydroxide and 3.4 mL of 30% aqueous hydrogen peroxide (30 mmol) in 5 mL of water. After stirring for 5 h at room temperature, the reaction mixture was acidified to pH 1 with dilute aqueous hydrochloric acid and extracted with ethyl acetate. After drying (sodium sulfate) and evaporation in vacuo, the oil crystallized upon trituration with ethyl acetate, 197 mg (67%), mp 116–117 °C (lit.[26] mp 115–115.5 °C). The overall yield for the three

Table IV. Preparation of Diacids by Ring Cleavage of Acetoxy Keto Sulfides

Acetoxy keto sulfide (wt, mmol)	NaOH, mg (mmol)	30% H_2O_2	THF, mL	H_2O, mL	Time, temp	Product[a] wt (%)	Mp, °C	Lit. mp, °C
18 (54 mg, 0.155)	200 (5)	1.6	1.0	2.5	4 h, 0 °C 16 h, RT	**24**[b] 36 mg (99)	127.5–128.5	129[e]
19 (102 mg, 0.30)	100 (2.5)	0.255	1.0	1.0	36 h, RT	**25**[c] 53 mg (80)	142.5–144	148[f]
20 (41 mg, 0.116)	200 (5)	0.330	0.5	1.5	1.5 h, RT	**26**[b,d] 23 mg (85)	112–115	116–117[g]
21 (152 mg, 0.275)	120 (3)	0.325	1.0	1.0	24 h, RT	**27**[c] 78 mg (65)	196–199	197.5–199[h]

[a] All products were characterized by IR and NMR spectroscopy in addition to melting point. [b] Recrystallized from ethyl acetate. [c] Recrystallized from benzene. [d] A sample was esterified with diazomethane and the latter characterized by mass spectroscopy. Calcd for $C_{15}H_{20}O_4$: 264.1360. Found: 264.1339. [e] Reference 27. [f] Reference 28. [g] Reference 29. [h] Reference 30.

Table V. Experimental Details for Direct Cleavage of Keto Sulfides[a]

Keto sulfide wt (mmol)	NaOH wt (mmol)	30% H_2O_2 wt	Solvent, mL	H_2O, mL	Time, temp	Product wt (%)
11 405 mg (1.55)[b]	750 mg (18.7)	2.60 g	THF, 5.0	5.0	3 h, 50 °C 12 h, RT	**23** 218 mg (69)[c]
12 553 mg (1.90)	1.260 mg (31.5)[d]	2.95 g[e]	CH_3OH, 10		60 h, reflux[f]	**24** 269 mg (83)[g]
13 370 mg (1.31)	550 mg (13.7)	1.70 g	THF, 3.0	5.0	16 h, 70 °C	**25** 196 mg (67)
14 100 mg (0.338)	135 mg (3.4)	190 mg	THF, 2.0	2.0	15 h, RT 14 h, 55 °C	**26** 50 mg (63)
16 689 mg (1.74)	700 mg (17.5)	1.80 g	CH_3OH, 10		16 h, reflux	*h,i* 394 mg (67)
28b 54 mg (0.153)	100 mg (2.5)	110 mg	THF, 1.0	1.0	12 h, RT 16 h, 50 °C	*j,k,l* 24 mg (55)

[a] All compounds were identified by comparison to previously obtained diacids except where noted otherwise. [b] Crude keto sulfide was employed directly. [c] Yield in this case is overall for the two steps. [d] Added in two portions of 769 and 500 mg (see footnote *f*). [e] Added in two portions of 1.95 and 1.0 g (see footnote *f*). [f] Initial reflux period was 3 h. After addition of second portions of oxidizing mixture, an additional 24-h reflux period was employed. [g] This yield is based upon consumed starting material since 102 mg of unreacted keto sulfide was recovered. [h] For structure of product see Table II, entry 6. [i] Recrystallized from acetone, mp 230–231 °C (lit.[31] mp 227–228 °C). Melting point of various recrystallization fractions can vary up to 249–252 °C depending upon state of hydration.[31] [j] For structure of product see Table II, entry 7. [k] Recrystallized from ether: mp 198–199 °C; IR ($CHCl_3$) 2400–3400, 1700, 1612, 1578, 1500 cm^{-1}; NMR ($CDCl_3$) δ 8.2 (b, 2 H), 7.2 (d, J = 7 Hz, 1 H), 6.76 (dm, J = 7 Hz, 1 H), 6.60 (bs, 1 H), 3.80 (s, 3 H), 1.5–3.0 (m, 9 H), 1.30 (s, 3 H). [l] A small sample was esterified with diazomethane to give the diester. Calcd for $C_{18}H_{24}O_5$: 320.1617. Found: 320.1589.

steps is 63%. The sample was also characterized by IR and NMR spectroscopy.

Table IV summarizes the reaction details for the remaining examples.

Ring Cleavage Directly from Keto Sulfides. Preparation of 2,3-Secocholestane-2,3-dioic Acid. A solution of 1.6 g (40 mmol) of sodium hydroxide and 4.62 g of 30% aqueous hydrogen peroxide (40.8 mmol) in 20 mL of water was added to a solution of 2.016 g (4.08 mmol) of keto sulfide **15** in 20 mL of THF. After stirring for 15 h at 65 °C, the reaction mixture was cooled and acidified to pH 1 with dilute aqueous hydrochloric acid. The mixture was extracted with 2 × 60 mL of ethyl acetate, dried (magnesium sulfate), and evaporated in vacuo to give 1.657 g (94%) of white plates, mp 199–199.5 °C (lit.[30] mp 197.5–199 °C), after recrystallization from benzene.

The experimental details for the remaining examples are summarized in Table V.

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Stereochemistry of the [1,4] Rearrangement of 10-Aryl-10-thiaanthracenes. Asymmetric Induction in the Transfer of Chirality from Sulfur to Carbon with Concomitant Pyramidal Inversion at Sulfur

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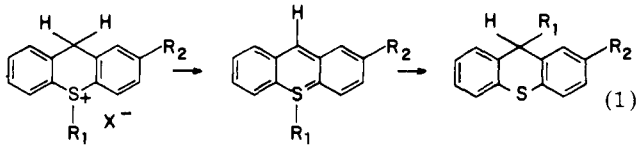
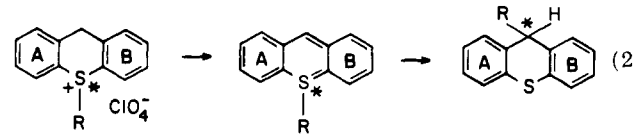
Abstract: Deprotonation of optically active 2-chloro-10-(2,5-xylyl)-10-thioxanthenium perchlorate, resolved via the (+)-camphor-10-sulfonate salt, yielded 2-chloro-10-(2,5-xylyl)-10-thiaanthracene, which rearranged to optically active 2-chloro-9-(2,5-xylyl)-10-thioxanthene. This constitutes the first example of an asymmetric induction in the transfer of chirality from sulfur to carbon accompanying an intramolecular [1,4] rearrangement. The low enantiomeric excess in the product thioxanthene, ca. 7% as determined by ^{1}H NMR, could be ascribed to the configurational instability of the intermediate thiaanthracene, which racemizes about ten times as fast as it rearranges at −15 °C.

Thiaanthracenes (**1**), formed by the deprotonation of thioxanthenium salts (**2**), are unstable compounds which undergo thermal rearrangements to yield the corresponding 9-substituted thioxanthenes (**3**) (eq 1).[1,2] These rearrangements can be formally described as six-electron [1,4] sigmatropic shifts, i.e., as thermal intramolecular rearrangements of cyclic sulfonium ylides.[2]



(1)

The objective of the present work was to determine whether asymmetric induction could be observed in the transfer of chirality from sulfur to carbon in the rearrangement of an unsymmetrically substituted 10-aryl-10-thiaanthracene (eq 2, chiral center starred).[3] Although such inductions had been reported for intramolecular 1,2 shifts,[4,5] no precedent existed for asymmetric inductions in a [1,4] rearrangement.



(2)

A ring ≠ B ring

The system of choice was 2-chloro-10-(2,5-xylyl)-10-thiaanthracene (**1**, R_1 = 2,5-xylyl; R_2 = Cl). Previous work[1,2] had shown that **1** rearranges to 2-chloro-9-(2,5-xylyl)-10-thioxanthene (**3**) intramolecularly (no crossover products were detected) and in high yield (70–80%), and that the rearrangement follows first-order kinetics. The experimental strategy called for resolution of the previously described[1] 2-chloro-10-(2,5-xylyl)-10-thioxanthenium (**2**) perchlorate, and deprotonation of the resolved salt to **1**: assuming pyramidal stability of **1** and **2** on the time scale of the rearrangement **1** → **3**, and stereospecificity in the rearrangement itself, this procedure should lead to enantiomerically enriched **3** and thus to detectable asymmetric induction.

Results and Discussion

Optical Activation of a Thioxanthenium Perchlorate. The chloride of **2**, prepared from the perchlorate by ion exchange